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Emergency use authorisation of Covid-19 vaccines: An ethical conundrum

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Abstract

Largescale vaccination with a safe and effective vaccine against Covid19 is the only way to conquer the ongoing lethal pandemic that has led to extraordinary social and economic upheaval globally. Fortunately, the world is on the verge of developing Covid19 vaccines in an unprecedentedly short time. More than forty vaccines are in different stages of clinical trials, and a few are in the crucial phase III studies stage. A new demand for emergency use authorisation and rapid deployment of these vaccines before scrutinising phase III trial data is raging in different quarters. Can advancement of the deployment of these vaccines by even a few weeks give us rich public health dividends? Would 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? Would it be ethical to deny vaccination of vulnerable populations 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 straightforward, as there are many complexities involved. This commentary attempts to discuss some ethical issues involved in a decision to deploy Covid19 vaccination before phase III trial results are declared.

Keywords: *Covid19, vaccine candidates, bioethics, clinical trials, emergency use*

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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 rest largely on the production of 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 immunisation to date. Adding further complexity to the existing issues is a new demand for allowing emergency use authorisation of Covid-19 vaccines before completion of the full phase III trials, which poses a new ethical challenge (1). Would it be ethical to deny vaccination to a vulnerable population against an untreatable infectious disease despite the availability of reasonably *safe and efficacious* vaccines for the want of phase III trial data? Would advancing the deployment of safe and effective vaccine(s) by even a few weeks 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 straightforward, as many complexities are 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 vaccination is carried out after obtaining the full informed consent of the vaccinees, there should not be any violation of the principle of respect for autonomy. Non-maleficence (do no harm) is a crucial component of bioethics principles that needs careful

deliberation concerning the 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.

If Covid-19 vaccine is deployed before thoroughly scrutinising phase-III trials, the vaccinees would be subjected to unknown risks. Since a huge population is to be vaccinated, the absolute number of subjects potentially suffering from even less common adverse effects would be significant. Of particular note is the risk of *immune enhancement* of the disease, that is, the paradoxical risk of more severe disease in individuals who are vaccinated (3). Such an effect has been noted with many vaccine candidates in the past including *in-vitro* studies of a SARS-CoV-1 vaccine candidate. Very recently, similar concerns have been raised regarding vaccine enhancement of disease about 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.

Beneficence and justice are two other principles of bioethics that are to be used as a touchstone to answer the above question. This implies the obligation to produce benefit and provide equal opportunities for everyone, along with fair distribution of benefit to everyone. What benefit the vaccine would provide would vary somewhat with the specific vaccine candidate and its efficacy. The gold standard for any vaccine is to prevent infection ("sterilising immunity") in all recipients. However, the published animal studies of candidate Covid-19 vaccines, mainly in non-human primates have so far failed to demonstrate that, though a decrease of viral load and protection from severe disease have been shown (5).

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 low 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 can also not 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 from just 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 been 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 parallel to deployment to generate scientifically strong data and find 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. Would this not go against the principle of justice? Would the said population not be deprived of the opportunity to get the vaccine that is licensed?

Is there a precedent?

During the serious epidemic of deadly haemorrhagic fever caused by Ebola virus in 2014, the World Health Organization (WHO) had approved an innovative, open-label phase III, cluster-randomised ring vaccination trial of a candidate Ebola vaccine, rVSV-ZEBOV, produced by Merck & Co. in contacts and contacts of contacts of confirmed cases of Ebola in Guinea (12). Around 2,100 subjects were vaccinated immediately with Merck'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 (13). The innovative "ring design" was chosen for operational, scientific, and ethical reasons, and it was considered ethically superior to individually randomised placebo-controlled trials. However, Covid-19 is not Ebola, which had an exceedingly high mortality (the average mortality of Ebola has been 50%, ranging from 22%-88%) (14). Even the average mortality rate of Ebola virus disease is much higher than mortality observed in the high-risk group with Covid-19 (10-20%) (15).

The pre-phase III efficacy assessment of Covid-19 vaccine candidates hovers around 50-60% which are far below the observed efficacy of Ebola vaccine, rVSV-ZEBOV. Furthermore, there are multiple uncertainties regarding the reliable immune-correlate of protection, duration of immunity, and potentially serious adverse effects like antibody enhanced disease (ADE), a phenomenon already observed with the predecessor of Covid-19 vaccines, the SARS-CoV candidate. 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, the absence of sterilising immunity as evident in the non-human primate studies, etc.

Additional complexities

The lack of transparency in many large Covid-19 vaccine trials has already adversely affected the public trust in these

vaccines (16). A few large vaccine developers like Moderna, Pfizer, AstraZeneca, and Johnson & Johnson have been forced by the academic community to make public their clinical-trial protocols for vaccine candidates in phase III clinical trials. 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 primary endpoint of many candidate vaccine trials is "prevention of mild disease" rather than "protection against severe disease and death".

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

Conclusions

Despite the undoubtedly urgent need for a vaccine to tide over the crisis, it cannot 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 potentially unsafe, and "partially tested" intervention offering modest protection to a section of society against a not so lethal illness may be ethically flawed. While innovations like parallel (rather than sequential) phase-I/II trials, studying multiple vaccine candidates in one trial (like the Solidarity vaccine trial proposed by WHO) and starting manufacturing processes in anticipation of licensing, and reducing red tape in the licensing process 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 options offering light at the end of the tunnel are 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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