Indian Journal of Medical Ethics Published online first on March 3, 2021.

THEME-DOUBLE STANDARDS REDUX: THE ETHICS OF FUTURE COVID-19 VACCINE RESEARCH

Problematic Covid-19 vaccine trials in times of vaccine nationalism

RAFFAELLA RAVINETTO

Abstract

Thanks to an impressive R&D effort, three vaccines for COVID19 have been conditionally approved by stringent regulators as of February 2021, and sixteen have entered the WHO evaluation process. However, they all need to keep on being evaluated in clinical trials. The WHO Ad Hoc Expert Group on the Next Steps for Covid-19 Vaccine suggested that countries with limited or no access to an effective vaccine could ethically permit placebo-controlled trials, even if effective vaccines were already being marketed elsewhere. Here, I argue that inclusion in a placebo-controlled trial is ethically sound for those who would be in any case ineligible for vaccination outside the trial, and as long as the access to the vaccine outside the trial depends on a transparent and just allocation framework. Conversely, carrying out placebo-controlled studies in countries where vaccines are not (or are insufficiently) available because of unequal global allocation, would be unethical, as an ethical strategy cannot be built on an unethical premise.

Key words: *Covid-19; vaccine; clinical trials; research ethics; equity, placebo controls*

The Covid-19 pandemic has led to rapid and dramatic changes in almost every aspect of individual, community and social life, on a global scale. The new coronavirus rapidly spread in high-income countries (HICs), where the health systems showed an unexpected lack of preparedness to respond to a large-scale outbreak.

Largely due to the high prevalence of Covid-19 in HICs, there was a rapid and massive deployment of funding for research and development (R&D) from the public, philanthropic, and private sectors, with impressive results (1, 2). At the time of writing, three vaccines (Pfizer/BioNTec, Moderna, AstraZeneca) have received a *conditional marketing authorisation* from the European Medicine Agency (EMA) (3). Two of them(Pfizer/BioNTec and Moderna) also have an *emergency use authorisation* (EUA) of the United States Food and Drug Administration (US FDA) (4); and two (Pfizer/BioNTec and AstraZeneca) have been listed for *emergency use* (EUL) by the World Health Organization (WHO) (5, 6). As on February 8, 2021, sixteen vaccines had entered the WHO EUL evaluation process, including some manufactured in India, China and Russia, and/or approved by regulators other than EMA and FDA (7). With other vaccines in an advanced stage of clinical development, this information should be frequently re-checked.

Thanks to the impressive R&D effort, vaccination campaigns have been started in different parts of the globe. However, there is a striking imbalance in distribution figures. As of February 13, 2021, out of 160 million single doses administered globally, about 60% were distributed in HICs, 35% in upper-middle-income countries, and 5% in lower-middle-income countries, with low-income countries completely left behind in the global effort to end or control the pandemic (8).

Conditional and emergency authorisations rely on less comprehensive clinical data than normally required. They were granted to Covid-19 vaccines based on a risk-benefit assessment, and came with pending regulatory obligations, such as completing ongoing or new clinical trials, and confirming the benefit-risk balance in the general population and in specific population groups. Furthermore, more vaccines will be needed to meet global short- and long-term needs (9), particularly if Covid-19 becomes endemic (10). Therefore, several vaccines need to keep on being evaluated in formal clinical trials. The WHO Ad Hoc Expert Group on the Next Steps for Covid-19 Vaccine believes that as long as "vaccine supplies are limited, available vaccines are still investigational, or public health recommendations to use those vaccines have not been made", it is ethically appropriate also "to continue blinded follow-up of placebo recipients in existing trials and to randomly assign new participants to vaccine or placebo" (9).

However, the acceptability of placebo-controlled trials may not be that straightforward. Placebo-controlled trials are generally justified when equipoise exists that is, a genuine uncertainty

Author: **Raffaella Ravinetto** (rravinetto@itg.be), Department of Public Health, Institute of Tropical Medicine, Antwerp, BELGIUM.

To cite: Ravinetto R. Problematic Covid-19 vaccine trials in times of vaccine nationalism. *Indian J Med Ethics*. Published online first on March 3, 2021. DOI: 10.20529/IJME.2021.014.

Manuscript Editors: Ruth Macklin, Amar Jesani.

Peer reviewer: Charles Weijer

exists within the expert medical community about the preferred treatment (11). A state of equipoise did exist when Covid-19 vaccine trials began in 2020. But as vaccines approved (under some degree of conditionality) by stringent regulators represent the current "gold standard", it would seem that equipoise no longer exists with regard to preventing Covid-19 symptoms (12), nor for short term safety. Equipoise still remains for other outcomes, such as the infectivity of vaccinated subjects, the duration of protection, and long-term safety (12), which are crucial to make science advance and to inform policy decisions. But the short-term prevention of Covid-19 symptoms is likely to be a more important consideration for some trial participants, particularly those belonging to groups at higher risk of severe Covid-19 (eg those above 55 years, or with co-morbidities). These individuals would feel better protected in trial designs without a placebo arm.

The call to altruism

The WHO Ad Hoc Expert Group noted that "people who enroll in clinical trials for altruistic reasons would probably understand the value of gathering data that will further elucidate the safety and efficacy of these vaccines and their appropriate use" (9). But reasons that influence a personal decision to participate in trials are complex and multifactorial. For instance, a systematic review listed altruism, personal health benefits, access to healthcare, monetary benefit, knowledge, social support and trust as the most important reasons for participation in biomedical research in low- and middle-income countries (LMICs); while primary reasons for non-participation were safety concerns, inconvenience, stigmatisation, lack of social support, confidentiality concerns, physical pain, efficacy concerns and distrust (13). Fisher and colleagues used the term "structural coercion" to underscore the ways in which broader social, economic, and political contexts act upon individuals to compel them to enrol, well beyond the researcher-participant relationship or the particular study protocols (14). Structural coercion can be particularly relevant in socio-economically vulnerable groups. For instance, structural coercion surfaced in the context of community engagement in global health research in a low-resource setting in Africa, due to an interplay of factors pertaining to social-economic context, study design and power relations among research stakeholders (15).

The particular reference to people who enrol in Covid-19 vaccine clinical trials for altruistic reasons, seems to underplay the complexity of individual decision-making around participation in clinical trials. The personal account of a vaccine trial participant, who was ready to make the altruistic choice, provides a real-life account of the trial's journey, from a situation where participation looks advantageous ("Although I had a 50–50 chance of getting the placebo, which was an injection of saltwater, I also had coin-flip odds of getting a vaccine that looked safe and efficacious in earlier trials months before everyone else"), to uncertainty once this particular vaccine appeared to be effective ("Did I get the vaccine or did I get the placebo?"), to the dilemma of choosing whether to continue in the study or get unblinded (for getting "the first dose of the vaccine right then and there", if found to be in the placebo group) (16). In this specific case, a collective decision to unblind and vaccinate people in the placebo arm was eventually made by the study sponsor. However, any personal decisions, whether to remain blinded and contribute to a global benefit; or to be unblinded and choose vaccination over altruism, would have been legitimate, and should have been respected.

A direct and unidirectional call to altruism could be seen as a form of structural coercion, as it might foster a sense of culpability in those who would decline participation, or would ask to be unblinded. Structural coercion could be stronger for some group of (prospective) participants. For instance, those made psychologically vulnerable by the loss of loved ones due to Covid-19 could be more likely to feel compelled to sacrifice their own health interests for the sake of a global aim.

The best standard: For whom, and where?

It may be argued that despite the limitations of the emergency and conditional approvals (eg. lack of data on long term safety, duration of protection, etc), if placebo-controlled trials continue, the newly recruited participants as well as those who decide not to be unblinded would be temporarily denied the benefit of the current gold standard. But not all of them would be eligible for vaccination outside the trial: global manufacturing capacity is severely insufficient to address global needs, and countries that are rolling out vaccines adopt a stepwise approach, generally prioritising the most vulnerable groups (17). Trial participants should not be worse off in the trial than outside. Thus, a key-question for evaluating their risks in a placebo-controlled vaccine trial is whether they are eligible for vaccination outside the trial. Those who would be eligible for vaccination outside the trial, should be offered access to the vaccines, while those who would still be ineligible outside the trial, may continue in the placebo arm (18). This criterion looks sound, as long as the access to the vaccine outside the trial depends on a transparent allocation framework, grounded in ethical values and social justice.

Unfortunately, if we broaden the perspective from the national level in HICs to the global level, we see a dramatic imbalance in access to the vaccines (8). Despite the creation of COVAX, a multilateral initiative that brings together more than 170 countries for coordinating the purchase, supply and allocation of Covid-19 vaccines, and that aims to deliver 2 billion doses by end 2021 (19), many HICs started very early bilateral negotiations with manufacturers. This fostered a sense of mistrust toward multilateral mechanisms, so some middle-income countries also started bilateral negotiations. The expression "vaccine nationalism" indicates a situation in which rich countries bid against each other to secure bilateral contracts with vaccine manufacturers, and stockpile vaccines for their own citizens (20, 21). According to an analysis of

publicly available data on premarket purchase agreements, HICs have reserved more than half of the world's vaccine doses despite representing just 14% of the world's population (22, 23). It is even feared that most people in low-income countries could have to wait until 2024 before being vaccinated (24). Debate is ongoing at international level on how to allocate vaccines between countries in an equitable manner. Besides the proportional allocation scheme embedded in the COVAX model, the Fair Priority Model would allocate vaccines in three phases, first aiming at minimising premature deaths, then adding socioeconomic factors such as the reduction of the poverty gap, and eventually aiming at returning countries to their pre-Covid-19 situation (25). Herlitz and colleagues underline that fair vaccine allocation must help us combat the pandemic's direct and indirect health effects for individuals, irrespective of country of origin or residence (26).

Unfortunately, vaccine nationalism is still the prevalent "model". It is leaving the poorest countries and communities behind, in what the WHO Director General has called a moral failure and an (epidemiologically) strategic mistake (27). In this scenario, a proposal that "countries with limited or no access to a known effective vaccine could thus ethically permit placebo-controlled trials of vaccines of potential relevance to them even if effective vaccines were already being marketed elsewhere" seems to add further offence to (the moral) injury. Indeed, these countries have, or will keep on having, limited or no access to the vaccines because of the lack of a coordinated, transparent and equitable response to the pandemic; or, in other words, because of the moral global failure to build the pandemic response in justice and solidarity.

We therefore argue that carrying out placebo-controlled studies in these countries because vaccines are not (or are insufficiently) available, would be unethical. First, an ethical strategy cannot be built on an unethical premise, which is, in this case, the inequitable allocation of vaccines between countries. Second, this strategy could even be seen as "ethics dumping", that is the practice of undertaking research in a low- or middle-income setting which would not, for different reasons, be permitted in a high-income setting (28). Third, it would *de facto* reverse the principle of benefit sharing in global research (29,30), as the burden of research would be only for the most vulnerable communities, while the benefit of research would be available to communities in more affluent countries.

Conclusion

To be framed in health and social justice terms, global health research (31) should generate knowledge that improves the health and well-being of disadvantaged and marginalised individuals and communities (28,32). Those who lack access to Covid-19 vaccination because of unequal allocation between countries should be seen as disadvantaged, and research involving them should be based on health and social justice, rather than building on structural injustice. Calling upon equipoise between placebo and the local standard, for justifying placebo-controlled-studies in settings where vaccines are not yet available due to vaccine nationalism and lack of equity, would be unethical.

Acknowledgment

I am grateful to Kristof Decoster, for critically reading and editing an earlier draft manuscript.

References

1. World Health Organization.(WHO). Draft landscape and tracker of COVID-19 candidate vaccines. [cited 2021 Feb 17]. Available from: https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines
2. Policy Cures Research. COVID19 R&D Tracker. [cited 2021 Feb 17]. Available from: www.policycuresresearch.org/covid-19-r-d-tracker
3. European Medicines Agency (EMA). Conditional marketing authorization. [cited 2021Feb 17]. Available from: www.ema.europa.eu/en/human-regulatory/marketing-authorisation/conditional-marketing-authorisation
4. US Food and Drug Administration (FDA). Emergency Use Authorization for Vaccines Explained. 2020 Nov 20[cited 2021 Feb 17]. Available from: https://www.fda.gov/vaccines-blood-biologics/vaccines/emergency-use-authorization-vaccines-explained
5. World Health Organization (WHO). Emergency Use Listing Procedure for vaccines. 2020 Jan 8[cited 2021 Feb 17]. Available from: https://www.who.int/teams/regulation-prequalification/eul/eul-vaccines
6. World Health Organization. WHO lists two additional COVID-19 vaccines for emergency use and COVAX roll-out. Geneva, Switzerland: WHO: 2021 Feb15[cited 2021 Feb 17].. Available from: https://www.who.int/news/item/15-02-2021-who-lists-two-additional-covid-19-vaccines-for-emergency-use-and-covax-roll-out
7. World Health Organization. Status of COVID-19 Vaccines within WHO EUL/PQ evaluation process. 2021 Feb 8[cited 2021 Feb17]. Available from: https://extranet.who.int/pqweb/sites/default/files/documents/Status_COVID_VAX_08Feb2021.pdf
8. Pandem-IC. Vaccine Equity Tracker. Updated 2021 Feb 13 [cited 2021 Feb 17]. Available from: https://pandem-ic.com/vaccine-equity-tracker/
9. WHO Ad Hoc Expert Group on the Next Steps for Covid-19 Vaccine. Placebo-Controlled Trials of Covid-19 Vaccines —Why We Still Need Them. *N Eng J Med.* 2021 Jan 14; 384(2); e2. Doi: 10.1056/NEJMp2033538. Epub 2020 Dec 2.
10. *Economist*. The pandemic. How well will vaccines work? Covid-19 may become endemic. *Economist.com*. 2021 Feb 13[cited 2021 Feb 17]. Available from: https://www.economist.com/leaders/2021/02/13/how-well-will-vaccines-work
11. Freedman B. Equipoise and the ethics of clinical research. *N Engl J Med.* 1987 Jul 16; 317(3): 141–5. Doi: 10.1056/NEJM198707163170304.
12. Friesen P, Caplan AL, Miller J. COVID-19 vaccine research and the trouble with clinical equipoise. *Lancet*. Epub 2021 Feb 1[cited 2021 Feb 17]. Doi: https://doi.org/10.1016/S0140-6736(21)00198-7.
13. Browne JL, Rees CO, van Delden JJM, Agyepong I, Grobbee De, Edwin A, et al. The willingness to participate in biomedical research involving human beings in low- and middle-income countries: a systematic review. *Trop Med Int Health*. 2019 Mar; 24(3):264-79. Doi:10.1111/tmi.13195.Epub 2019 Jan 8.
14. Fisher JA. Expanding the frame of "voluntariness" in informed consent: structural coercion and the power of social and economic context. *Kennedy Inst Ethics J.* 2013 Dec; 23(4):355-79.
15. Nyirenda D, Sariola S, Kingori P, Squire B, Bandawe C, Parker M, Desmond N. Structural coercion in the context of community engagement in global health research conducted in a low resource setting in Africa. *BMC Med Ethics.* 2020 Sep 21; 21(1):90. Doi: 10.1186/s12910-020-00530-1.
16. Storrs C. I'm in the Pfizer Trial. Should I Get Vaccinated Early? One participant's ethical quandaries. Elemental. *Medium.com*. 2021 Jan 21[cited 2021 Feb 17].Available from: https://elemental.medium.com/amp/p/9d13328bd7ce?__twitter_impression=true
17. Giubilini A, Savulescu J, Wilkinson D. Queue questions: Ethics of COVID-19 vaccine prioritization. *Bioethics.* Epub 2021 Feb 8; Doi: 10.1111/bioe.12858.
18. Rid A, Lipsitch M, Miller FG. The Ethics of Continuing Placebo in SARS-CoV-2 Vaccine Trials. *JAMA.* 2021 Jan 19; 325(3): 219-20. Doi: 10.1001/jama.2020.25053.

19. COVAX homepage.*Gavi.org.* Updated 2021 Feb 24[cited 2021 Feb 25]. Available from: www.gavi.org/covax-facility
20. Kupferschmidt K. 'Vaccine nationalism' threatens global plan to distribute COVID-19 shots fairly. *Science.* 2020 Jul 28[cited 2021 Feb 17]. Available from: https://www.sciencemag.org/news/2020/07/vaccine-nationalism-threatens-global-plan-distribute-covid-19-shots-fairly
21. Bollyky TJ, Bown CP. The tragedy of vaccine nationalism. *Foreign Affairs.* 2020 Jul 27 [cited 2021 Feb 17]. Available from: https://www.foreignaffairs.com/articles/united-states/2020-07-27/vaccine-nationalism-pandemic
22. Kuehn BM. High-income countries have secured the bulk of COVID-19 vaccines. *JAMA.* 2021; 325(7):612.
23. *Economist.* There will be enough vaccines for all—if rich countries share. *Economist.* 2021 Feb 13 [cited 2021 Feb 17]. Available from: https://www.economist.com/graphic-detail/2021/02/13/there-will-be-enough-vaccines-for-all-if-rich-countries-share
24. Safi M. Most poor nations 'will take until 2024 to achieve mass Covid-19 immunisation'. *Guardian.* 2021 Jan 27[cited 2021 Feb 17]. Available from: www.theguardian.com/society/2021/jan/27/most-poor-nations-will-take-until-2024-to-achieve-mass-covid-19-immunisation
25. Herzog LM, Norheim OF, Emanuel EJ, McCoy MS. Covax must go beyond proportional allocation of covid vaccines to ensure fair and equitable access. *BMJ.* 2021 Jan 5;372:m4853. Doi: 10.1136/bmj.m4853.
26. Herlitz A, Lederman Z, Miller J, Fleurbaey M, Venkatapuram S, Atuire C, et al. Just allocation of COVID-19 vaccines. *BMJ Glob Health.* 2021 Feb; 6(2):e004812. Doi: 10.1136/bmjgh-2020-004812.
27. Ghebreyesus TA. Vaccine Nationalism Harms Everyone and Protects No One. *Foreign Policy.* 2021 Feb 2[cited 2021 Feb 17]. Available from: https://foreignpolicy.com/2021/02/02/vaccine-nationalism-harms-everyone-and-protects-no-one/
28. Chatfield K, Schroeder D, Guantai A, Bhatt K, Bukusi E, Odhiambo JA, et al. Preventing ethics dumping: the challenges for Kenyan research ethics committees. *Res Ethics.* 2021 Jan 1; 17(1) 23–44.
29. Schroeder D. Benefit sharing: it's time for a definition. J Med Ethics. 2007; 33(4):205–9.
30. Council for International Organizations of Medical Sciences (CIOMS). *International ethical guidelines for health-related research involving humans.* 4th ed. Geneva: CIOMS; 2016 [cited 2021 Feb 17]. Available from: https://cioms.ch/shop/product/international-ethical-guidelinesfor-health-related-research-involving-humans/
31. Pratt B. Research for Health Justice: an ethical framework linking global health research to health equity. *BMJ Glob Health.* 2021 Feb 15;6: e002921.
32. Benatar SR, Singer PA. Responsibilities in international research: a new look revisited. *J Med Ethics.* 2010 Apr;36(4):194–7. Doi: 10.1136/jme.2009.032672.