Ethical limits to placebo use and access to Covid-19 vaccines as a human right

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Abstract

The world is currently facing another severe pandemic, Covid-19, just four decades after the start of AIDS, and the still increasing incidence of HIV infection continues to be one of the greatest global health challenges. The way the latter was confronted is of fundamental importance for a serious discussion on global health, ethics and human rights, and this experience could and can still be applied to Covid-19.

The Covid-19 pandemic has specific characteristics and these will be discussed, in relation to vaccine research and especially to the global right to equal access to products proven to be safe and effective.

The article focusses primarily on issues related to Covid-19 vaccines, especially the appropriate use and limits on placebo, the right to post-trial access to placebo arm participants, and the use of an active control for subsequent Phase-3 trials after the approval of other safe and efficacious vaccines. Most importantly, it will emphasise that access to Covid-19 vaccines is a human right, which presupposes the establishment of appropriate ethical standards to ensure universal, equal, and affordable access to healthcare and to vaccines for all, and the imperative need for suspension of patents for products developed for Covid-19. It will consider the role of social determinants that contribute to the severity of Covid-19 and that must be addressed to effectively curb the current syndemic.

Key words: *Covid-19 vaccines, access, human rights, equity, double standards*

Introduction

The unequal access to healthcare of most vulnerable communities/populations, not only between countries but also within countries, is having a significant and unacceptable impact in increasing the morbidity and mortality of Covid-19. This is not a unique characteristic of the current pandemic, as it has been noted earlier in connection with Acquired Immune Deficiency Syndrome (AIDS).

The prevailing inequality covers access to diagnosis, to initial care, to intensive care (ICU) beds and to developed vaccines.

To counteract this situation there is an urgent need to boost production of the vaccines that have been authorised for use and, most importantly, to have them deployed in a timely and just manner throughout the globe. As some of the available vaccines have been authorised only for emergency use (six as of February 21), there is also the need to closely follow up the vaccinees, through pharmacovigilance or Phase-4 trials.

Both the unequal access and the clinical trials raise several ethical issues, similar to those associated with the AIDS epidemic — the issues of ethics of human trials, access to affordable vaccine, drugs and related products, intellectual property (IP) issues, such as non-patenting of developed products for Covid-19 vs compulsory licensing, and generic production, among others.

This article focusses primarily on issues related to Covid-19 vaccines, especially on the use and limits of placebo, and the right to post-trial access for control group participants, and more importantly, the right of access to affordable, safe and effective vaccines to all who need them; and defends the suspension of patents for products developed for Covid-19.

Placebo use

Currently there are 20 vaccines in large-scale Phase-3 efficacy tests (1) and these trials used placebo or other agents for the control group.

Several ethical dilemmas arise regarding placebo use and post-trial access in:

1. *Ongoing first-generation vaccine trials.* A vaccine receives an emergency use authorisation or designation and, as of this writing, there are nine of them in this condition. This should mean that placebo arm participants are entitled to receive the authorised vaccine.

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2. *Subsequent or second-generation vaccine trials.* Other vaccines, besides those already authorised for emergency use or full use, are scheduled for testing in Phase-3 trials using a placebo as a control arm. However, directives for placebo use in three current research ethics guidelines (two international and one regional), state upfront the condition :

   - *...that research participants in the control group of a trial of a diagnostic, therapeutic, or preventive intervention receive an established effective intervention.* (Council for International Organizations of Medical Sciences (CIOMS) Guidelines 2016, Guideline 5.(2)

   - *The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances: Where no proven intervention exists, the use of placebo, or no intervention, is acceptable.* (Declaration of Helsinki (DoH), 2013, Article 33). (3)

   - *when using placebo, such use shall be fully justified as to its non-maleficence and methodology requirements, where the benefits, risks, difficulties and effectiveness of a new therapeutic method shall be tested, comparing it to the best current prophylactic, diagnostic and therapeutic methods. Placebo or any other treatment may be used when there are no proven methods of prophylaxis, diagnosis or treatment.* (Brazilian National Research Ethics Guidelines, 2012) (4):

However the first two (CIOMS, 2016 and DoH, 2013) allow for departures from this requirement, although with added conditions such as:

> … *delaying or withholding the established effective intervention will result in no more than a minor increase above minimal risk to the participant and risks are minimized, including through the use of effective mitigation procedures* (CIOMS , 2016)(2)

and in the DoH when:

> …*the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention. Extreme care must be taken to avoid abuse of this option.* (DoH, 2013)(3)

On the other hand, the Brazilian National Research Ethics Guidelines do not offer any exception for allowing placebo use when an active comparator exists (4).

For a considerable time now, especially after the 2000 version of the DoH was issued, post-trial access, placebo use, and its limits have brought fierce ethical and even scientific discordances involving serious and experienced researchers/ bioethicists. There are some who propose the continuation of the trial and the maintenance of placebo, even when the tested vaccine has been authorised for emergency deployment; their rationale being that such studies could be ethically acceptable in countries with limited or no access to a known effective vaccine. This is proposed in a publication of the WHO Ad Hoc Expert Group, in the *New England Journal of Medicine* of January 14, 2021, (5) and their position is related both to post-trial access for control arm participants and to the use of placebo in subsequent trials. They say:

> *What about vaccine candidates that do not become available for phase 3 study until after effective vaccines have already been deployed in some locations? […] 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.* (edited, emphasis added).

This affirmation implies a double standard, because researchers would be taking unfair advantage of the unequal distribution of vaccines to perform a trial which would not be ethically permissible in countries with access to emergency or final use vaccines, as it follows from the unsaid pragmatic implications of the statement above.

There is a sense of *déjà vu* about these arguments and those used regarding HIV trials which were considered a clear case of double-standards, a position defended in many publications (6,7). Macklin revisited the double-standards issue in a comprehensive chapter under the heading "Ethical Standards: Universal or Relative" (8), where she discussed conflicting positions on this theme. In relation to universal views, one view expressed there was:

> *If it is unethical to carry out a particular research project in a developed country, it is unethical to do that same research in a developing country. This requirement for uniformity seeks to protect vulnerable populations from exploitation, implying that decision makers in those countries might agree to research that would be rejected in industrialized countries because of high risk to subjects or other ethical concerns. (8)*

She supports this position citing an opinion (8) from the European Group on Ethics in Science and New Technologies (EGE) no17 (February 4, 2003):

> …*research activities involving human subjects cannot exclusively be assimilated to an economic activity subject to market rules. On the contrary, in the context of solidarity, regarding health as a public good, rather than a commodity, it needs to be regulated according to fundamental principles. The general approach chosen within this Opinion is that*

> *fundamental ethical rules applied to clinical trials in dustrialized countries are to be applicable everywhere. Even if some difficulties may arise in their implementation, a weakening of the standards would be in contradiction to the fundamental principles of human rights and dignity and their universal guarantee and protection.*

These positions reinforce the need to defend a universal ethical standard in research involving humans, where all participants, independent of origin, gender, race or economic situation must be equally treated. Macklin mentions another consideration used by some to justify double-standards which is related to:

> *... economic disparities between industrialized countries and resource-poor countries. This disparity has been used to justify some research in developing countries that could not be conducted in industrialized countries. This latter justification does not appeal to cultural factors but rather, to different needs in resource-poor and wealthier countries.*

Many reject the idea that different and unequal economic conditions among countries "can justify research in a poor country that could not be ethically conducted in a rich country". This is unequivocally stated in a publication criticising the pressures to lower ethical standards set in the 2000 version of the Declaration of Helsinki:

> *It is clear that the pressures to lower the ethical standards set by the DoH [Declaration of Helsinki] are primarily economic—it costs less to run a trial where you do not have to provide for medical care….So let us push to keep the highest ethical standards applied everywhere…* (7)

It is worth emphasising that double standard situations and the risk of exploitation occur not only in LMIC, but also in high income countries amongst the unserved and underserved, by the prevailing health systems. As Dal-Ré et al put it clearly: "there are millions of individuals living in North America and the European Union who lack access to healthcare services", both citizens and migrants (9).

This situation of social vulnerability could act as a facilitator to possibilities of exploitation as potential participants may see a trial, even with quite different levels of ethical protection, as a unique opportunity to access needed interventions. The current situation with Covid-19 vaccines is, in this aspect, similar to what occurred just after the development of effective treatment for HIV. This was clearly shown in a South African HIV activist's 1997 publication where he stated that "Although there is a strong feeling that it is unethical to allow people to enter trials when the treatment will cease after a specified time, many people feel that access to limited and potentially beneficial treatment is better than no treatment at all." (10) Although the activist above refers to post-trial access, the general rationale of this position is criticised in the literature (11) with the affirmation that "exploitation is no better than neglect", and this is elaborated below.

The same barriers to access to efficacious anti-retrovirals for persons living with HIV have arisen with Covid-19 in the unequal distribution and global access to vaccines. In the latter case, researchers by conducting placebo-controlled trials, though with consent, even after safe and effective vaccines have been developed, are taking advantage of structural unfairness or background injustices, including structural factors, such as lack of education, insufficient access to healthcare, political and economic instabilities, or distributive inequalities (11,12). Malmqvist has argued "that mutually beneficial and voluntary exploitation can be worse than neglect when — as is typically true of exploitative international research — it takes advantage of unjust background conditions" and that researchers may be "complicit in the injustice" (11). An alternative definition of such a possibly exploitative situation is that of Holzer (12), who calls it "systemic exploitation", if it shows that the probability of an exploitative event "increases significantly under injustice, compared to a (negligible) exploitation rate under just circumstances." In the 2010 UNAIDS/WHO guidance document on ethical considerations in biomedical prevention trials (13: p 32), the commentary of Guideline Point 8 ("Vulnerable Populations") stated that:

> *…in some potential research populations (countries or communities), conditions affecting potential vulnerability or exploitation may be so severe that the risk outweighs the benefit of conducting the study in that population. In such populations, biomedical prevention trials should not be conducted.*

Post-trial access

In Covid-19, the risks of exploitation and inequalities must be counteracted with the necessary rapid expansion of production and access to affordable vaccines, and with global and egalitarian distribution mechanisms, such as proposed under the COVAX Initiative, which will be discussed later (14).

It is worth quoting again the 2010 UNAIDS/WHO Guidance Point 14, on Care and treatment, in its commentaries, as it can also be applied to Covid-19 vaccine trial participants:

> *The obligation on the part of sponsors and investigators to ensure access to HIV care and treatment, including antiretroviral treatment for participants who become infected derives from some or all of three ethical principles. The principle of beneficence requires that the welfare of participants be actively promoted. The principle of justice as reciprocity calls for providing something in return to participants who have volunteered their time, been inconvenienced or experienced discomfort by enrolling in the trial. The principle of justice, meaning treating like cases alike, requires that trial participants in high-income and low- and middle-income countries be treated equally regarding access to treatment and care."* (13: p 48)

This will be further discussed in two sub-items: access in a clinical trial environment and access to vaccines as a human right.

Access in a clinical trial environment

The provision for post-trial access to all participants to safe and effective products of the trial is unequivocally stated in the Brazilian Resolution 466/2012, as also in the 2000 DoH version (15), but was made more flexible in the current 2013 version; and is not very clear in the 2016 CIOMS guidelines. These distinctions are explained below:

- In the Brazilian Research Ethics Commission Resolution 466/2012: III.3.d – *guarantee to all participants, at the end of the study and for unlimited time, free access to the best prophylactic, diagnostic and therapeutic methods that have proven their efficiency."* (4) This is probably a unique position and as such has been applied to all clinical trials approved in Brazil since 2012.
- In the 2013 Declaration of Helsinki- Article 33: In advance of a clinical trial, sponsors, researchers and host country governments should make provisions (emphasis added) for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent prcess.

  When compared to the wording of the 2000 DoH (item 30): At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study) (15), the current DoH is more lax on this issue, as "should make provisions" is not equal to actual post-trial access.
- The 2016 CIOMS guideline 5 is also less clear on this issue as instead of defining the obligations to post-trial access, it just requires that researchers and sponsors make plans (emphasis added) for, among others, "providing continued access to study interventions that have demonstrated significant benefit". And again, "make plans" is not synonymous with actually ensuring access.

On the other hand, CIOMS 2016 Guideline 1 may be understood as an added protection for post-trial access: "Scientific and social values cannot legitimate subjecting study participants or host communities to mistreatment, or injustice." And this protection is also included in the UNESCO Universal Declaration on Bioethics and Human Rights (16), especially in Article 2:

> *The aims of this declaration are: (f). to promote equitable access to medical, scientific and technological developments as well as the greatest possible flow and the rapid sharing of knowledge concerning those developments and the sharing of benefits, with particular attention to the needs of developing countries.*

Also in Article 15 – Sharing of Benefits:

> 1. *Benefits resulting from any scientific research and its applications should be shared with society as a whole and within the international community, in particular with developing countries.*

Access to vaccines as a human right

There is an indisputable and urgent need to deploy Covid-19 vaccine or vaccines that have been shown to be safe and effective to all, in an egalitarian way. To this end, a vaccine or vaccines shown to be safe and efficacious in Phase-3 trials must be evaluated and eventually approved by regulatory authorities, locally or using known international agencies. Following this, the complexity is increased and these are related to, for example, how to ensure sufficient production, egalitarian local and global distribution, affordability, accountability, long term follow-up, intellectual property issues, and non-patentability of developed products for Covid-19.

Covid-19 vaccines must be a global public good, aiming at significantly contributing to the equitable protection and promotion of human rights among all people of the world.

It must be emphasised that the Covid-19 pandemic, which may be better considered a syndemic (17), has characteristics in common with AIDS, such as that they are not caused by "democratic viruses" as is often mentioned in the lay press – although they may similarly infect exposed individuals; the consequences are different and much more severe among the most socially vulnerable. This is confirmed by the much higher morbidity and mortality of non-white individuals, which is more pronounced in LMIC (18) but is also seen in industrialised countries, with the USA as an example (19). And access to technological progress, such as to vaccines, is also very dissimilar and great care should be taken to avoid exploitation and increase their vulnerability.

To reach the objective of egalitarian and timely access to affordable vaccines, the following must be ensured, both in research and in public health access:

- The protection and promotion of human rights including health, social, gender and economic security.
- Equity in vaccine access among people living in all countries, particularly to the most socially vulnerable (19).
- The assurance of equity in vaccine access and adequate care within countries for groups experiencing greater burdens from the Covid-19 pandemic which are usually, but not exclusively, living in low- and middle-income countries.
- Respect for persons and communities, ensuring their privacy. This includes the recognition that all human beings have

equal rights and moral status and cannot be subject to any kind of discrimination and/or exploitation.

- That research must be based on fairness, reciprocity, non-exploitation and without double standards.
- That vaccines and other developed products to curb the pandemic must be accessible, affordable, non-patentable and available to everyone.
- That decisions on vaccine research, allocation and national decisions on vaccine prioritisation must be taken through transparent processes based on shared values, best available scientific evidence, and appropriate stakeholder representation and participation.
- To make sure that the vaccines already authorised or on the verge of being authorised for emergency use are equitably distributed to all countries. The COVAX Initiative (GAVI, WHO, CEPI) (14) is a good start as it involves around 190 countries, with the participating high-income countries contributing to access for LMIC. COVAX must be properly financed to actually reach its objectives, which are modest, as it assures that at least 20% of the world population is immunised. It is worth quoting the opening remarks of WHO Director-General Tedros Adhanom Ghebreyesus on the ethics of egalitarian access to Covid-19 vaccines at the 148th Session of the WHO Executive Board on January 18, 2021 (20):

  > *I need to be blunt: 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. Even as they speak the language of equitable access, some countries and companies continue to prioritize bilateral deals, going around COVAX, driving up prices and attempting to jump to the front of the queue… This is wrong. Forty-four bilateral deals were signed last year, and at least 12 have already been signed this year. The situation is compounded by the fact that most manufacturers have prioritized regulatory approval in rich countries where the profits are highest, rather than submitting full dossiers to WHO* (20).

- This initiative alone will probably not be sufficient to provide vaccine access to all who will need them, and as an addition, in May 2020, WHO launched, in partnership with the Government of Costa Rica and 40 Member State co-sponsors with the Solidarity Call to Action, the COVID-19 Technology Access Pool (C-TAP), calling to action the global community to voluntarily share knowledge, intellectual property and data necessary for Covid-19 (21).
- However, in the current severe public health situation and despite efforts and statements, such as by WHO Director General, quoted above, aiming at making Covid-19 medical developed products to be treated as 'global public goods,' the pharmaceutical industry continues signing bilateral commercial licensing and purchase agreements that undermine access for vulnerable and neglected people in many low- and middle-income countries. (22)
- To overcome these obstacles and facilitate the urgent transfer of technology, the production of generic products and their wide and equal distribution I second the recent proposal to the World Trade Organization led by South Africa and India for immediate suspension of issuing of patents to Covid-19 vaccines (and other new technologies) (23). And this is in line with the opinion defended by Kavanagh et al (24), and with the position emanating from the Brazilian Society of Bioethics, and other Brazilian public health institutions (25)

This urgency to overcome inequity is also confirmed by the fact that as of March 18, 2021, only 1.2% of the world population is fully vaccinated (26) and 75% of all vaccines were applied in only 10 countries; and one hundred and thirty countries have not yet accessed *any* vaccine (27).

The Covid-19 pandemic will not be controlled without immunising the majority of the world population and this is clear in the WHO motto: "No one is safe until everyone is safe", which means that the sooner safe and efficacious vaccines are made available, affordable and widely deployed, the sooner this appalling health and social crisis and the unique economic slump can be overcome. The slower the pace of worldwide vaccination, the higher the risks of the appearance of more viral mutants, which could not only be more infectious (28); but against which the current vaccines may not offer effective protection.

Conclusion

The position defended here with regard to Covid-19 vaccines is:

In clinical trials (placebo and post-trial access):

Placebo arm participants in Phase-3 trials have the right of access to the vaccine as soon as interim safety and efficacy are confirmed. This is the responsibility of the sponsors/ investigators and this right must be clearly stated in the informed consent process/form. This responsibility should also be shared by the researcher's institutions. This access should be followed by the invitation to these volunteers to participate in an observational open-label or pharmacovigilance protocol. The position taken here is that the possibility of partially continuing the trial as initially proposed, balancing social value with individual health needs, maintaining those supposedly at low risk in a placebo arm, is flawed, considering the global expansion of variants of concern with a higher infectivity and lethality (28). However, another recommendation of a WHO expert working group on placebo use and unblinding in Covid-19 vaccine trials may be considered an acceptable exception to immediate access to the vaccine to all trial participants: (29):

> *.... Candidate vaccines granted an EUD [emergency use designation] will probably be deployed in a phased manner to ensure the prioritization of those deemed to be at considerable risk. In settings in which candidate vaccines are*

introduced under an EUD, investigators should explain the scientific benefit of continued trial participation and the implications of unblinding to trial participants deemed to be at substantial risk of infection, severe morbidity or mortality. Participants should then be offered the opportunity to be unblinded, so that they can make an informed decision about whether to withdraw from the trial and access an EUD vaccine programmatically as soon as practically possible, should they wish to do so. Trial participants who are not deemed to be at substantial risk of SARS-CoV-2 infection and COVID-19 morbidity or mortality and who do not meet prevailing eligibility criteria to access a candidate vaccine granted an EUD should be informed of the scientific benefits of continuing with the trial and should be encouraged to remain enrolled, with full acknowledgment of their right to withdraw from a trial at any point, without penalty."

It must be added that this is an exceptional and dynamic situation and as soon as the local eligibility criteria are changed, placebo group participants must be unblinded and receive the effective and safe product as soon as the local eligibility criteria is changed. However, when vaccine or vaccines are approved for emergency or full use, subsequent Phase-3 trials should use one of them for the control arm. Exceptions could be accepted when the approval did not include other specific conditions of the participants, eg, other age brackets, pregnancy, or conditions related to the virus (such as new variants that have been shown to be resistant to available vaccines). Any new situation should be evaluated on a case-by-case basis. A new situation could be the local development and testing of a vaccine, such as Cuba's Phase-3 trial of its *"Soberana"* vaccine. But even in this case, if this product shows interim safety and efficacy, their planned Phase 3 trial with the new *Abdala* and *Mambisa,* should use *Soberana 1* for the control group. (30)

The use of an active control in subsequent trials is ethically sound, is a possible and feasible alternative even considering the expected impacts in trial design as detailed by Singh and Upshur (31). They state that

…In such instances, later vaccine trials might be forced to shift from superiority designs to non-inferiority designs as they would have to show that new vaccines are not inferior to the vaccine granted emergency use designation, instead of showing that the new vaccines are superior to placebos. As the difference in efficacy between the vaccine granted emergency use designation and another candidate vaccine will be smaller than that between a vaccine and a placebo, subsequent trials might have to become bigger and run for longer to generate a statistically significant finding, notwithstanding that endpoints, levels of efficacy, and non-inferiority margins all involve value-based decisions and are not necessarily informed by objective criteria.

This conclusion considers the ethical guidelines discussed above, including the very stringent Brazilian guidelines regarding placebo, the limits established in the exceptions in the CIOMS 2016 and DoH 2013, plus the safety and efficacy data on more than 400 million vaccine doses that have been administered worldwide, as of March 17, 2021 (254). This ethical decision is scientifically reinforced by the fact that SARS-CoV-2 infection may be severe and fatal and there is no pharmacological treatment available to mitigate these risks imposed on trial participants

In public health

Access to safe and efficacious vaccines must be considered a human right and to effectively curb the Covid-19 epidemic, safe and efficacious vaccines and other developed products, must timely be available, patent-free and affordable to all the world population.

Perspectives

The worldwide confrontation of AIDS can be considered a global health model (32,33). To effectively combat Covid-19, the lessons previously learned with HIV/AIDS, in both research and in public health practice, must be used to counteract isolationism, boost international solidarity/cooperation with the participation of all relevant stakeholders, to confront anti-science/anti-vaccine movements, to adequately finance science and quality public health accessible to all, to ensure egalitarian access to technological progress, which includes an urgent decision on non-patentability of products for Covid-19. And also, to make sure that exploitation/double standards, both in research and in public health access will not be permitted. This will need strong cooperation among several stakeholders, with WHO leadership, adequate financing, respect for, and participation of, individuals/communities, government, universities, researchers and health professionals. Only with such an involvement will it be possible to address the social determinants of health that have facilitated the establishment and spread of the current syndemic (17) and to prepare for adequate confrontation of others that will certainly come in the future.

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