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Title: **COVID-19 Vaccine Trials and Ethics**

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Conflict of interests: None

Word count: 1479

**COVID-19 Vaccine Trials and Ethics**

*Protection delayed is protection denied.*

During the relentless march of the COVID-19 pandemic, globally we face the unprecedented problem of the highly contagious SARS coronavirus-2 (SARS-CoV-2) spreading like influenza. The world is prepared for an influenza pandemic, with global network of laboratories in every continent collecting virus strains constantly, for detecting any genetically shifted virus capable of seeding a pandemic. Vaccine platform is available and well-oiled. Add the new virus, and we get a new vaccine. When genetic drift in influenza viruses are detected vaccines are modified and tailor-made, annually.

We urgently need a safe and effective vaccine to prevent death, for which severe disease must be avoided and vaccination is the ideal solution. If a vaccine is available after the epidemic is over, still it is good; but if one can be fast-tracked by revisiting rules of trials, and vaccine made available while the epidemic is still raging, that would be best.

For registration by any National Drugs Regulatory Agency, a vaccine candidate must go through three Phases of clinical trials. There are several vaccine candidates that have completed Phase 1 and 2 and are moving into Phase 3. Phase 1 trial passes if the product is non-toxic, already proved in laboratory animals, in pre-clinical studies. Non-toxic means without serious adverse effects -- any medical event that makes the subject sick enough for hospitalisation, or life-threatening. Phase 2 pushes the envelope further to document immunological responses in study subjects. These Phases do not require placebo control arm. Phase 3 trial is on a very large number of subjects, placebo controlled and double blind. The purpose is to check by what frequency the vaccine protects, if it does so. Rare adverse reaction, if any, can also be detected.

Can pre-defined immunological parameters documented in Phase 2 trial be used as an interim surrogate for protection for offering the vaccine under trial, to those who desire it and are willing to take the twin risks of rare serious adverse reaction and vaccination turning out as not protective against disease. If the regulatory agency allows this step, anticipating protection, the vaccine can be allowed in individuals at high risk of severe disease and death, without interfering with the Phase 3 trial. It may be qualified as emergency or compassionate use to borrow the terms from drug trials for serious life-threatening diseases.

Who should be eligible for this option? Healthcare workers, particularly above 55 years, those with co-morbidities and anyone above 65 could be defined as eligible. Vaccine may be offered strictly on voluntary application, with informed consent and declaration of no liability on manufacturer or vaccinator. In order not to interfere with the epidemiology of infection in locations where Phase 3 is conducted, emergency use of vaccine must not be allowed in the catchment area of study volunteers.

Our purpose in this paper is to verify if such a procedure will be ethical. The basic principles of medical ethics are non-maleficence, beneficence, justice and autonomy (1). In public health ethics, there are two disparate opinions called deontology (intervention must not harm individuals) and utilitarianism (intervention beneficial for the majority, even if harmful in a minority is acceptable).

While vaccine candidates are undergoing the traditional trial phases in western countries and India, Russia announced the temporary registration of a vaccine in the second week of August, valid until 1 January 2021 (2). The available published report mentioned 76 subjects given vaccine in Phase 1 and 2 trials (3). The purpose, as stated in the media is to make the vaccine available to healthcare workers, while Phase 3 trial will continue – illustrating the process we described above. This procedure came under severe criticism from scientists in and out of Russia.

China, on the other hand, vaccinated an undisclosed number of military personnel, overseas workers and all staff of the vaccine manufacturing company, without registering it (4). The ethical questions are the same as in Russia, but the additional issue is of a vaccine being given to individuals even without registration.

Covid-19 pandemic is a humanitarian crisis and we believe unchartered ethical waters are in front of us and we need to sail right and fast carrying the vaccine as cargo. There are ethical implications in even a day’s delay as that might make the difference between death and health of individuals vulnerable to severe COVID-19 and high risk of death.

What are the ethical requirements for a vaccine under testing to be released to at-risk individuals who understand and accept the realities of incomplete information on safety and efficacy? The rules regarding trials in 3 phases apply under ordinary circumstances when the need for a vaccine is not as urgent as now.

Ervobo, an experimental Ebola vaccine not having undergone Phase 3 trial, was, by consensus of all involved parties directly applied during Ebola outbreak in Guinea in early 2015 without placebo control (5). Ebola cases were documented: in one set, all persons in contact with cases were immediately vaccinated, and in another set, all contacts were vaccinated 21 days after case confirmation. None in the former group developed Ebola while many in the second group did. As soon as the result was available, the vaccine was declared suitable for widespread application. Later, in 2019, with more data, Ervobo was approved by European Commission and US Food and Drug Administration(6). WHO had concluded in 2014, that there was “ethical imperative to offer available experimental interventions that have shown promising results in the laboratory, to people at high risk”(7).

COVID-19 is not Ebola which has 80% case fatality. However, COVID-19 does have unacceptably high death rates in the elderly and in those with co-morbidities. Preventing death is not the sole goal: survivors of severe disease are prone to debilitating chronic morbidity. Vaccine candidates with safety from serious adverse reactions, and ability to induce laboratory markers of immunity -- virus neutralising antibodies and T-cell immunity are already available and the question is about an ethical imperative to allow its use pending registration. This is call for the regulatory agencies in every country.

During World War 2, influenza was a threat to the health and life of US soldiers in the European theatre. An Influenza Commission was established who created an inactivated virus vaccine, tested in lab animals first and then in soldiers themselves. With positive results not yet published or made available to peer scientists, the vaccine was registered, manufactured, used, with remarkable success. Peace-time procedures were bypassed in war-time. Intentions were altruistic; science impeccable; *dramatis personae* were Jonas Salk and Thomas Francis.

For Phase 3 trial study volunteers are selected on the basis of criteria like age (between 18 and 60), healthy, and without history of COVID or SARS-CoV-2 infection. If healthy adults can be given the vaccine candidate, under coded condition of placebo versus vaccine, is there any additional harm or risk in individuals who are priority candidates for protection once the vaccine is registered? Benefit is unquestionably present, and if the trial confirms protective efficacy, these out-of-trial vaccinees have already started enjoying the benefit of protection. If the trial concludes that the vaccine is not protective, no harm has been done either. When there is reasonable evidence of protection and absence of harm, delaying the use of vaccine in those in urgent need of protection is the “moral dilemma” in our context. We believe that beneficence and non-maleficence are satisfied in this *modus operandi*.

Do intentions matter? When scientists or vaccine companies take a vaccine candidate forward, and if the disease is endemic, the intention could be a mixture of altruism, scientific satisfaction/credit and/or profit motive. Under those circumstances, vaccine trials are the best for protection of the public from undue haste to market a product which may have safety or efficacy problems. In the middle of COVID pandemic, the motive ought to be to offer protection to the vulnerable and to control the epidemic than for financial profit.

Autonomy is ensured by requiring voluntary application, accepting all risks for probable benefit. The principle of justice is satisfied as high priority of probable protection is offered to the vulnerable population. Utilitarian ethics support ways to bring ‘greatest good for the greatest number’ whereas deontological ethics argues that actions should be in accordance with a defined set of principles irrespective of outcome. The parallel use of vaccine with Phase 3 trial is neutral between deontology and utilitarianism.

In summary we see no ethical impediments in the emergency use of a vaccine that has cleared Phases 1 and 2 and is already in, or ready for, Phase 3 trial. On the contrary, we feel the strict adherence to the rule requiring the completion of Phase 3 trial and vaccine registration, while superficially ethical, may actually be contrary to the spirit of ethical principles, as lives and health of many could be protected by the principle of emergency use.

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