Standard of care imposed by rich countries and “Placebo-Controlled Trials of Covid-19 Vaccines”-Why we **do not** need them’

Aasim Ahmad\* and Murtaza F Dhrolia†

\*Professor Aasim Ahmad FCPS MHSc (Bioethics)

Dean & Chief Nephrologist, member WHO Ethics & COVID-19 Expert Group

The Kidney Centre Postgraduate Training Institute

197/9, Rafiqui Shaheed road, Karachi 75530, Pakistan

Tel: +9221 35661000 (10lines) Mob: +923002388191

ahmadaasim@yahoo.com

†Dr. Murtaza F. Dhrolia FCPS, PGD Bioethics (CBEC)

The Kidney Centre Postgraduate Training Institute

197/9, Rafiqui Shaheed road, Karachi 75530, Pakistan

Tel: +9221 35661000 (10lines) Mob: +923002388191

[mfdhrolia@hotmail.com](mailto:mfdhrolia@hotmail.com)

**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.**

*“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,"* WHO Chief Tedros Adhanom Ghebreyesus “blasted” the behavior of rich countries' as this would make the COVID 19 pandemic last longer and the economic cost of required restrictions would only increase human and economic suffering.1

We presume that to make the most of a very bad global situation, the WHO Ad Hoc expert group proposed that in countries *“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 marketedelsewhere*”. They also *“believe that trial sponsors are not ethically obligated to un-blind treatment assignments for participants who desire to obtain a different investigational vaccine”*. They are proposing this because they think or believe that “*there is a risk of missing or exaggerating less common but clinically important event”* 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 two counts, the global equity & justice issue and the science vs research ethics issue and 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 global population had bought 51% of yet to be manufactured COVID vaccine candidates even before the vaccines received ‘Emergency Use Authorization’ 3 Now they have bought more vaccines than they can administer . People 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 and the WHO expert ad hoc group instead of giving recommendations on how to rectify this ‘wrong’, is giving a free pass to exploit them once again by using placebo in the control group.

Vaccines supplies have started to be delivered from early February to poorer countries via COVAX (co-led by Gavi, the Vaccine Alliance, the Coalition for Epidemic Preparedness Innovations (CEPI) and the WHO) but that may not be good news for research participants as the ‘WHO Ad Hoc expert group’ has absolved the sponsor of any ethical obligations to un-blind the participant if investigational vaccine becomes available.

The WHO ad hoc expert group have pushed forward the usual science 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 the need to continue doing placebo control trials. However, in the paper they themselves have accepted that “*Randomized, non-inferiority trials can provide clinically relevant data in some cases”* but they do not recommend this approach because of *“considerable cost to efficiency”*. If the research can be satisfactorily be conducted in more than one way, why not to select the approach that minimizes morbidity and the loss of life? An example was the HIV trail for pregnant women in Thailand 6 and Uganda 7 that didn’t include placebos as researchers considered having a placebo group would be unethical. Similarly study design for COVID 19 vaccine trails can easily be made to compare established vaccine with the newer vaccine so that all participant at least gets some vaccine even though it might be of lower efficacy than the established vaccine leaving no one unprotected.. Creative study designs such as cluster randomization that can produce useful scientific evidence while minimizing the risk to patients with this serious disease should also be explored. Long term safety concerns may be addressed by following the individuals who have been vaccinated, a kind of Phase-4 study.

On the degree of harm and exploitation the question ‘should we still continue or permit Placebo-Vaccine trails for COVID-19 disease, when effective vaccines were found safe, efficacious and publicized globally and marketed and used in many countries?’ seems very similar to ‘Should West African human immunodeficiency virus (HIV)-positive pregnant women receive placebo in HIV placebo-controlled trails 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?’

Very similar to the recommendations of 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 thus were not leaving the participants worse off 8.We completely disagree with this WHO Ad hoc Expert group’s argument in the case of COVID 19 vaccine placebo-controlled trails, that the subjects in placebo arm will be treated at least according to the standard of care in these countries, meaning no vaccine especially when this ‘standard’ was thrusted upon by global injustice and then to use this, as standard of care for research is clearly unethical and furthers the exploitation.

While proposing these arguments in favor of COVID 19 vaccine placebo controlled trails, WHO Ad hoc Experts group ignores the very fundamental guiding principles of research involving human subjects which was made explicitly clear in the earlier Declaration of Helsinki 2000, that stated “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” 9. This in the latest version 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” 10, and Council of international organizations of medical sciences (CIOMS), also noted that use of placebo is acceptable “when withholding an established, effective intervention would expose subjects to, at most, temporary discomfort or delay in relief of symptoms” 11 We unequivocally agree with Lurie & 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” 12.

Even if obtaining a rapid, unambiguous answer regarding long term safety be considered here as primary social and ethical obligation to overcome the global need, the risk of forgoing vaccination for the life-threatening condition as COVID-19 are so high that withholding intervention would be unethical. If accepted, this may also set a precedence for future research, making it difficult to protect the welfare of the research participants especially in countries with limited or no access to a known effective intervention.

We disagree with the argument that informed consent and independent review are good enough mechanisms that exist to protect research participant from unjustified or excessive risks. In many developing countries, doctors are seen as ‘next to God’ and there is also high probability of asymmetry in knowledge and authority between researchers and their participants. The fear of morbidity and mortality associated with COVID -19 disease, together with global and national promotion of COVID 19 vaccination in presence of limited or no access to a known effective vaccine in developing countries, makes participants extremely vulnerable to therapeutic misconception. , Informed consent in such vulnerable situation, by itself cannot be considered as sufficient protection for study participants and can only works as license to participants’ exploitation. Independent review is also highly variable in its responsiveness to patient’s, especially in matters related to placebos and standard of care, because there is no specific guidance in international documents.

Unfortunately, historical Tuskegee study and placebo controlled trials for prevention of maternal transmission of HIV held in developing countries opened the door for the use of placebos even when effective interventions were available. With increasing burden of COVID 19 and severe resources limitations in developing countries, these kind of studies are likely to increase especially after the recommendation WHO ad hoc expert group.

We should strive to have a single research ethics standard where the exploitation of research participants does not occur because of the standard of care that is thrust upon them by global economics and inefficient and sometime corrupt national governments.

As Hans Jonas in 1969 13 stated *“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 repeated a similar statement in 2021 by saying “*in less than a year since the start of the pandemic a "stunning scientific achievement"* in the form of vaccine was achieved but “*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”*. Hecautioned that the hopes of ending the pandemic quickly isunlikelyif rich nations continue with the *"me-first approach" ignoring* the needs of the world's poorest and most vulnerable*14.*

**References:**

1. Coronavirus: WHO chief blasts rich countries for hoarding, Jan-2021, vaccines https://www.dw.com/en/coronavirus-who-chief-blasts-rich-countries-for-hoarding-vaccines/a-56271314)
2. 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. New England Journal of Medicine. 2021 Jan 14;384(2):e2.
3. Small group of rich nations have bought up more than half the future supply of leading COVID-19 vaccine contenders, SEP-2020, https://www.oxfam.org/en/press-releases/small-group-rich-nations-have-bought-more-half-future-supply-leading-covid-19.
4. Cohen R, COVID vaccines: rich countries have bought more than they need – here’s how they could be redistributed. FEB-2021, https://theconversation.com/covid-vaccines-rich-countries-have-bought-more-than-they-need-heres-how-they-could-be-redistributed-153732.
5. Rich countries buy up majority of COVID-19 vaccine doses, People’s Vaccine Alliance says, https://www.europeanpharmaceuticalreview.com/news/136170/rich-countries-buy-up-majority-of-covid-19-vaccine-doses-peoples-vaccine-alliance-says/)
6. Khongphatthanayothin M, Sirivichayakul S, Rongkavilit C, Poolcharoen W, Kunanusont C, Bien DD, Phanuphak P. Thai Red Cross zidovudine donation program to prevent vertical transmission of HIV: the effect of the modified ACTG 076 regimen. Aids. 2000 Dec 22;14(18):2921-7.
7. Guay LA, Musoke P, Fleming T, Bagenda D, Allen M, Nakabiito C, Sherman J, Bakaki P, Ducar C, Deseyve M, Emel L. Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: HIVNET 012 randomised trial. The Lancet. 1999 Sep 4;354(9181):795-802.
8. World Health Organization. Recommendations from the Meeting on Mother-to-Infant Transmission of HIV by Use of Antiretrovirals. Geneva: World Health Organization, June 23–25, 1994. Web. 7 Apr. 2012. <http://www.columbia. edu>.
9. Declaration of Helsinki IV, 52nd WMA Assembly, Edinburgh. Oct. 2000.
10. Declaration of Helsinki 64th WMA General Assembly, Fortaleza, Brazil, October 2013
11. Council for International Organizations of Medical Sciences, World Health Organization. International ethical guidelines for biomedical research involving human subjects. World Medical Association; 2002. Guideline 11.
12. Lurie P, Wolfe SM. Unethical trials of interventions to reduce perinatal transmission of the human immunodeficiency virus in developing countries. N Engl J Med. 1997 Sep 8;337(12):853-6. doi: 10.1056/NEJM199709183371212. PMID: 9295246.
13. Jonas H. Philosophical reflections on experimenting with human subjects. In Biomedical ethics and the law 1969 (pp. 219-247). Springer, Boston, MA.
14. Coronavirus: WHO chief blasts rich countries for hoarding vaccines, 19-01-2021, https://www.dw.com/en/coronavirus-who-chief-blasts-rich-countries-for-hoarding-vaccines/a-56271314