

Placebo-controlled trials of Covid-19 vaccines – Are they still ethical?

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Abstract

A World Health Organization (WHO) Ad Hoc Expert Group on the Next Steps for Covid-19 Vaccine Evaluation recently recommended placebo-controlled trials (PCT) of Covid-19 vaccines. PCTs are ethically acceptable when there is no proven effective and safe treatment for a certain condition. However, there are already some vaccines that have been approved and which have high levels of efficacy and safety. Any new vaccine under development must be tested against the most effective vaccines available. PCTs go against the participants' best interests, by putting them in a position of disadvantage while taking part in a trial, compared with people who are not in the trial and who could get vaccinated. Particularly in high-income countries, many people are getting vaccinated. This means that, following a recent trend in clinical trials, PCTs would have to be conducted in low- and middle-income countries, where there a number of advantages for drug companies, but where fatality rates of Covid-19 are, in many cases, much higher. For this and other reasons having to do with equal rights, participants in control groups should be protected with the most effective vaccines available.

Key words: Covid-19, vaccines, placebo-controlled trials, low- and middle-income countries, exploitation

Do we still need placebo-controlled trials?

On January 14, the World Health Organization (WHO) Ad Hoc Expert Group on the Next Steps for Covid-19 Vaccine Evaluation—a group consisting of vaccine experts of several countries—published a paper in which they advocate for placebo-controlled trials (PCT) of Covid-19 vaccines (1). They argue that even if there are already some effective and safe vaccines

available, we are at a crucial stage in which we can develop and evaluate the additional vaccines that the world needs. The best way to collect high-quality information about these vaccines, they claim, is through randomised, double-blinded, PCTs. In these trials, there is a double-blinded follow-up of participants who are randomly assigned either a vaccine or a placebo designed to have no real effect. It is explained to participants in these clinical trials that they may receive either one of these, and they are asked to sign an informed consent document. Neither the researchers nor the participants know who is getting the real vaccine. The idea behind the placebo is to account for the “placebo effect,” that is, effects from vaccination that do not depend on vaccination itself (such as believing that one is receiving a vaccine or biases or expectations of the vaccine efficacy by researchers when assessing the vaccine). In the absence of a placebo group to compare with, it is usually claimed, there is no way of knowing whether the vaccine itself had any effect, or of getting information about the vaccine that would be hard to obtain otherwise, so researchers could get unreliable answers about safety and efficacy. With unreliable results, if unrelated events happen by chance after vaccination, these may be wrongly attributed to the vaccine, and this could generate skepticism and doubts among people who are already hesitant about the vaccine. Anti-vaccination groups may take advantage of this situation as well.

However, even though PCTs are widely accepted whenever there is no proven effective and safe treatment for a certain condition, there is controversy over PCTs when there is already an effective treatment for that condition. In this case, the new treatment must be tested against the best current available treatment. This applies also to PCTs of Covid-19 vaccines. Even when several Covid-19 vaccines have been approved for emergency use, they have already proved to have high levels of efficacy and safety (the Pfizer-BioNTech vaccine has an efficacy rate of 95%, Moderna vaccine of 94.5%, AstraZeneca's of 90%, Novavax's of 89.3%, and the Russian Sputnik V of 91% (2-6)). The clinical research community was expecting efficacy rates of 50 to 70%, and the US Food and Drug Administration (FDA) had said that it would consider granting emergency approval for vaccines that showed at least 50% efficacy (7). According to the WHO, there are 242 vaccine projects around the world, 66 of them in clinical trials on humans, and 19 have

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already reached phase 3 (8). Many of these projects may fail, but many others will succeed, as has already happened with the ten approved for emergency or limited use in various countries. Why should new vaccines be tested against placebos rather than some of the highly efficacious vaccines already available? Once there is a current available vaccine, that happens to have a high level of safety and efficacy, new candidate vaccines should be tested against the approved vaccines—and ongoing PCTs of Covid-19 vaccine candidates should be unblinded.

PCTs of new vaccines in conditions for which efficacious vaccines already exist contravene the bioethics principle of beneficence. PCTs go against the participants' best interests, by putting them in a position of disadvantage while taking part in a trial compared with people who are not in the trial. In many countries (especially in high-income countries) all these highly efficacious vaccines are beginning to be available to a considerable number of people. To enrol people in a clinical trial and give them placebos is to harm them, in the sense of making them worse off than they would have been had they not participated. If they had not participated in the trial, they would probably have sought and received one of the Covid-19 vaccines already available. Researchers have a duty not to harm participants in clinical trials, so if they fail to treat participants by giving them placebos this would be ethically objectionable. The harm participants in the control group are exposed to is not minor. The fatality rate of Covid-19 is considerable, and even in young adults it is higher than originally thought (9).

Placebo controlled trials in LMIC

It is not only going to be ethically objectionable, it is also going to be very hard for any pharmaceutical company to get participants in high-income countries, where people are starting to get rapidly vaccinated, and where people in Covid-19 vaccine trials are dropping out because they have been told that they might have to wait up to two years to get the vaccine (10). It would be easier for pharmaceutical companies to conduct an active-control trial (ACT) comparing the new vaccines to one of the vaccines already approved. So whoever insists on conducting a PCT for vaccine development should know that these trials would have to be conducted in low- and middle-income countries (LMIC), where the vaccines already used in high-income countries are not likely to be available for some years. According to some estimates, while high-income countries have reserved enough doses to immunise their own populations multiple times over, it could take until 2024 for many LMIC to get enough doses to immunise their people (11).

As a matter of fact, the number of patients recruited for clinical trials in LMIC, as compared with high-income countries, has grown significantly in the last few decades. An analysis of FDA approvals showed that 86% of new therapies were supported in part by data of trials conducted outside the US and Canada, mostly in LMIC (12). This is particularly true in the case of

Covid-19. Many LMIC are participating in phase 3 clinical trials of Covid-19 candidate vaccines: many of these countries are in Latin America, Sub-Saharan Africa, South-East Asia and Eastern Europe. Several are participating in the trials with the explicit purpose of securing a certain amount of doses from the pharmaceutical companies, once the vaccines have been approved. But there are other reasons for this tendency to recruit participants in developing countries, where treatments and vaccines are not easily available. For many people in these countries this may be their only chance to get vaccinated soon. Otherwise, they may have to wait several years until vaccines become available to the majority of the population. For pharmaceutical companies, the promptness with which they recruit participants for trials is also crucial: more than 80% of clinical trials fail to enrol on time, and this vastly increases their costs (13).

It is more cost-effective to conduct PCTs than ACTs in LMIC because the latter would imply providing vaccines to all the participants and, in some cases, improving the medical facilities of the host country. For instance, many countries in Africa or Latin America do not have the cold-chain infrastructure to handle some of the vaccines already available, such as the Pfizer/BioNTech vaccine, which needs to be transported and stored at (-70°C), prior to use. If an ACT were conducted in an LMIC, this infrastructure would have to be provided. By conducting PCTs there, drug companies not only do not have to provide the infrastructure that an ACT would imply, but they save money because the wages of healthcare personnel, researchers and trial coordinators tend to be lower than in developed countries. Another reason is that ACTs have to be considerably larger than PCTs, thereby costing more and taking longer.

There is another reason for conducting PCTs in LMIC: in many of these countries either there are no regulations regarding PCTs or the existing regulations tend to be lax at approving and supervising the research protocols. Some countries have intentionally weak regulatory frameworks in order to facilitate the direct foreign investment that comes with externally sponsored research. Research ethics committees in these countries tend to be less rigorous, and some of their members lack the required expertise (14). All this makes it easier to conduct trials in LMIC.

Conducting PCTs in LMIC might expose participants in the control groups to excessive risks. Taking into account that Covid-19 is potentially fatal, participants in the control group may be at a significant risk of dying. In fact, participants in control groups of Covid-19 vaccine trials conducted in LMIC have died (15, 16). Fatality rates tend to be higher in some LMIC (for example, in Latin America) than in most high-income countries. People in the former are hardest hit by Covid-19 because of the non-availability and poor access to basic health infrastructure, such as ventilators, ICUs, and hospital beds, among others. In general, in these countries there is a greater prevalence of diseases such as hypertension, diabetes and the

so-called diseases of poverty (AIDS, malaria and tuberculosis, which account for 18% of all diseases in low-income countries (17)). In a study on the differences in fatality rates across countries, Banik et al state that the poverty rate is among the most important factors determining the fatality rate due to Covid-19 (18). This is true about poverty in high-income countries as well as low-income countries, the difference being that poverty is more extensive in the latter.

If people in control groups in PCTs carried out in developing countries contracted Covid-19, access to emergency medical services would have to be provided by the drug company conducting the trial, because in many of these countries access to these services is not as prompt as in developed countries. In fact, participants in these countries should receive an equivalent standard of care and the same or similar treatment options as clinical trial participants in the sponsoring country. This position is supported by the rights to equal access to scientific advancements, to the protection of health, and to non-discrimination (13).

Some clinical research guidelines allow no more than minimal risks, and they exclude any risks of serious or irreversible harm (19, 20). The risk of getting Covid-19 is serious and may ultimately be irreversible, since it may result in the death of the participant in the control group. Why will the health and lives of thousands of phase 3 participants be put at risk by giving them a placebo—basically no treatment at all—when we know that Covid-19 is a life-threatening disease, and we already have vaccines to immunise them? It has been argued that PCTs may be ethically justifiable when the available vaccines are just moderately or inconsistently effective, and a new vaccine is expected to be more effective and safe. However, as already mentioned, some of the available Covid-19 vaccines have high levels of efficacy and safety. And even if they were less effective or safe, new vaccines may be developed comparing them to these already approved vaccines. Participants in a clinical trial should be protected with the most effective vaccines available. Also, it has been argued that a necessary condition for the ethical justification of PCTs is that participants are among the first people to benefit from the research (21). However, recent experiences in drug development for HIV/AIDS and other diseases show us that these trials have not benefited participants in LMIC—or if they have, it has been only long after the trial has been concluded (22). Making sure that participants in clinical trials are going to be among the first beneficiaries of vaccine development may help to avoid the feeling in participants and their communities that they have been used and exploited, particularly when vaccines tested upon a group of people become available to them long after the trial has been conducted or when vaccines are not affordable for the host government. This situation may foster distrust towards pharmaceutical companies and may make it harder for researchers to conduct future clinical trials in these populations.

There may be situations in which a PCT may be ethically justifiable. In 2014, a WHO expert panel argued that the use of placebos in vaccine trials was ethically justifiable in four situations (23):

- (i) when an existing vaccine is inaccessible in a country's public health system and may remain inaccessible in the future, so there is a need to develop an affordable vaccine locally;
- (ii) when there is a need to evaluate the local safety and efficacy of an existing vaccine;
- (iii) when a new vaccine needs to be tested because an existing vaccine is considered inappropriate for local use (for instance, due to epidemiologic or demographic factors);
- (iv) and when the local burden of disease must be determined, eg, when the vaccine's effect on the burden of morbidity and mortality due to Covid-19 is unknown or uncertain.

If the Pfizer/BioNTech vaccine were the only safe and efficacious vaccine available (which was so in the early days when it was the only authorised vaccine), given the logistical conditions it requires (-70°C), then (i) above and perhaps (iii) above and may apply and PCTs might be justified. Thus there are reasonable cases where a PCT may be ethically justified. However, this is currently not the case, as approved vaccines are beginning to be available in LMIC, though gradually; they do not seem to be inappropriate for local use; and the vaccines' effect on the burden of morbidity and mortality is not unknown.

Alternatives

The WHO Ad Hoc Expert Group seems to be worried that the vaccines already approved will not be enough to meet the world's needs. According to them, more vaccines must be developed and tested through PCTs. But the problem does not seem to be that there are not enough vaccines under development and that more need to be tested through PCT as if there were no effective vaccines already approved as mentioned before, today there are 242 vaccine projects around the world. Many of the successful vaccines that come out of these projects may not reach people in LMIC if the mechanisms of production and distribution of vaccines are not revised and modified. If we want to meet world needs, and especially those of LMIC, the WHO should consider the proposal of India and South Africa that have called on the World Trade Organization to temporarily waive intellectual property protections related to Covid-19 vaccines, at least until the world population has developed collective immunity. This temporary waiver of pharmaceutical patents, copyrights and industrial designs would enable some middle-income countries to access active pharmaceutical ingredients and benefit from technology transfer—as was done in the past for HIV treatments. This would also allow them to manufacture

vaccine at lower costs. Alternatively, the WHO should consider ways in which pharmaceutical companies could work with local partners to make their vaccines available to LMIC. The Covid-19 Vaccines Global Access (COVAX) should also be revised to ensure global equitable access to Covid-19 vaccines. COVAX is a global initiative, led by the Global Alliance for Vaccines and Immunization (GAVI), the Coalition for Epidemic Preparedness Innovations (CEPI), and the WHO, which aims at coordinating international resources to enable equitable access to Covid-19 diagnostics, treatments, and vaccines (24). If the distribution of vaccines continues in the current fashion, many LMIC could have to wait until 2024 to gain access to Covid-19 vaccines—and many people will unnecessarily fall seriously ill or even die in the meantime. We all agree that the world desperately needs more vaccines, so we should look not only for all the possible ways to develop and produce them, but also to distribute them fairly so that everybody is vaccinated promptly, regardless of where they live. The same is also true about clinical trials: people should be treated fairly, regardless of where they live.

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References

1. WHO Ad Hoc Expert Group on the Next Steps for Covid-19 Vaccine Evaluation. Placebo-controlled trials of Covid-19 vaccines—Why we still need them. *N Engl J Med*, 2021 Jan 14:e2. Doi: 10.1056/NEJMp2033538. Epub 2020 Dec 2.
2. Pfizer. Pfizer and BioNTech conclude phase 3 study of COVID-19 vaccine candidate, meeting all primary efficacy endpoints. 2020 Nov 18 [cited 2021 Feb 20]. Available from: <https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-conclude-phase-3-study-covid-19-vaccine>.
3. Moderna. Moderna's COVID-19 vaccine candidate meets its primary efficacy endpoint in the first interim analysis of the phase 3 COVE study. 2020 Nov 16 [cited 2021 Feb 20]. Available from: <https://investors.modernatx.com/news-releases/news-release-details/modernas-covid-19-vaccine-candidate-meets-its-primary-efficacy/>.
4. AstraZeneca. AZD1222 vaccine met primary efficacy endpoint in preventing COVID-19. 2020 Nov 23 [cited 2021 Feb 20]. Available from: <https://www.astrazeneca.com/media-centre/press-releases/2020/azd1222hr.html>.
5. Novavax. Novavax COVID-19 Vaccine Demonstrates 89.3% Efficacy in UK Phase 3 Trial. 2021 Jan 28 [cited 2021 Feb 20]. Available from: <https://ir.novavax.com/news-releases/news-release-details/novavax-covid-19-vaccine-demonstrates-893-efficacy-uk-phase-3>.
6. Logunov DY, Dolzhikova IV, Shcheblyakov DV, Tukhvatulin AI, Zubkova OV, Dzharullaeva AS, et al. Safety and efficacy of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine: an interim analysis of a randomised controlled phase 3 trial in Russia. *Lancet*, 2021 Feb 20; 397(10275): 671-81 Doi:[https://doi.org/10.1016/S0140-6736\(21\)00234-8](https://doi.org/10.1016/S0140-6736(21)00234-8).
7. Zimmer C. 2 companies say their vaccines are 95% effective. What does that mean? *New York Times*, 2020 Nov 20 [cited 2021 Feb 20]. Available from: <https://www.nytimes.com/2020/11/20/health/covid-vaccine-95-effective.html>.
8. World Health Organization (WHO). Draft landscape and tracker of COVID-19 candidate vaccine. 2021 Feb 12 [cited 2021 Feb 20]. Available from: <https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines>.
9. Faust JS, Krumholz HM, Du C, Mayes KD, Lin Z, Gilman C, et al. All-cause excess mortality and COVID-19–related mortality among US adults aged 25–44 years, March–July 2020. *JAMA*. 2021 Feb 23;325(8):785-7. Doi: 10.1001/jama.2020.24243. doi:10.1001/jama.2020.24243.
10. Zimmer C, Weiland N. Many trial volunteers got placebo vaccines. Do they now deserve the real ones? *New York Times*, 2020 Dec 2 [cited 2021 Feb 20]. Available from: <https://www.nytimes.com/2020/12/02/health/covid-vaccine-placebo-group.html>.
11. Duke Global Health Innovation Center. Launch and Scale Speedometer. Duke University. 2020 Feb 8 [cited 2021 Feb 20]. Available from: <https://launchandscalefaster.org/covid-19>.
12. Robbins R. Most experimental drugs are tested offshore—raising concerns about data. *Scientific American*. 2017 Sep 10 [cited 2021 Feb 20]. Available from: <https://www.scientificamerican.com/article/most-experimental-drugs-are-tested-offshore-raising-concerns-about-data/>.
13. Pavone IR. Legal responses to placebo-controlled trials in developing countries. *Global Bioethics*, 2016; 27(2-4):76-90, Doi: 10.1080/11287462.2016.1192979.
14. Nwabueze RN. *Legal and Ethical Regulation of Biomedical Research in Developing Countries*. London: Routledge; 2016.
15. McCoy T, Traiano H, Johnson C. Volunteer in Oxford coronavirus vaccine trial dies, reportedly did not receive experimental vaccine. *Washington Post*. 2020 Oct 21 [cited 2021 Feb 20]. https://www.washingtonpost.com/world/the-americas/coronavirus-oxford-astrazeneca-vaccine-trial-death/2020/10/21/3f5bedac-13c0-11eb-ad6f-36c93e6e94fb_story.html.
16. Reuters. Sinopharm Peru vaccine trial volunteer dies of COVID-19 pneumonia, received placebo. *Alarabiya News*. 2021 Jan 29 [cited 2021 Feb 20]. Available from: <https://english.alarabiya.net/coronavirus/2021/01/27/Coronavirus-Sinopharm-Peru-vaccine-trial-volunteer-dies-of-COVID-19-pneumonia-received-placebo>.
17. Stevens P. *Diseases of Poverty and the 10/90 Gap*. International Policy Network. 2004 Nov [cited 2021 Feb 20] Available from: <https://www.who.int/intellectualproperty/submissions/InternationalPolicyNetwork.pdf>.
18. Banik A, Nag T, Chowdhury SR. Why do COVID-19 fatality rates differ across countries? An explorative cross-country study based on select indicators first. *Global Business Review*. 2020; 21(3):607-625. <https://doi.org/10.1177/0972150920929897>.
19. World Medical Association (WMA). WMA Declaration of Helsinki—ethical principles for medical research involving human subjects. Ferney-Voltaire: WMA; 2013.
20. Council for International Organizations of Medical Sciences (CIOMS). International ethical guidelines for biomedical research involving human subjects. Geneva: CIOMS; 2002.
21. Hawkins J. Exploitation and placebo controls. In: Ezekiel A, Hawkins J, eds. *Exploitation and Developing Countries*. Princeton: Princeton University Press; 2008.
22. Cleaton-Jones PE. An ethical dilemma. Availability of antiretroviral therapy after clinical trials with HIV infected patients are ended. *BMJ*. 1997 Mar 22; 314(7084):887-8.
23. Rid A, Saxena A, Baqui Ah, Bhan A, Bines J, Bouesseau MC, et al. Placebo use in vaccine trials: Recommendations of a WHO expert panel. *Vaccine*. 2014 Aug 20; 32(37):4708-12. <http://dx.doi.org/10.1016/j.vaccine.2014.04.022>.
24. Berkley S. COVAX explained. Global Alliance for Vaccines and Immunization (GAVI). 2020 Sep 3 [cited 2021 Feb 20]. Available from: <https://www.gavi.org/vaccineswork/covax-explained>.