**Tricky COVID19 vaccine trials in times of vaccine nationalism**

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The COVID19 pandemic has led to rapid and dramatic changes in almost every aspect of individual, community and social life, at 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 COVID19 in HICs, there was a rapid and massive deployment of funding for research and development (R&D) from the public, philanthropic, and private sector, with impressive results[[1]](#endnote-1),[[2]](#endnote-2). At the time of writing, the vaccines of Pfizer/BioNTec, Moderna and AstraZeneca have received a *conditional marketing authorization* from the European Medicine Agency (EMA)[[3]](#endnote-3). Those of Pfizer/BioNTec and Moderna also have an *emergency use authorization* (EUA) of the United States Food and Drug Administration (US FDA)[[4]](#endnote-4); and those of Pfizer/BioNTec and AstraZeneca have been listed for *emergency use* (EUL) by the World Health Organization (WHO)[[5]](#endnote-5),[[6]](#endnote-6). As to 8th February 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]](#endnote-7). Thanks to the impressive R&D effort, vaccination campaigns have been started in different parts of the globe. However, there is a striking unbalance in distribution figures. As of 13 February 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]](#endnote-8).

Conditional and emergency authorizations rely on less comprehensive clinical data than normally required. They were granted to COVID19 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 the global short- and long-term needs[[9]](#endnote-9), particularly if COVID19 becomes endemic[[10]](#endnote-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 “while 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 in presence of equipoise, and a state of clinical equipoise existed when COVID-19 vaccine trials began in 2020. But as vaccines approved (under some degree of conditionality) by stringent regulators now represent the “gold standard”, equipoise no longer exists with regard to preventing COVID-19 symptoms11. Equipoise remains for other outcomes, such as the infectivity of vaccinated subjects, the duration of protection, and long-term safety[[11]](#endnote-11), 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 individual trial participants, whose health and well-being would be 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 health care, 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, stigmatization, lack of social support, confidentiality concerns, physical pain, efficacy concerns and distrust[[12]](#endnote-12). 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 enroll, well beyond the researcher-participant relationship or the particular study protocols[[13]](#endnote-13). 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[[14]](#endnote-14).

The assumption that people (only or predominantly) enroll in COVID19 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)[[15]](#endnote-15). 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, either 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 beloved 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 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 gold standard. But not all of them would be eligible for vaccination outside the trial: global manufacturing capacity is severely insufficient to address the global needs, and countries that are rolling out vaccines adopt a stepwise approach, generally prioritizing the most vulnerable groups[[16]](#endnote-16). 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[[17]](#endnote-17). 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 prospective from the national level in HICs to the global level, we see a dramatic unbalance in the access to the vaccines8. Despite the creation of COVAX, a multilateral initiative that brings together more than 170 countries for coordinating the purchase, supply and allocation of COVID19 vaccines[[18]](#endnote-18), 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[[19]](#endnote-19),[[20]](#endnote-20). According to an [analysis](https://www.bmj.com/content/371/bmj.m4750) 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[[21]](#endnote-21),[[22]](#endnote-22). It is feared that most people in low-income countries could have to wait until 2024 before being vaccinated[[23]](#endnote-23). 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 minimizing 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[[24]](#endnote-24). 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[[25]](#endnote-25).

Unfortunately, vaccine nationalism is still the prevalent “model”. It is leaving the poorest countries and communities behind, in what the WHO General Director has called a moral failure and an (epidemiologically) strategic mistake[[26]](#endnote-26). 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 (solely) carrying out placebo-controlled studies in these countries, would be unethical. First, an ethical strategy cannot be built on an unethical premise, which is in this case the unequitable allocation of vaccines between countries. Second, this strategy could even be seen as “ethical 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[[27]](#endnote-27). Third, it would de *facto* reverse the principle of benefit sharing in global research[[28]](#endnote-28),[[29]](#endnote-29), 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, global health research[[30]](#endnote-30) should generate knowledge that improves the health and well-being of disadvantaged and marginalized individuals and communities28,[[31]](#endnote-31). Those who lack access to COVID 19 vaccination because of inequal allocation between countries should be seen as disadvantaged, and research involving them should be framed in 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.

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