Ethical considerations for epidemic vaccine trials

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ABSTRACT

Vaccines are a powerful measure to protect the health of individuals and to combat outbreaks such as the COVID-19 pandemic. An ethical dilemma arises when one effective vaccine has been successfully developed against an epidemic disease and researchers seek to test the efficacy of another vaccine for the same pathogen in clinical trials involving human subjects. On the one hand, there are compelling reasons why it would be unethical to trial a novel vaccine when an effective product exists already. First, it is a firm principle of medical ethics that an effective treatment or vaccine should not be withheld from patients if their life may depend on it. Second, since epidemic outbreaks often emerge in settings with less-resourced health systems, there is a pronounced risk that any trial withholding an effective vaccine would disproportionately affect the vulnerable populations that historically have been exploited for biomedical research. Third, clinical trials for novel vaccines may be at odds with efforts to control active outbreaks. On the other hand, it may be justified to conduct a trial for a candidate vaccine if it is expected to have certain advantages compared with the existing product. This essay discusses key factors for comparing vaccines against epidemic pathogens, including immunological, logistical and economic considerations. Alongside a case study of the development of vaccines for Ebola, the essay seeks to establish a general framework that should be expanded and populated by immunologists, epidemiologists, economists and bioethicists, and ultimately could be applied to the case of COVID-19 vaccines.

INTRODUCTION

Throughout the 20th century, vaccines have become one of the most prominent tools in the arsenal against epidemic outbreaks.[1] However, for many infectious diseases on the WHO's list of priority pathogens, no licensed vaccine exists. Moreover, when a novel disease like coronavirus disease 19 (COVID-19) emerges, the global community faces the challenge of swiftly developing a vaccine, which typically involves many years of scientific research followed by extensive clinical trials.[2] Whenever vaccine trials occur in the context of an epidemic, unique ethical challenges arise. This is not because these conditions alter research ethics principles directly: as a comprehensive 2017 report of the National Academy of Sciences reaffirmed, '(even in emergency circumstances), the substantive ethical requirements governing research with humans do not change'.[3] Rather, the circumstances of an active outbreak can create difficulties for carrying out clinical trials in accordance with these ethical principles.[4] For example, the presence of severe risks to populations during an epidemic may limit the ability of human subjects to give legitimate, uncoerced consent.[5] Additionally, emergency circumstances can heighten the risk that research ethics are deprioritised or disregarded; for instance, the urgency of an active outbreak may compel researchers to speed up, abbreviate or modify informed consent procedures.[3] In other cases, emergencies will inspire proposals for new, extraordinary research strategies, such as the human challenge trials that recently have received renewed attention as a potential component of stage III clinical trials for COVID-19 vaccines.[6] Rather than necessitating entirely novel medical ethics, such extraordinary proposals must be—and are being—scrutinised through the lens of well-established ethical frameworks.[7]

There are certain conditions, where researchers and bioethicists have raised questions as to whether clinical trials should proceed in the first place. For example, Adebamowo and colleagues have argued that the circumstances of a highly lethal infectious disease outbreak may make it ethically inappropriate to deploy potentially life-saving treatments (and, by extension, vaccines) through a randomised controlled trial that, by design, withholds the medical product from sick or susceptible individuals.[8] Others, like London, have presented arguments to support a different position; that it may be ethically permissible to do randomised trials of unproven medical interventions during an active outbreak.[9]

Much of the bioethical debate surrounding epidemic vaccine trials focuses on a particular kind of situation: where no vaccine with proven efficacy exists, and the ethical dilemma essentially comes down to whether a promising candidate should be tested in a randomised study or simply provided to as many susceptible individuals as possible, foregoing a randomised control group. This was the situation that presented itself during the 2014–2015 Ebola outbreak. Several candidate vaccines had passed safety trials in healthy volunteers and some had shown promising results in non-human animal trials but no Ebola vaccine candidate had yet been supported by phase III efficacy trials. For each of the promising vaccine candidates, there was genuine uncertainty as to whether it would confer protection in humans. In other words, it could be credibly argued that a state of equipoise existed; a criterion that often is thought to constitute sufficient ethical justification for having a control group in a study. It is a similar situation that we as a global community will find ourselves in when a candidate vaccine for COVID-19 advances to phase III efficacy trials. Health officials, researchers and ethicists will once again face important questions about the permissibility of withholding potentially effective vaccines from a control group of patients.

This situation, where no effective vaccine for an epidemic disease exists, certainly demands additional research and bioethical inquiry. However,

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another situation has received comparatively less attention in the relevant literature: when a vaccine has already been shown to be safe and effective and has been licensed for use against an epidemic outbreak. This situation arose during the latest outbreak of Ebola in the Democratic Republic of the Congo (DRC). One vaccine, produced by the pharmaceutical firm Merck, had shown promise in phase I and phase II trials during the 2014–2015 outbreak.[10] Since some uncertainty remained concerning the vaccine's protective effects,[3 11] other candidates were also being considered for clinical trials, including one produced by Johnson and Johnson (J&J). As the outbreak progressed and preliminary results were collected for the Merck vaccine, it became increasingly clear that the vaccine was remarkably effective at conferring protection from Ebola to vaccinated individuals, and the vaccine was ultimately licensed for use.[12] The existence of a proven vaccine raised serious questions regarding whether the J&J trials should continue. Some, including the erstwhile minister of health of the DRC, opposed trialling the J&J vaccine, arguing that susceptible Congolese people ought to receive the proven Merck vaccine.[13 14] Others, including highly reputed public health professionals from leading international organisations, argued in favour of the trials, citing the potential benefits of adding another vaccine to the epidemic response arsenal.[15 16] Ultimately, J&J conducted their trial, and thousands of Congolese people at risk of Ebola have received the shot, even as others in the country were offered the already-licensed Merck vaccine. Throughout the ensuing debate, the involved parties rarely, if ever, appealed to any ethical frameworks or existing guidelines in support of their case, perhaps because the issue has received scant attention so far. Accordingly, this essay endeavours to fill a gap in the medical ethical literature, by enumerating and discussing a range of crucial considerations for the ethical status of follow-up vaccine trials for epidemic diseases. This discussion will both shed some light on whether it was appropriate to carry on with the J&J trial in the DRC, and it will be informative when similar situations arise in the future. Perhaps most pertinently, the framework presented here may be valuable if or when multiple phase III trials commence for desperately needed COVID-19 vaccine.

THE PRIMA FACIE ARGUMENT AGAINST SECONDARY VACCINE TRIALS

The basic structure of the situation under consideration is as follows. A vaccine for an infectious pathogen has been tested for safety and efficacy through rigorous phases I–III trials and is being deployed to combat an active outbreak. Subsequently, researchers and pharmaceutical companies are considering whether to conduct trials for another vaccine for the pathogen—we can call this a 'secondary epidemic vaccine trial'. In such a trial, the control group could consist of people receiving either the existing vaccine or a simple placebo injection. The framework presented below will apply to both of these scenarios, but since the head-to-head comparison is more ethically appealing than the placebo-only trial, readers should have the former kind of case in mind for the present discussion. This situation is structurally somewhat similar to that of any other follow-on therapeutic but as the discussion below will reveal the case of secondary epidemic vaccine trials has certain unique characteristics that demand particular bioethical attention.

The first crucial feature of this case to note is that there are very plausible arguments for why a secondary vaccine trial involving randomised controlled groups may *not* be ethically permissible. Namely, doing so would be ethically problematic because (1) it would involve withholding the vaccine from people in the control group, who have a moral right to immunisation against the deadly pathogen; (2) deprivation of proper treatment historically and presently has affected vulnerable, marginalised populations disproportionately and (3) maintaining a control group might limit the effectiveness of efforts to contain an epidemic.

The first and foremost reason not to conduct a secondary clinical trial during an infectious disease outbreak is simply that it is impermissible to deliberately withhold a proven medical countermeasure from human subjects during clinical research, unless this research plausibly may confer considerable benefits to patients and society at large. This principle is the primary reason why clinical research must only be conducted under conditions of equipoise,[17] and it is firmly established in key normative guidelines governing clinical research.[4 18 19]

An important corollary to this principle is that particular care must be taken to ensure that especially vulnerable populations are not exploited in the name of scientific advances. Although frequently used in medical ethics, the categorisation of 'vulnerable populations' is itself hard to pin down in a way that is neither too broad nor too rigid.[20] For present purposes, I will adopt the definition proposed by Schroeder and Gefenas, on which vulnerability involves facing a heightened risk of incurring identifiable harms during research—such as invalid consent or denied access to the benefits of research—while lacking the ability or means to protect oneself.[21] In the context of biomedical product development, it is especially critical to scrutinise how such vulnerability arises in interactions between well-resourced researchers from Western institutions and predominantly white communities in lower-income countries. The history of global health research holds far too many examples of researchers violating the core principles of medical ethics—autonomy, beneficence, non-maleficence and justice—when recruiting human subjects in developing world communities.[22–25] Since novel pathogens often emerge—and are particularly devastating in—contexts of limited health systems capacity, there is a pronounced risk that the harms of an unethical secondary vaccine trial would disproportionately affect populations in lower-income countries, thereby creating the conditions for vulnerability laid out by Schroeder and Gefenas.[21]

Finally, pursuing a randomised controlled trial of a novel vaccine during an active outbreak may be at odds with epidemic control efforts. In addition to the health of the individual, highly infectious diseases necessitate that consideration is given to those who might become infected by an individual who was not given the existing vaccine due to an experimental trial. For pathogens with high reproduction numbers, deploying a vaccine with unknown efficacy can involve a risk of allowing the continued spread of an epidemic. Moreover, randomised trials may require a process for selecting subjects that is not ideal from the perspective of controlling an epidemic, where targeted approaches, such as ring-vaccination or prioritisation of healthcare workers, are preferred to the randomisation of a clinical trial.

In summary, we may say that researchers have strong prima facie reasons not to conduct a secondary vaccine trial. This statement suggests that the onus is on proponents of a secondary vaccine to demonstrate sufficient cause to override the countervailing reasons. However, it does not necessarily imply that secondary trials are *never* permissible. The rest of this essay outlines some of the most important factors that, if applicable with sufficient force, may render a secondary trial ethically permissible, all things considered. Importantly, while some combination of these factors will be necessary for a secondary trial to be permissible, neither of them are independently sufficient.

POTENTIALLY JUSTIFYING FACTORS FOR A SECONDARY VACCINE TRIAL

Equipoise regarding relative efficacy

Perhaps the most compelling reason to engage in a secondary vaccine trial would be that there is genuine equipoise concerning the relative efficacy of the existing and candidate vaccines. In some cases, the first successfully licensed vaccine may confer immunity to some, but not all, vaccinated individuals. In such a situation, the efficacy of a candidate vaccine could possibly surpass that of the existing one, creating the potential for genuine equipoise. The ethical viability of such an argument from potentially improved efficacy depends on a variety of factors: the estimated efficacy of the existing vaccine; plausible reasons to think that the candidate might be superior and the public health importance of obtaining a better vaccine.

The higher the estimated efficacy of the existing vaccine, the lower is the likelihood that a secondary trial would lead to an improved product. In the case of Ebola, for example, the Merck vaccine was shown to be effective as much as 97.5% of the time, which meant that it was rather unlikely that the J&J vaccine would have considerably greater efficacy.[12] By contrast, in cases where existing vaccines are effective in much less than 100% of patients, the efficacy-argument for a secondary trial may be stronger. When considering efficacy, researchers must also account for any compelling reasons to believe that a candidate vaccine might offer gains to efficacy. These reasons could include theoretical immunological arguments or evidence from head-to-head comparisons of efficacy conducted with nonhuman primates. In the absence of such arguments, the efficacy-based case for a secondary trial is weakened, and it may be implausible to argue for genuine equipoise between the existing and candidate vaccines.

Since the most plausible argument for a secondary trial will often take the form of a consequentialist appeal to the overall societal benefits of obtaining a vaccine with improved efficacy, researchers must consider the *scope* of these potential benefits to determine whether they outweigh the reasons against conducting a trial. This argument will apply with particular force in the case of pathogens that pose pandemic threats such as COVID-19, and especially for pathogens that have the potential to radically affect the trajectory of human civilisation.[26 27]

Vaccine characteristics beyond efficacy

While efficacy may be the most salient characteristic of a vaccine and the primary focus of phase III trials, it is not the only important factor when comparing an existing vaccine with a potential candidate. Another such factor is the estimated length of immunity conferred by the respective vaccines. Some vaccines, like the one for measles, offer life-long immunity in almost all vaccinated individuals. Others, like the one for pertussis, offer more limited immunity and requires booster shots at regular intervals or before particular events, such as travel or pregnancy. If the duration of immunity conferred by the existing vaccine is considered too short, a secondary vaccine may represent an opportunity to improve the overall protection of communities. In the case of the Ebola vaccines, the potential for longer lasting immunity has been voiced as a reason to investigate vaccines beyond the Merck shot.[28]

Another important immunological characteristic is the reactogenicity of the vaccine; that is, how likely it is to produce adverse immunological responses and symptoms that are harmful, but mild enough not to be disqualifying from a safety perspective. If a vaccine is prone to cause symptoms like fever or soreness, this is both harmful to individual patients and it also complicates general preventive vaccination programmes for at-risk populations. Consequently, a novel vaccine candidate with potentially reduced reactogenicity may present an improvement in terms of both general welfare benefits and in terms of realising the core medical ethical principle of non-malevolence.

Beyond effects on the human body, there are other characteristics of a novel vaccine that may make it an attractive alternative to the existing product. For example, a candidate vaccine may hold the promise of being easier to store in a cold chain. Alternatively, it may have advantages in terms of ease of administration to patients; for example, by being administered in one, as opposed to two doses. Since these factors directly affect access to care and can be ascertained before conducting a phase III trial, there is a clear onus on vaccine developers to demonstrate that their candidate offers a valuable addition to the epidemic response arsenal.

Economic and logistical factors

Another class of arguments relate to the production and distribution of vaccines, rather than to the medical countermeasure itself. During the recent Ebola outbreak in the DRC, proponents of the J&J trial raised concerns about a potential shortage of the existing Merck vaccine.[15] While it is unclear whether these concerns were substantiated—forecasts made in January suggested that supplies were expected to be sufficient[29] and expert witnesses at a congressional testimony in July denied concerns about a shortage[30]—there is a certain appeal to the general argument that a novel candidate could offer a strict improvement for anyone who otherwise would receive no vaccine at all due to presumed scarcity. In addition to concerns about shortages, proponents of a secondary vaccine trial may also argue that it is critical to have multiple producers responsible for vaccines against the same epidemic diseases, for the sake of both supply chain security and pricing concerns.[16] First, they may argue, having multiple producers makes the vaccine supply more robust to disruptions in the event of an emergency. Second, the existence of a competing manufacturer may be welcomed from a perspective of avoiding excessive monopoly pricing. Given these considerations, the argument goes, secondary vaccine developers should be allowed to trial their candidate, so that the arsenal of medical countermeasures against a given disease may be expanded.

These arguments are certainly appealing insofar as they are grounded in legitimate concerns pertaining to equitable access to care as well as global health security. Given that production for many of the most important vaccines is concentrated in a very small selection of facilities, it is desirable to reduce the fragility of the supply by relying on multiple manufacturers. Moreover, since vaccine affordability is a key challenge for global health equity, the prospect of avoiding monopoly pricing may also be important. However, what each of these concerns have in common is that they are economic and logistical challenges which can often be addressed through economic and logistical solutions that pose fewer moral concerns. Indeed, for each of the challenges, it is not obvious that the appropriate solution would be to develop an entirely new product. To avoid shortages during an active outbreak, governments can invest more heavily in procuring robust vaccine supplies prior to and during outbreaks. To mitigate concerns over vaccine supply fragility, governments can work to facilitate licensing agreements between multiple manufacturers. Indeed, two different manufacturers currently produce what is essentially the same cholera vaccine. Similarly, pricing concerns can be addressed through other policy solutions

that already exist (such as the Advance Market Commitment),[31] or have been proposed in recent years (such as the Health Impact Fund).[32] To be sure, policy-based solutions will often be costly and can in some cases sacrifice some of the efficiency that can be associated with purely market-based production and distribution of goods. However, given the strong prima facie reasons against trialling secondary vaccines during epidemics, it stands to reason that policy-based solutions should be considered carefully before turning to the technical solution of aiming for an entirely new vaccine.

CONCLUSION

When a vaccine has been successfully developed for an epidemic disease like Ebola virus disease or COVID-19, there often will be strong reasons not to conduct randomised controlled trials for another candidate vaccine. Thus, the onus is on vaccine developers to demonstrate that their candidate is likely to be appealing relative to the existing product through holistic analyses of the expected advantages and disadvantages. In the case of Ebola, for example, the J&J candidate vaccine had the benefit of potentially offering a shot associated with lower reactogenicity, while its downsides included that it had to be administered in two shots instead of one and that it was not guaranteed to confer the near-perfect efficacy of the Merck vaccine. For every new case, it will require careful research and deliberation by immunologists, epidemiologists, economists and bioethicists to determine the ethical legitimacy of a given trial. The relevance of analysing potential secondary vaccine trial benefits and costs is most salient within a consequentialist framework. However, to the extent that the analysis is rooted in the fundamental goal of improving patient outcomes—a concern that permeates every medical ethical tradition—it is relevant independently of any commitments to consequentialism. Moreover, insofar as the approach I have presented here aims to ensure that more patients—particularly from vulnerable groups—access a better standard of care in the form of the best available vaccine, it is fully consistent with models of medical ethics grounded in equity or social justice.[33]

I should emphasise that the vaccine characteristics listed above are not intended to serve as a laundry list of arguments for vaccine developers to cite as they seek to trial a secondary vaccine. Rather, claims concerning the superiority of a candidate vaccine along any of the enumerated dimensions should be supported by robust theoretical reasoning, as well as any kind of preliminary evidence that may be gathered prior to phase III trials. In emergency situations, appeals to consequences as justifications for extraordinary actions are abound, especially when the stakes are as high as they are during the COVID-19 pandemic. To avoid that such appeals are misused to further the vested interests of certain parties—such as pharmaceutical developers with financial incentives to carry out clinical trials—it is of paramount importance to move towards a more principled framework. Paired with evidence-based arguments, such a framework can guide the development novel vaccines for epidemic diseases and avoid repeating past transgressions of clinical research ethics in global health.

My purpose here has not been to present a finalised account of when secondary vaccine trials are permissible or not. Instead, I have sought to point to an issue that requires further research and ethical discussion. Future enquiries could extend the discussion of the vaccine characteristics already discussed here, or highlight other key points of comparison between vaccines for any given pathogen. Moreover, the general framework presented here can be applied to retrospectively examine the ethics of past clinical trials —such as the previously mentioned case of Ebola—or prospectively to frame future decisions concerning epidemic vaccine trials. Crucially, such examinations should be mindful of the ways in which vaccine development processes vary across different diseases. For example, although the present discussion has referred to the cases of both Ebola and COVID-19, there are important differences between these two, in terms of the amount of available evidence as well as the exact characteristics of the pathogens. Accordingly, researchers should be careful not to make inappropriate generalisations from one case to another, a mistake that is most easily avoided by relying on the expertise of vaccine scientists in addition to bioethicists. Finally, it is critical that the conversation around ethics does not end when it is concluded that a novel vaccine should be pursued in efficacy trials. Neither the potential for identifiable harms nor the limited means for self-protection that constitute vulnerability are removed simply because a vaccine candidate is considered promising. Accordingly, pharmaceutical companies, health agencies and researchers implementing global vaccine trials must take concrete steps to protect vulnerable human research subjects. Such steps include, but are not limited to, providing commensurate compensation to trial participants, sharing financial rewards of successful product development with involved communities and guaranteeing that consent is obtained in culturally and linguistically appropriate formats.[34]

The world is currently following the development of vaccines for COVID-19 with trepidation. Once candidates reach phase III trials, a host of ethical dilemmas will arise, while urgency, political interests and strong financial incentives will create pressures to forge rapidly ahead. To ensure that these dilemmas are resolved appropriately, the time is now to begin the necessary ethical discussion well in advance.

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This article was published with an error. In the following section the term 'white' should read 'non-white'. 'In the context of biomedical product development, it is especially critical to scrutinise how such vulnerability arises in interactions between well-resourced researchers from Western institutions and predominantly white communities in lower-income countries' The text has now been updated online.

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