

“No” to placebo-controlled trials of Covid-19 vaccines

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Abstract

Recently the WHO Ad Hoc Expert Group proposed that it is ethical to continue placebo-controlled Covid-19 vaccine trials in countries where vaccines are not available even if this vaccine is marketed and being used elsewhere. The reason for this proposal is the usual scientific argument claiming that these trials are the most efficient method to obtain reliable results, and individuals in these countries will continue to get the local standard of care, meaning no vaccination, and thus participants are not being left worse off. We refute this argument on two counts. First the global equity and justice issue, that the scarcity of vaccines in most countries is created by the rich nations that have hoarded vaccines. Second, the science versus research ethics issue, that there are valid scientific methods like non-inferiority trials which can give reliable results, and that applying a standard of care imposed by rich nations is both unethical and possibly exploitative. Thus, we feel that the WHO Ad Hoc Expert Group is wrong in proposing to continue placebo-controlled Covid-19 vaccine trials.

Key words: Placebo, vaccine trials, Covid-19, standard of care

The first Covid-19 vaccine was administered in early December 2020, and on January 18, 2021, the World Health Organisation (WHO) chief, Tedros Adhanom Ghebreyesus, said “More than 39 million doses of vaccine have now been administered in at least 49 higher-income countries. Just 25 doses have been given in one lowest-income country. Not 25 million; not 25,000; just 25.” He “blasted” the behaviour of rich countries as this would make the Covid-19 pandemic last longer, and the economic cost of the required restrictions would only increase

human and economic suffering (1).

We presume that to make the best of a very bad global situation, the WHO Ad Hoc Expert Group proposed that “While vaccine supplies are limited ...it is ethically appropriate to continue blinded follow-up of placebo recipients in existing trials and to randomly assign new participants to vaccine or placebo... even if effective vaccines were already being marketed elsewhere.” They are proposing this because they think or believe that: “there is a risk of missing or exaggerating less common but clinically important events” and “...people who enroll in clinical trials for altruistic reasons would **probably** [emphasis added] understand the value of gathering data that will further elucidate the safety and efficacy of these vaccines and their appropriate use”(2).

Their arguments can be debated on two counts: the global equity and justice issue, and the science vs research ethics issue; on both these counts, we feel that the WHO Ad Hoc Expert Group is wrong.

On the global justice and equity front, “vaccine nationalism” and economic bullying are the main reasons for the limited vaccine supplies in many developing countries. Oxfam, in September 2020, had already warned that rich countries representing 13% of the global population had bought 51% of yet-to-be manufactured Covid vaccine candidates even before the vaccines received Emergency Use Authorisation (3). Now they have bought more vaccines than they can administer (4). People’s Vaccine Alliance reported that “70 poor countries will only be able to vaccinate one in 10 people against COVID-19 next year after rich countries bought up most prophylactics” (5). This situation of limited supplies to developing countries was created by rich countries. The WHO Expert Ad Hoc Group, instead of providing recommendations on how to rectify this wrong, is giving a free pass to exploit the developing countries once again by approving usage of placebo in the control group.

Delivery of vaccine supplies to the poorer countries has begun from February 2021 via COVAX (led by Gavi, the Vaccine Alliance, the Coalition for Epidemic Preparedness Innovations (CEPI) and WHO); but that may not be good news for research participants, as the WHO Ad Hoc Expert Group has said that “trial sponsors are not ethically obligated to unblind treatment assignments for participants who desire to obtain a different

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investigational vaccine” This would absolve the sponsor of any ethical obligation to unblind the participants if an investigational vaccine becomes available.

This leads us to the second argument of science vs research ethics. The WHO Ad Hoc Expert Group states that “reliable information will still be needed on longer-term safety and duration of protection...these numbers should suffice for detecting relatively common adverse events, there is a risk of missing or exaggerating less common but clinically important events,” thereby justifying the need to continue carrying out placebo-controlled trials. Long-term safety concerns may be addressed by following the individuals who have been vaccinated, a kind of Phase-4 study. The authors have also pushed forward the usual “scientific” arguments that “Randomized, placebo-controlled trials are the bedrock of modern clinical decision making and remain the most efficient way to obtain reliable results”(2), therefore justifying the need to continue doing placebo controlled trials. Another method would be noninferiority trials, comparing established vaccines with the trial vaccine so that all participants get vaccinated, although some may get a vaccine that might be of lower efficacy, thereby leaving no one completely unprotected. The authors in their brief do not recommend this approach because of “considerable cost to efficiency”. If the research can satisfactorily be conducted in more than one way, then why not select the approach that minimises morbidity and loss of life?

The research ethics question that arises here is about the degree of harm to and possible exploitation of participants in the control group, and the standard of care to be applied. The question “Should we continue or permit placebo-controlled vaccine trials for Covid-19 disease when available vaccines have been found to be safe, efficacious and in use in many countries?” seems very similar to “Should West African human immunodeficiency virus (HIV)-positive pregnant women receive placebo in HIV placebo-controlled trials when Zidovudine was found safe and efficacious for the prevention of vertical transmission of HIV infection elsewhere in the world?” or “Should African American men of Tuskegee, Alabama remain untreated even when penicillin was found safe and efficacious for the treatment of syphilis?” These historical contexts (and possibly, the Covid-19 vaccine trials with placebo) involve vulnerable populations living in appalling conditions with potentially life-threatening diseases, trying to get access to interventions which researchers and/or sponsors are in a position to provide, but are deliberately deciding not to do so.

On the issue of standard of care, the argument in favour of such placebo-controlled trials is that the participants are treated at least according to the standard of care in their countries, which may consist of unproven regimens or no treatment at all. Very similar to the current recommendations of the WHO Ad Hoc Expert Group, the WHO in 1994 had justified the use of placebo in the control arm for HIV-infected

pregnant women because there was no effective alternative treatment available in those countries, and researchers were thus not leaving the participants worse off (6). Unlike some trials for reduction of maternal transmission of HIV to infants, done in Thailand (7) and Uganda (8), that used placebos as control, there are two historical examples, also in Thailand (9) and Uganda (10), that did not include placebos, as researchers considered having a placebo group to be unethical. We unequivocally agree with Lurie and Wolfe that “[t]he ethical standards applied [in the developing country] should be no less exacting than they would be in the case of research carried out in [the sponsoring] country”(11). Therefore, we completely disagree with the arguments of the WHO Ad Hoc Expert Group, especially in the case of Covid-19 vaccine, as this “standard of care” was thrust upon developing countries by global injustice, and to continue to use this as the standard of care for research would clearly be unethical and further the exploitation.

While proposing these arguments in favour of Covid-19 vaccine placebo-controlled trials, the WHO Ad Hoc Expert Group ignores the very fundamental guiding principles of research involving human subjects, which were made explicitly clear in the earlier Declaration of Helsinki 2000, which stated that “In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society”(12). This document in its latest version of 2013, states “While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects”(13). In addition, the Council of International Organisations of Medical Sciences (CIOMS), has noted that the use of placebo is only acceptable “when withholding an established, effective intervention would expose subjects to, at most, temporary discomfort or delay in relief of symptoms”(14)

Even if long-term safety is considered as a primary social and ethical obligation to overcome the current global emergency, the risks of forgoing vaccination for a life-threatening disease are so high that withholding an intervention would be completely unethical. If accepted, this may also set a precedent for future research, making it difficult to protect the welfare of research participants, especially in countries with limited or no access to a known effective intervention.

We also disagree with the argument that informed consent and independent review are good enough mechanisms to protect research participants from unjustified or excessive risks. In many developing countries, a doctor’s profession is considered the sacred profession of saving lives; thus doctors are seen as “next to God” and as always doing what is best for patients, thereby making participants extremely susceptible to the therapeutic misconception. Physicians are also considered authority figures wielding much power, and saying “no” to them would be very difficult. The added fear of the morbidity and mortality associated with Covid-19 disease, together with

limited or no access to a known effective vaccine in the developing countries, would make truly informed consent unlikely in such a vulnerable situation. Independent review in resource-poor countries is also highly inconsistent in its responsiveness to patients, especially in matters related to placebo and standard of care. This leaves the review committee, which may not be that well-versed in the subject, to make decisions that may be very variable.

Even though the historic Tuskegee study, and the placebo-controlled trials for prevention of maternal transmission of HIV held in developing countries were hotly debated with ethical counterarguments, they, unfortunately, opened the door to the use of placebos even when effective interventions were available. With the increasing burden of Covid-19 and severe resource limitations in developing countries, such studies are likely to increase, especially after the recommendation of the WHO Ad Hoc Expert Group; however, they need to be debated and possibly stopped.

We should strive to have a single research ethics standard where the exploitation of research participants by global economics does not occur, taking advantage of the standard of care that exists in many developing countries, compounded by inefficient and sometimes corrupt national governments.

As Hans Jonas stated in 1968 (15), "Let us not forget that progress is an optional goal, not an unconditional commitment... Let us also remember that a slower progress in the conquest of disease would not threaten society, ...but that society would indeed be threatened by the erosion of those moral values whose loss, possibly caused by too ruthless a pursuit of scientific progress, would make its most dazzling triumphs not worth having." The WHO chief has made a similar statement in 2021, by calling the production of vaccine "in less than a year since the start of the pandemic a 'stunning scientific achievement'; but adding that "the world is on the brink of a catastrophic moral failure — and the price of this failure will be paid with lives and livelihoods in the world's poorest countries." He cautioned that the hopes of ending the pandemic quickly are unlikely to bear fruit if rich nations continue with the "me-first approach" *ignoring* the needs of the world's poorest and most vulnerable(1).

Declaration

The views expressed in this article are those of the authors and do not necessarily represent those of the affiliated institution or the WHO Ethics & COVID-19 Expert Group.

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