Emergency use authorization of Covid-19 Vaccines: An Ethical Conundrum

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**ABSTRACT**

*Large-scale vaccination with a safe and effective vaccine against Covid-19 is the only way to conquer the ongoing lethal pandemic that has led to extraordinary social and economic upheaval globally. Fortunately, with the unprecedented speed and scale of development, the world is on the verge of developing Covid-19 vaccines in an amazingly short time. More than forty vaccines are in different stages of clinical trials, and few are in the crucial phase III studies. A new demand for emergency use authorization and rapid deployment of these vaccines before scrutinizing phase III trial data is raging in different quarters. Will advancement of deployment of these vaccines by even a few weeks can give us rich public health dividends? Will it be ethical to deploy these novel vaccines based only on the safety and immunogenicity data generated by the phase-I and II clinical trials? Will it be ethical to deny vaccination of vulnerable population against an untreatable infectious disease despite the availability of reasonably safe and efficacious vaccines for the want of phase III trial data? The answer is not as straight forward, as there are many complexities involved. This writeup attempts to deliberate some of the ethical issues involved with the decision of early deployment of Covid-19 vaccines before phase III trial results.*

*Keywords*: *Covid-19, vaccine candidates, bioethics, clinical trials, emergency use*

**Background**

The Severe Acute Respiratory Syndrome Coronavirus type-2 (SARS-CoV-2) pandemic has caused great social and economic upheaval globally. Nearly ten months into the pandemic, hopes of conquering COVID-19 still largely rest on a vaccine. Thanks to the unprecedented speed and scale of development, more than forty candidates are now in advanced stages of clinical trials. Yet whether vaccines will meet our hopes for a return to normal—now, or in the years to come—will depend on our ability to meet a new kind of challenge, one as logistical, operational, and cultural as it is epidemiological, and far more complex than any the world has faced in the history of immunization to date. Adding further complexities to the existing issues is a new demand for allowing emergency use authorization of Covid-19 vaccines before completion of full phase III trials that poses a new challenge—ethical **[1].** Will it be ethical to deny vaccination of vulnerable population against an untreatable infectious disease despite the availability of reasonably safe and efficacious vaccines for the want of phase III trial data? Will advancing the deployment of safe and effective vaccine(s) by even a few weeks can provide rich public health dividends? This new ethical dilemma has posed a formidable challenge.

**Applying the four principles of bioethics**

Would it be ethical to deploy the Covid-19 vaccine(s) based on safety and immunogenicity data generated by phase-I and II clinical trials alone, without waiting for the crucial phase-III trials? The answer is not as straight forward, as there are many complexities involved. The issue needs to be deliberated in detail to see if the four basic principles of bioethics (respect for autonomy, non-maleficence, beneficence, and justice) **[2]** are satisfied. If any Covid-19 vaccine is deployed without waiting for the phase-III trial data and the vaccinees are vaccinated after obtaining full informed consent, there should not be any violation of the principle of **respect for autonomy. Non-maleficence** (do no harm) is a crucial component of bioethics principle that needs careful deliberation concerning our question. While common adverse effects are less likely to be missed by the phase I/II trials, these trials are underpowered to detect less common adverse effects.

By skipping phase-III trials, the vaccinees would be subjected to unknown risk. Since a huge population is to be vaccinated, the absolute number of subjects suffering from even less common adverse effect would be significant. Of particular note is the risk of immune enhancement of the disease, that is the risk of paradoxically more severe disease in individuals who are vaccinated **[3].**  Such event has been noted with many vaccine candidates in the past and in in-vitro studies of SARS-CoV-1 vaccine. Very recently, similar concerns regarding vaccine enhancement of disease have been raised regarding certain SARS-CoV-2 vaccine candidate approaches **[4].** Thus, we cannot be sure of satisfying the principle of non-maleficence based on our current state of knowledge.

Next principles of bioethics that are to be used as a touchstone to find out the answer are **beneficence** and **justice.**Or in other words, the obligation to produce benefit and providing equal opportunities for everyone along with fair distribution of benefit to everyone. What benefit the vaccine would provide would vary a bit with the vaccine and its efficacy. The gold standard for any vaccine is to prevent infection (“sterilizing immunity”) in all recipients. However, the published animal studies, mainly in non-human primates ~~(NHP)~~ of candidate Covid-19 vaccines till now have failed to show that, though the decrease of viral load and protection from the severe disease has been shown **[5].** It is expected that the upcoming vaccine would be, in all probability, modestly effective (50-60%) against moderate to severe Covid-19 disease. Now, it is also known that the risk of moderate to severe disease is highest in elderly patients and those with co-morbidities. However, phase-I and II trials of the vaccine candidates have enrolled only young volunteers without any comorbidity. So, the amount of benefit a vaccine that prevents moderate/severe disease in young, healthy people where the incidence of the disease is quite less even otherwise is not difficult to imagine. Furthermore, the safety and immunogenicity data from young and healthy subjects cannot be extrapolated to the elderly population. Alternative vaccine platforms or the addition of adjuvants may be required for adequate immunogenicity in older age groups, as has been the case with influenza vaccines **[6].** Further, the durability of the immune response also cannot be elucidated from phase I/II trials. The waning of immune responses is known with most human coronavirus infections **[5].** The common cold coronaviruses like HCoV-229E and HCoV-OC43 are known to provide immunity that lasts only a few weeks to months **[7].** These coronavirus infections do not provide lasting protection as challenge experiments suggest, despite having detectable antibodies **[8].** Re-infections have also documented with SARS-CoV-2 **[9].** Thus, unless we have reliable data on the durability of the immune response to the vaccine(s) in question, the degree of beneficence is difficult to ascertain. Even if the Covid-19 vaccine(s) are deployed without undergoing rigorous phase-III trials as has been done in China and Russia **[10, 11],** these trials would continue to run parallelly to generate scientifically strong data and find out answers to unanswered questions. However, this would add some more ethical issues to the cauldron. Vaccination in the same population where the phase-III trial is going on would affect the trial results. To avoid this, the vaccine would not be offered in the catchment area of the trial. But then would it not go against the principle of justice? Would not the said population be devoid of the opportunity to get the vaccine that is licensed?

**Is there a precedent?**

During the large epidemic of deadly haemorrhagic fever by Ebola virus in 2014, the WHO had approved an innovative, open-label phase III, cluster-randomised ring vaccination trial of a candidate Ebola vaccine, rVSV-ZEBOV by Merck & Co. in contacts and contacts of contacts of recently confirmed cases of Ebola in Guinea. Around 2,100 subjects were vaccinated immediately with Merck & Co’s rVSV-ZEBOV, and a similar number of subjects in a control arm received a delayed vaccination 21 days later. No Ebola cases occurred within 10 days or more of treatment in the patients who received immediate vaccination, whereas 23 cases occurred in the control group. The candidate vaccine was found to offer substantial protection against Ebola virus disease with 100% efficacy **[12].**  The innovative ‘ring design’ was chosen for operational, scientific, and ethical reasons, and it was considered as ethically superior to individually randomized placebo-controlled trials.

However, Covid-19 is not Ebola, which had exceedingly high mortality (the average mortality of Ebola has been 50%, ranging from 22%-88%) **[13].** Even the average case fatality rate of Ebola virus disease is much higher than mortality observed in the high-risk group with Covid-19. The pre-phase III efficacy assessments of Covid-19 vaccine candidates hovers around 50-60% which are much below the observed efficacy of Ebola vaccine, rVSV-ZEBOV. Furthermore, there is a huge amount of uncertainties regarding the reliable immune-correlate of protection, duration of immunity, and potentially serious adverse effects like ADE-antibody enhanced disease, a phenomenon already observed with the predecessor of Covid-19 vaccines, the SARS-CoV candidates. Hence, there is a lot of scepticism around the success of Covid-19 vaccines owing to our inadequate knowledge of immunity associated with Covid-19, our past-experience with SARS-CoV-1 vaccines, absence of sterilizing immunity as evident in non-human primate studies, etc.

**The other complexities**

Moreover, the lack of transparency in many large Covid-19 vaccine trials has adversely affected the public trust in these vaccines **[14].** Few large vaccine developers like Moderna, Pfizer, AstraZeneca, and Johnson & Johnson are forced by the academia to make their clinical-trial protocols for vaccine candidates that are in phase III clinical trials public. Concerns about approvals being rushed, fears of political interference, undue pressure on regulatory authorities to approve a vaccine before data show that it is effective and safe, suspicion of the vaccine industry and an outbreak of vaccine misinformation are combining to erode the public’s trust in the vaccine development and approval processes. The ongoing trial designs have not enthused academia with many leading vaccine developers have kept modest efficacy estimates of around 50%. The ‘primary endpoint’ of many candidate vaccines’ trials is ‘prevention of mild disease’ rather than ‘protection against the severe disease and death’.

The growing vaccine hesitancy secondary to ‘tsunami’ of misinformation and conspiracy theories has the potential to hamper vaccine uptake. The politicization of Covid-19 vaccination in a few countries has created suspicion amongst the community. Covid-19 has been an emergency and the ethical values vary among countries. Any mishap during pre-emptive COVID-19 vaccination without last approval may have far-reaching negative consequences on the overall vaccine confidence and acceptance.

**Conclusions**

Thus, despite the undoubted need to have a vaccine urgently to tide over the crisis, it is not to be forgotten that the vaccine needs to be safe and effective to achieve the desired outcome. Deliberately delaying a safe and effective intervention against mounting morbidity and mortality due to the long trial and licensing process may have some ethical consequences. But allowing a modest, potentially unsafe, and ‘partially tested’ intervention in a section of society against a not so lethal illness may be ethically flawed. While innovative ways like parallel phase-I/II trials (rather than sequential), studying multiple vaccine candidates in one trial (like solidarity vaccine trial being proposed by WHO) and starting manufacturing processes in anticipation of licensing and reducing the “red tape” in the processes of licencing might be considered as means to fast track vaccine development and deployment, skipping crucial phase-III trials does not seem to pass the test of ethical scrutiny. While light at the end of the tunnel is welcome, we should tread very carefully with this new virus and not be blinded by the light: everything that glitters is not gold!!

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