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VIEWPOINT

How to Test Severe Acute Respiratory Syndrome Coronavirus 2 Vaccines Ethically Even After One Is Available

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Although vaccines against severe acute respiratory syndrome coronavirus 2 have now been found safe and efficacious, there remains an urgent global health need to test both these vaccines and additional vaccines against the same virus. Under variable conditions, either standard or unusual designs would for both familiar and often-missed reasons make continued testing possible and ethical.

Keywords. randomized controlled trials as topic; COVID-19 vaccine; ethics.

Several severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines have now proven highly efficacious, but there remains enormous value in completing the efficacy testing of others. Some of the more than 200 in development may be more efficacious at blocking infections, provide more durable protection, be more successful against particular strains, be easier to store and deliver, work better in some subpopulations, or be cheaper, encourage price competition, or simply increase the total supply of vaccines available for all nations. There is also value in testing proven vaccines further for their impact on infections [1] and new viral strains, and a number of other open scientific and public health questions [2, 3]. In short, even after approval and the beginning of rollout, we still need to test both first-generation vaccines (1GV) and second-generation vaccines (2GV).

Some presume that there are "compelling reasons why it would be unethical to trial a [2GV] when an effective [1GV] exists already" [4], eg,

1. *Risk to individual participants.* It may seem wrong for participants to randomize them to anything short of the proven-efficacious vaccine: "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" [4]. Randomization to placebo may seem especially problematic [5–7].
2. *Large local public health toll.* Statistically meaningful trial results usually require trial sites with high community spread, but what such communities need is proven vaccines, not merely experimental vaccines or placebo [4, 5].
3. *Difficulties recruiting.* Inasmuch as individuals understand the risk, it would be hard to obtain their free consent to trial participation [8]. Although a true altruist may enlist (and remain) in the trial occasionally, testing whether a 2GV is superior to 1GV would require even more participants than the ongoing 1GV trials.

Various trial designs can, under certain conditions, overcome this reasoning. What follows focuses on testing 2GV yet to enter efficacy testing. Presumably, our conclusions apply a fortiori to 2GV already in efficacy testing and in whose trials some or all vaccine doses have already been administered.

A RANDOMIZED CONTROLLED TRIAL COMPARING ONE OR MORE 2GV TO 1GV

Trials comparing standard of care to more promising, yet still experimental, interventions happen routinely. Trials comparing two vaccines proven highly efficacious (eg, to ascertain their comparative efficacy with specific, and perhaps the very same, dose schedules, viral strains, incidence levels [9], and other factors that may influence efficacy) would be entirely legitimate—although potentially too large to be manageable.

A randomized controlled trial (RCT) comparing 2GV to 1GV could also be legitimate if the 2GV is slightly less promising than the 1GV, giving the 2GV-arm participants slightly worse prospects than participants of the 1GV arm (and slightly worse than their own prospects if they received 1GV outside the trial). For example, it would be permissible to trial a 2GV with (thus far) a slightly higher risk of mild side effects that does not require cold storage, a hurdle to vaccine delivery that some warn may leave 3 billion people without vaccine access. That's because a small diversion

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from 2GV participants' best interests would be easily condoned by these participants' autonomous altruistic consent to the diversion and the compelling public health need to test 2GV [10]. That same rationale may also permit testing a 2GV in young college students, who are at very low risk of developing severe disease, for its impact on infections.

A comparative trial could also be ethical and possible when what blocks access to it at the trial site is a simple shortage of the 1GV, and not injustice [3, 7]. The trial would then not deny 1GV to anyone who, in a just world, would have accessed it at that point. The public health and recruitment issues mentioned here would not arise either. Participation in the study should not delay participants' access to authorized vaccines when they become available.

If, more realistically, vaccines are not always distributed fairly, that might initially raise worries of exploitation. The trial's justification, or patients' motivation for enlisting in it, might take advantage of such patients' unfair lack of access to the 1GV supplies that rich nations have cornered. It is possible that this is what may underlie the curious dearth of open consideration for conducting RCTs in low-income countries with virtually no vaccine access: what blocks that access is rich nations' wrongful hoarding of the global 1GV supplies. Surely, however, if lower income countries, which are not responsible for the injustice, set up a trial comparing the proven 1GV to 2GV to serve their own goals (eg, to tell how these vaccines compare in local conditions), that would seem permissible: "agreements are not unjust or exploitative simply because they arise out of unjust background conditions . . . there is a distinction between taking advantage of unfairness (or misfortune) and taking unfair advantage of unfairness (or misfortune)" [11]. Low-income nation trialists would be able to recruit easily thanks to unfair misfortune, but that would not necessarily make their interaction with participants exploitative. Vaccine developers should endeavor to ensure their vaccine is made available to the general population in the country or region where it is tested, if it is proven to be efficacious and authorized or licensed.

AN RCT COMPARING ONE OR MORE 2GV TO PLACEBO

A placebo-controlled 2GV trial may generate useful public health knowledge; that is, if either (1) doses of the 1GV, necessary for a comparison to 2GV, are unavailable or (2) the designated use of the 2GV is not as a substitute for an otherwise available 1GV, but as the only available and affordable vaccine for certain populations. Under such conditions, rather than how the vaccines compare, the decision-relevant scientific question would be whether the 2GV imparts substantial protection, a question better explored by comparing it with placebo (as was the case in a rotavirus vaccine study in India) [10].

Nevertheless, a World Health Organization group assumed that once a SARS-CoV-2 vaccine is proven, "subsequent vaccines would then have to be compared with it rather than with a placebo" [6]—perhaps for reasons 1–3 outlined previously. We would contend, partly based on earlier World Health Organization work [10], that conditions equivalent to the ones described here for 2GV versus 1GV trials may obtain and permit 2GV versus a control that involves placebo, delayed vaccination, or another comparison that clearly denies the control arm the proven 1GV for a period.

Note first that when a placebo-controlled trial offers the 2GV to participants in one arm (and placebo to those randomized to the other), participating can be beneficial in prospect. It raises the prospects of the individual from no imminent chance of obtaining a vaccine to a chance (often 50%) of being randomized to receiving that 2GV. The person loses no opportunity to get vaccinated inasmuch as he or she would lack such an opportunity otherwise. As mentioned, ethical worries might arise that this benefit exploits an unjust lack of access to vaccine protection outside the trial. However, placebo-controlled study recruitment can likewise sometimes occur when the candidate participant's delayed access to vaccine protection is perfectly just in the face of scarcity [3, 7]. The first modern randomized control trial, which tested streptomycin against pulmonary tuberculosis in the United Kingdom in 1948, did that when streptomycin was scarce in the United Kingdom. The 2008 Oregon health insurance experiment was undertaken when Oregon wanted to expand Medicaid coverage to some of the many people who could use such coverage. Similar ideas of random allocation in the service of both science and ethical distribution were recently floated for testing the effects of Remdesivir in coronavirus disease 2019. Finally, a low-income country unjustly deprived of access to 1GV could ethically test a locally produced or otherwise accessible 2GV versus placebo (eg, to answer what is unfortunately most relevant to its public health needs: whether the 2GV is much better than nothing).

Even in a country with good 1GV access for participants, some suggest that "Inviting participants who are at low risk of severe disease to remain blinded and stay in the trial for a longer period can be acceptable when it offers the potential to collect data that might be helpful for addressing the pandemic," so long as their consent to remain in the trial and incur that risk is fully informed, and that period is short enough to keep that risk "low and justified" [7]. We concur, but also wish to extend this to new recruits and to longer periods. In principle, even when the risk of joining a new trial or of remaining in an existing one is not so low, that risk can remain justified per US regulations. What is needed is for the risk to remain reasonable in comparison to the study's social value—but the value of helping to quash a disease that directly or indirectly affects billions is usually extremely high. And in our own view, volunteers' informed willingness to take on those risks increases the magnitude of risks that can be legitimately taken. The main problem with this option is its utter impracticality. It is unlikely that thousands of people around a

few trial sites would agree, with full information, to take on substantial risks. There is also the complex moral and epidemiological question of whether this is fair to their contacts.

CHALLENGE TRIALS, COMPARING ONE OR MORE 2GV TO 1GV, PLACEBO, AND/OR EACH OTHER

Scientifically, human challenge trials are particularly suitable for testing some of the most important questions that remain open (eg, how much 1GV and 2GV affect infection and infectiousness; the correlates and duration of their protection). Preparations for a vaccine challenge trial may be complete by the time 2GV are ready for testing, averting a central argument from summer 2020 against 1GV challenge trials [12]. Far from burdening high-transmission area response [13], challenge trials could be anywhere located and recruit from anywhere, with a low number of participants and hospitalizations, competing well on the public health and recruitment issues noted previously. Challenge trials would rely on the altruism of a small number of well-informed participants, a more realistic prospect than that of altruism among tens of thousands of patients eligible to 1GV. Indeed, challenge trials require much fewer participants, so this could make a superiority trial for 2GV dramatically more feasible. Challenge trial volunteers would remain isolated while infectious [14], largely blocking infection risks to their contacts. Although there are ethical and technical considerations for and against challenge designs [13–17], in our opinion, those are fully answerable [18], and this design should be given open-minded consideration, especially by those reluctant to permit large RCTs.

IMMUNE-BRIDGING STUDIES

If correlates of vaccine protection are discerned for 1GV (through earlier RCTs or, more easily, through earlier challenge trials), then fast and safe studies to verify that these specific immune responses are elicited by 2GV as well could provide important, and potentially sufficient, data in lieu of field studies.

Immune-bridging studies could serve as alternatives to field trials and challenge trials. They could also complement 2GV challenge trials, generalizing their efficacy findings to populations at high risk of progression to severe coronavirus disease 2019, and provide the occasion for widescale safety testing of 2GV [14, 15]. The difficulty of holding RCTs urges closer consideration to relying on immune-bridging studies more widely.

Billions around the world need 2GV, and the compelling evidence for their safety and efficacy. Multiple conditions would make obtaining that evidence both ethical and possible.

Notes

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REFERENCES

1. Mehrotra DV, Janes HE, Fleming TR, et al. Clinical endpoints for evaluating efficacy in COVID-19 vaccine trials. Ann Intern Med **2021**; 174:221–8.
2. WHO Ad Hoc Expert Group on the Next Steps for Covid-19 Vaccine Evaluation. Placebo-controlled trials of covid-19 vaccines—why we still need them. N Engl J Med **2020**; 384: e2.
3. Rid A, Lipsitch M, Miller FG. The ethics of continuing placebo in SARS-CoV-2 vaccine trials. JAMA **2021**; 325:219-20.
4. Monrad JT. Ethical considerations for epidemic vaccine trials. J Med Ethics **2020**: **46**:465–9.
5. Cohen J. Early approval of a COVID-19 vaccine could stymie the hunt for better ones. Science **2020**; 370:389–90.
6. Krause PR, Fleming TR, Ellenberg SS, Henao-Restrepo AM; WHO Ad Hoc Clinical Trial Expert Group. Maintaining confidentiality of emerging results in COVID-19 vaccine trials is essential. Lancet **2020**; 396:1611–3.
7. Wendler D, Ochoa J, Millum J, Grady C, Taylor HA. COVID-19 vaccine trial ethics once we have efficacious vaccines. Science **2020**; 370:1277–9.
8. Beckett F. Is it worth carrying on as a guinea pig, if a vaccine has already been found? Guardian 28 November **2020**.
9. Kaslow DC. Force of infection: a determinant of vaccine efficacy? medRxiv **2021**. doi:10.1101/2021.01.21.21250235.
10. Rid A, Saxena A, Baqui AH, et al. Placebo use in vaccine trials: recommendations of a WHO expert panel. Vaccine **2014**; 32:4708–12.
11. Wertheimer A. Exploitation. Princeton NJ: Princeton University Press, **1999**.
12. Deming ME, Michael NL, Robb M, Cohen MS, Neuzil KM. Accelerating development of SARS-CoV-2 vaccines—the role for controlled human infection models. N Engl J Med **2020**; 383:e63. doi:10.1056/NEJMp2020076.
13. Kahn JP, Henry LM, Mastroianni AC, Chen WH, Macklin R. Opinion: for now, it's unethical to use human challenge studies for SARS-CoV-2 vaccine development. Proc Natl Acad Sci U S A **2020**; 117:28538–42.
14. Eyal N, Lipsitch M, Smith PG. Human challenge studies to accelerate coronavirus vaccine licensure. J Infect Dis **2020**; 221:1752–6.
15. WHO Working Group for Guidance on Human Challenge Studies in COVID-19. Key criteria for the ethical acceptability of COVID-19 human challenge studies. Geneva: WHO, **2020**.
16. Shah SK, Miller FG, Darton TC, et al. Ethics of controlled human infection to address COVID-19. Science **2020**; 368:832–4.
17. Steel R, Buchak L, Eyal N. Why continuing uncertainties are no reason to postpone challenge trials for coronavirus vaccines. J Med Ethics **2020**; 46:808–12.
18. Eyal N, Caplan A, Plotkin SA. Human challenge trials of covid-19 vaccines still have much to teach us. BMJ Opin 8 January **2021**.