OPINION

It's ethical to test promising coronavirus vaccines against less-promising ones

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With multiple candidate vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) entering efficacy testing, researchers and ethicists should come to grips with the distinctive medical ethics questions that could arise. An important one is determining the most ethical way to proceed when comparing a purportedly promising vaccine against a purportedly less-promising one. Imagine a situation in which neither vaccine is proven; one or both could fail. But one does look promising, and more promising than the alternative vaccine, as agreed by all informed experts.

Some approaches to research ethics would suggest that no participants should get a less-promising intervention tested on them than ones offered in any other arm or trial, or otherwise available. Is this the right path in such a situation? Or how otherwise to handle the situation?

We shall argue that it would remain ethical to test either vaccine against the other or against placebo, at least if doing so would create only a minimal delay in obtaining compelling evidence on the more-promising vaccine. The practical implication is that this fall, timely testing of all vaccine candidates can continue full steam, subject to the usual ethical constraints but free from this particular ethical worry. We also underscore the case for testing vaccines in a shared platform.

A Vaccine Governance Dilemma

A clinical trial's data safety monitoring board (DSMB) may be the first to perceive that a candidate vaccine is

Researchers are currently pursuing multiple coronavirus disease 2019 (COVID-19) vaccine candidates and will have to come to grips with the ethics of how to proceed with clinical trials. When weighing the various public health priorities, it is, in the final analysis, ethical to test one purportedly less-promising vaccine against the other or against placebo. Image credit: Dave Cutler (artist).

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promising, and more promising than another candidate. Indeed, these vaccines could be part of a single trial, with a single DSMB, consistent with the World Health Organization's (WHO's) Research and Development (R&D) Testing group's proposal for a large international platform trial of SARS-CoV-2 vaccine candidates (1). If that happens, the likely situation we described may also be known to the shared platform's DSMB or even to some of its investigators (e.g., if testing is complete for the promising vaccine but not yet fully analyzed or not yet peer reviewed, and the track record of the other vaccine, which may have just completed phase II testing, is widely known). With interim analyses, preprints, and even press releases now being presented publicly for SARS-CoV-2 studies, the situation described may also be known to the scientific and public health communities more generally.

In such a situation, continued testing of both unproven vaccine candidates will have obvious public health importance. At that point, no one will know yet which vaccine, if any, would be found to work best, or even to work adequately. Assuming that no vaccine would be rolled out without a randomized trial, an ethical problem may seem to arise. It may appear as though it'd be unfair to give study participants the less-promising vaccine, or to give them placebo, which is also less promising. Shouldn't investigators give participants what, at that stage, is thought to be in their best interests by all reasonable experts—namely, guarantee of the more-promising vaccine?

On first blush, it may seem unethical to continue to give participants vaccines or placebo that researchers consider less promising than the most promising intervention. Recently, one ethicist criticized what he calls "follow-up vaccine trials" because, he says, it is unethical to trial a novel vaccine when an effective product already exists (2). For example, as he points out, in spring 2019, the Democratic Republic of Congo's (DRC's) health ministry fiercely opposed testing new vaccine candidates against Ebola, given that a different vaccine (rVSV-ZEBOV) had already been deemed safe and efficacious/effective enough to be dispatched for compassionate use in individuals at high risk of infection (2, 3), although at the time, WHO wrote, "more scientific research is needed before the vaccine can be licensed" (4). Many ethicists object to placebo control for other prophylactic measures (5–7) and, in some cases, for prophylactic use of vaccines (2, 8). And inasmuch as the two vaccines would be part of a single shared platform, proponents of "equipoise" in clinical research, who demand that participants of no arm of a single trial receive a less-promising intervention than ones offered in any other arm (9–11), might seem committed to rejecting such a shared platform. Nevertheless, we shall argue that continued testing remains ethical in such a situation.

A New Question

Debates on testing vaccine and treatment candidates usually focus on circumstances different from the likely fall 2020 situation we've outlined. One oft-discussed situation is the comparative testing of advanced vaccine candidates when neither vaccine looks more promising overall and neither is more promising than placebo. For example, whereas one vaccine looked safer in phases I and II, the other had higher or more rapidly achieved immunogenicity in phase II, and there is no agreement that one of them is more promising, or more promising than placebo. Reasonable experts disagree on these questions. Indeed, with uncertainty about how well SARS-CoV-2 vaccines may work in the elderly, their ability to prevent infection and infectiousness (as opposed to disease only), and the number of doses required, there may be many dimensions on which vaccines could outperform one another, making different vaccines preferable for different uses. In such a situation, no one would object to using either other vaccines or a placebo for controls.

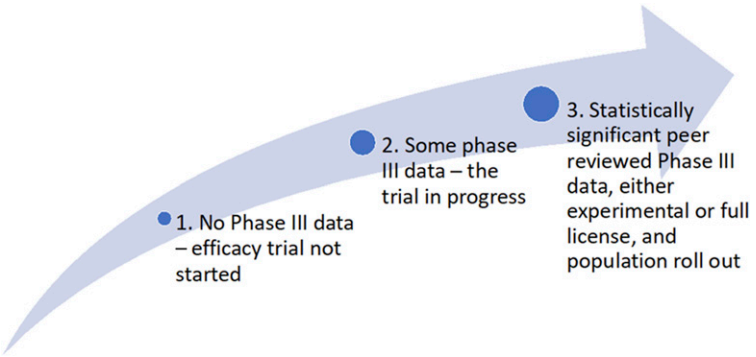

Fig. 1. The continuum of evidentiary stages for vaccine candidates around phase III testing. Note that the future coronavirus vaccine trial dilemma is likely to occur at Stage 2, whereas the DRC Ebola situation occurred at Stage 3.

Nevertheless, we focus here on the realistic possibility that there will be a time during which the decision on (further) efficacy testing must be made, and one of these alternatives looks more promising than either the other vaccine or placebo to all reasonable experts. In such a situation, no one would object to using either other vaccines or a placebo for controls.

Other debates pertain to circumstances in which only one candidate vaccine is being tested. In that case, many would usually agree that it is ethical to test the vaccine against placebo. Indeed, the efficacy of vaccines against human papillomavirus, dengue, and other infections have been recently tested with placebo control, when there was no licensed alternate vaccine candidate.

Still other ethical debates pertain to very different circumstances in which an intervention is already approved or otherwise available to some patients (e.g., to patients in richer countries). In that case, debates rage on the ethics of testing alternatives to that intervention, instead of giving the ready countermeasure to all study participants. (For the record, we believe testing should usually continue.)

But the situation in which we may be in fall 2020—where one vaccine is promising, and more promising than others, but not proven—falls in the middle. In that likely situation, an alternative vaccine exists, but it remains experimental. The situation is best captured by Stage 2 of Fig. 1.

Note also the difference between our question—namely, what alternatives it is ethical to offer to participants at that point in efficacy testing—and other, more familiar questions about vaccine efficacy testing ethics. More familiar questions include whether treatment assignment should be individually or cluster randomized (12), whether randomization should be between arms or stepped wedge (12), and whether exposure should be natural or artificial (13).*

No Better Vaccine Available

Following are the reasons why, in the scenario presented here, research should clearly continue. First, during the few months succeeding the decision on (further) efficacy testing, an approved vaccine for SARS-CoV-2 will remain unavailable for patients except those enrolled in the trial. So participants receiving only the less-promising vaccine would not be deprived of a beneficial intervention that they might have received outside the trial. In that respect, the situation would be very different from the spring 2019 Ebola-related circumstances in DRC, where one of the arms contained a vaccine candidate that was already being dispatched. So there was a reasonable case to be made that some participants might be deprived of a more-promising alternative available to them in the conventional care system. Anyone who opposed the situation in DRC could therefore remain unambivalently supportive of continued testing in the current crisis.

Efficacy testing, at least before approval and rollout, can and should proceed without delay.

In the realistic scenario described, there is likewise no concern about exploiting disadvantaged or disenfranchised participants' unfair lack of access to vaccines available to wealthier or better connected people, at home or abroad. In the likely fall 2020 dilemma we imagine, the trial could not exploit anyone in this way because the vaccine would remain unavailable to all outside the trial (11).

Some may insist that trialists ought to promote the very best interests of study participants, regardless of what is available for them or for others outside the trial. According to some ethicists, it is crucial to do so—even at the expense of using the scientifically (very) best study designs (14). Any of the alternatives discussed here offers at least some participants (e.g., recipients of the less-promising vaccine) less than the very best realizable prospects. A patient's clinician, thinking only of her clinical benefit, would usually advise her to take the most-promising vaccine if that option were offered, rather than take part in randomization that risks allocation to the less-promising vaccine. So investigator doctors should do the same, so the claim goes.

But there is simply no way to complete testing of either vaccine if the more-promising vaccine is simultaneously given to all study participants. Therefore, although being offered the more-promising vaccine would have been in all participants' best interests, this course of action is simply incompatible with continued testing—which we shall assume to be imperative. Put differently, to offer the very best prospects to everyone in the trial would make it all but impossible, in this case, to conduct a valid trial. What would the trial consist in, if not in comparison of a promising vaccine with something else, namely, with these candidates, or with placebo?

Broad Acceptance of Similar Designs

It may seem especially hard to justify giving some participants a less-promising alternative than to others when both groups are part of the very same trial. These are precisely the cases that raise demands for equipoise. Therefore, a further word is needed about a shared platform that tests both vaccines.

Note, however, that the WHO R&D Blueprint draft proposal, at least, can be seen as one for an adaptive platform trial, which is a recent newcomer in drug testing—in this case, applied to vaccines in the circumstances of a global public health emergency. According to the Adaptive Platform Trials Coalition, such platforms "study multiple interventions in a disease or condition in a perpetual manner, with interventions entering and leaving the platform on the basis of a predefined decision algorithm" (15). Many use "response-adaptive randomization" rules. Those rules preferentially assign interventions that perform most favorably; they also trigger the addition or termination of a study arm or spur the transition from one study phase to another (15). Such a common protocol has been recommended for emerging infections, albeit for therapeutics not vaccines (16). Although adaptive platform trials may have never been used for evaluating vaccines, the WHO group's proposal simply translates this strategy to vaccine testing in a public health emergency.

Tellingly, even bioethicists who are generally committed to a requirement of equipoise in clinical research, and who generally demand that participants of no particular arm get a less-promising intervention tested on them than ones in any other arm, approve of adaptive platform trials and consider their risk–benefit balances for participants to be fair (17, 18). Offering some participants less-promising interventions than those offered to other participants should therefore be widely accepted during vaccine testing in the current public health emergency, even in different arms of a single-platform trial.

For these two reasons, comparison of the efficacy of all vaccine candidates with that of others and with placebo could remain permissible even after preliminary efficacy testing in the possible fall 2020 situation we described, in which one candidate is more promising than either placebo or other candidates but is not (yet) proven. Indeed, an adaptive-platform trial would

*WHO Ethics Working Group (2014) Ethical issues related to study design for trials on therapeutics for Ebola virus disease, October 20–21, 2014 meeting.

be appropriate and help limit any delay to rollout; tests based on WHO's R&D Testing draft proposal for a shared platform [which could use the testing method espoused by WHO, or faster methods (13)] could offer participants a fair balance of risks to benefits.

In the practical dilemma that we may well face in the coming months, let no ethicist's sheer misunderstanding of the nature of the situation become a barrier to vaccine testing. Efficacy testing, at least before approval and rollout, can and should proceed without delay.

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