OPINION

For now, it's unethical to use human challenge studies for SARS-CoV-2 vaccine development

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The prospect of a widely available severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccine is an increasingly high priority for an effective response to the coronavirus disease 2019 (COVID-19) pandemic and an area of intense interest and attention for professionals, politicians, and the public alike. The understandable desire for such a vaccine has led to significant discussion and even some planning for the possibility of human challenge studies (HCS) as a tool for accelerating the process for identifying, testing, and developing an effective vaccine (1–3).

Typically, undertaking HCS in vaccine development requires that the disease for which a challenge would be introduced either has an available rescue therapy to treat those who become infected or the disease is known to be self-limiting. There is no rescue therapy for SARS-CoV-2 infection, and proponents of HCS have claimed that the infection is likely to be self-limiting and mild in young, healthy volunteers based on current understanding of the infection. If accurate, the basic requirements for undertaking an HCS could

Proponents of human challenge studies suggest that they will accelerate the time to approved vaccines. But the facts don't support those claims. Image credit: Shutterstock/REDPIXEL.PL.

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be met if conducted with that population. Proponents further argue that such HCS are ethically acceptable in the current pandemic. Most critically, they contend that these studies are likely to speed the development of effective vaccines.

But based on our assessment of these arguments, we disagree. We believe it is unethical to move forward with such trials at the current time. Whereas proponents of these studies suggest that such studies will accelerate the time to approved vaccines, the facts fail to support these claims. HCS to address SARS-CoV-2 face unacceptable ethics challenges, and, further, undertaking them would do a disservice to the public by undermining already strained confidence in the vaccine development process.

Accelerating Vaccine Approval

There is general consensus among researchers, ethicists, and oversight bodies that HCS can be ethical, provided certain conditions are satisfied (4–6). Key among those criteria is the requirement that HCS generate sufficient social value to justify exposing healthy volunteers to uncertain risks with no prospect of direct benefit. Proponents of SARS-COV-2 HCS, notably a nonprofit called 1DaySooner started in April to advocate for such trials (7), contend that such studies will provide "enormous social value" by accelerating the timeframe for vaccine development and distribution, thereby saving thousands of lives (8).

The acceleration argument relies on several interconnected assumptions that prove problematic under deeper scrutiny. The first is that SARS-CoV-2 HCS can provide vaccine efficacy data faster than the standard vaccine pathway. Although comparative speed is an accepted scientific justification for conducting HCS, its conventional application is to circumstances in which conducting field studies would be prohibitively difficult because the target pathogen is rarely transmitted in the natural local environment (9). The opposite is true of conducting HCS in a pandemic environment. During the Zika pandemic, for instance, the ability to conduct field trials played a prominent role in a federal ethics committee determination that it was premature to proceed with Zika virus HCS (10). Widespread transmission of SARS-CoV-2 is already facilitating close to 10 active Phase III trials of SARS-CoV-2 vaccine candidates (11). With more field studies likely to follow, the necessity and relative speed of HCS becomes even less compelling.

Technical and logistical aspects of developing and implementing HCS further undercut the assumption that SARS-CoV-2 HCS would result in a viable vaccine faster than the traditional vaccine pathway. Before initiating definitive SARS-CoV-2 efficacy HCS, researchers must develop a suitable challenge model. This requires carefully selecting the challenge strain, manufacturing it in a BSL-3 laboratory that adheres to current Good Manufacturing Practice (cGMP), receiving regulatory approval from the Food and Drug Administration (FDA) or other regulator to administer it to human volunteers, and conducting dose-escalation studies to determine the target dose of the challenge agent that will elicit the level of illness necessary for determining the primary outcome of the efficacy studies. Vaccine experts estimate that in the context of SARS-CoV-2 HCS those steps will collectively take one to two years to complete, leading them to conclude that such studies are "unlikely to accelerate the establishment of vaccine efficacy" (12).

Even if SARS-CoV-2 HCS were to accelerate vaccine development, it is unclear that the FDA will consider data from HCS in its licensing decision. Although the FDA's recent approval of a cholera vaccine based on efficacy data from HCS might signal the agency's willingness to make similar determinations in the future (13), the agency is not likely to do so in the context of SARS-CoV-2. The FDA's latest Guidance for Industry on developing SARS-CoV-2 vaccines not only omits HCS from its discussion of expedited trial designs but also states that to meet vaccine approval standards, "late phase clinical trials. . .will likely need to enroll many thousands of participants," including "adequate representation of elderly individuals and individuals with medical comorbidities" (14). Although it is conceivable that HCS initiated 12–24 months from now could generate efficacy data to support the necessary Phase III results for licensing (12), those HCS would not accelerate the current pathway, in which multiple Phase III trials are underway and a licensed vaccine is possible within 6 months.

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Ultimately, the social value of SARS-CoV-2 HCS (in terms of deaths averted) hinges on the premise that people at greatest risk of COVID-19–related mortality will receive a safe and efficacious vaccine sooner than they would without HCS. Those high-risk groups include older adults and people who are immunocompromised or have comorbidities, as well as members of Black, Latinx, and Native American communities—groups who are, as emerging evidence demonstrates, at disproportionate risk of serious COVID-19–related outcomes (15). Current proposals and guidelines for conducting SARS-CoV-2 HCS, however, recommend only enrolling young, healthy adults (7, 8, 16, 17). Although that strategy arguably reduces the risks associated with HCS, it jeopardizes the generalizability of trial results (18, 19).

Because the safety and efficacy of vaccine formulations and dosing may differ between populations (e.g., based on age), the social value of HCS—in terms of reducing mortality among those at greatest risk—is likely limited. Moreover, the social value of vaccines depends in large part on whether people get vaccinated (20). Ongoing, standard SARS-CoV-2 vaccine trials, however, are currently struggling to recruit participants from some communities of color, and in

recent polls respondents who self-identified as Black were more than twice as likely as white respondents to be leery of taking a SARS-CoV-2 vaccine (21). Well-intentioned recruitment from communities of color into HCS may nevertheless evoke historical mistrust over discrimination in research and elicit concerns of exploitation, either of which could detrimentally impact vaccine uptake in at-risk communities.

Acceptable Risk–Benefit

For research to be ethically sound, the relationship between risks and potential benefits must be reasonable. IRBs are charged with making that assessment, but in the case of human challenge studies, knowledge about infection with SARS-CoV-2 and potential resulting COVID-19 illness continues to evolve; many unknowns remain. Despite the earlier belief that young, healthy adults (the proposed subjects) experience a mild form of COVID-19 and recover quickly, recent data have revealed that this population can experience significant adverse effects when they become infected (22–24). An additional shortcoming of HCS is that some risks of the vaccine itself may emerge only when a larger number of individuals have been vaccinated.

We find such HCS proposals to be flawed in their core claim about speeding vaccine development, and we believe that the risk–benefit balance for such HCS is both too uncertain and likely to be unacceptable, even with greater information.

Because the proposed HCS will enroll only young adults, the result is a much narrower potential benefit than proponents have assumed. Vaccine trials using the standard methodology would still be needed to ensure safety and efficacy for the vast numbers of people who do not fit the narrow inclusion criteria of HCS.

Taken together, these considerations make it virtually impossible for IRBs to make an appropriate assessment of the risk–benefit balance. If the potential benefit is low because Phase III field efficacy studies would still be necessary, and larger numbers of participants would be needed to obtain adequate safety data, this would call into question an acceptable balance of benefits over the risks to participants in HCS.

The uncertainty of information about risks to participants from both the infection and the vaccine makes adequate disclosure next to impossible in the informed consent process. Along with the unknown potential benefits to groups other than the age cohort in the study, accurate, detailed information in informed consent documents is bound to be limited. Despite acknowledgment in consent forms that participants may not experience direct benefits from the experimental intervention, it is entirely possible that volunteers may labor under a "preventive misconception" that they will receive some protection from infection by their participation. This is analogous to the so-called "therapeutic misconception" in research on experimental therapies, in which research subjects agree to participate in part based on the misconception that they are likely to gain some therapeutic benefit as a result.

Very little has been said so far in the literature about payment or other incentives to potential HCS volunteers (25, 26). A misconception about immunological protection is only one of several such incentives, which could include monetary payments, a common inducement in HCS for other diseases. More information is needed about such incentives or misconceptions before IRBs can meaningfully assess the ethical acceptability of proposed HCS for COVID-19.

Resources Required

Current arguments in favor of SARS-CoV-2 HCS fail to account for the pandemic realities of global, national, and local resource constraints and the extent to which diversion of scarce health care resources could compromise local pandemic response.

Any proposed SARS-CoV-2 HCS would necessarily provide all medical care for study participants who become infected during the trial. Some have even advocated that participants receive "priority" access to critical care resources (clinical support, ventilators, drugs, and other interventions) "notwithstanding the possibility of severe shortages" (16). Others who have closely examined the ethical requirements for these trials, in contrast, argue convincingly that HCS sponsors should be required to show that HCS do not "unduly compete for scarce resources" that affect local pandemic response (5).

As part of a risk minimization strategy, trial sites should be geographically located in high prevalence areas to reduce the risk associated with intentional infection [i.e., recruiting those who have an otherwise high baseline risk of exposure (16)]. Unfortunately, these are areas with the most demands on essential public health resources.

The reality is that essential supplies for conducting SARS-CoV-2 HCS are already limited because of the pandemic (18), with communities, states, and even national governments competing for access (e.g., personal protective equipment, ventilators, oxygen, supportive care, treatments such as remdesivir and convalescent plasma, and even testing). Human resources are similarly strained by the pandemic, and HCS may remove critical trained personnel from provision of urgent health care: Highly sought-after health care workers on the study team must have training in biocontainment and infection control, and planning must further account for worker quarantine and medical treatment if they test positive.

We believe that the unique impact that a SARS-CoV-2 HCS places on scarce and already strained resources during a pandemic must be given considerable weight in any justification of these trials. In contrast to community-based field studies, which are effectively outpatient rather than inpatient trials, a SARS-CoV-2 HCS will place greater demands on

medical resources, including specially trained personnel, biocontainment units, and dedicated hospital rooms. Decisions to further burden an already battered public health system with intentional infection—including the potential for unintentional release—will involve hard choices and consultation with, and buy-in from, affected stakeholders, including public health authorities, regulators, regional and local institutions, health care providers, and communities already hard hit by infection. Coordination is essential to ensure that decisions are not made unilaterally (27). These efforts will take time, further slowing any hoped for promise of acceleration.

HCS and Public Mistrust

Undertaking an HCS in the context of this pandemic risks fueling and potentially worsening levels of public mistrust. All aspects of the public health response to the pandemic have been politicized, feeding concerns across a wide spectrum of the population (20). This includes those traditionally skeptical about vaccine policy (so-called anti-vaxxers) as well as proponents of vaccine development and drug discovery who fear that approval will be hasty in response to intense political pressures, a concern only reinforced by both Russian and Chinese "approval" of candidate vaccines that had not gone through a phase III trial. Concerns within the science community have prompted hundreds of medical and public health experts to issue an open letter to the FDA calling for assurances that full and transparent review of vaccine candidates will be undertaken, and nine pharmaceutical companies have felt the need to make a collective pledge "to uphold the integrity of the scientific process" (28, 29). Introducing HCS that do not meet basic principles of research ethics and vaccine development are likely to play into concerns that shortcuts are being taken and that science is being politicized, further undermining public trust (19).

In sum, the severity of COVID-19, and the lack of a cure or effective treatment, make it unethical, at this point in time, to institute HCS for the development of a SARS-CoV-2 vaccine. We think proponents' core claim about speeding vaccine development is flawed, and we believe that the risk–benefit balance for such HCS is both too uncertain and likely to be unacceptable, even with greater information. In addition, issues of resource allocation are critically important and difficult to justify. Vaccine trials aiming to undertake risky and uncertain steps in human subject research—particularly those that depart from standard approaches to protection of subjects in HCS—risk further exacerbating increasing levels of public mistrust related to SARS-CoV-2 vaccine development. Taken together, we believe that these arguments make undertaking SARS-CoV-2 HCS both unwarranted and unethical. At this critical moment in the response to the pandemic, it would do more harm than good.

1 J. Steenhuysen, U.S. to make coronavirus strain for possible human challenge trials. *Reuters*, 14 August 2020. https://www.reuters.com/article/us-health-coronavirus-vaccine-challenge/exclusive-u-s-to-make-coronavirus-strain-for-possible-human-challenge-trials-idUSKCN25A1EL. Accessed 14 September 2020.
2 H. Devlin, Coronavirus vaccine: Oxford team aim to start lab-controlled human trials. *The Guardian*, 16 July 2020. https://www.theguardian.com/science/2020/jul/16/coronavirus-vaccine-oxford-team-volunteers-lab-controlled-human-challenge-trial. Accessed 14 September 2020.
3 E. Callaway, Dozens to be deliberately infected with coronavirus in UK 'human challenge' trials. *Nature*, 10.1038/d41586-020-02821-4 (2020).
4 F. G. Miller, C. Grady, The ethical challenge of infection-inducing challenge experiments. *Clin. Infect. Dis.* **33**, 1028–1033 (2001).
5 S. K. Shah *et al.*, Ethics of controlled human infection to address COVID-19. *Science* **368**, 832–834 (2020).
6 World Health Organization (WHO) Working Group for Guidance on Human Challenge Studies in COVID-19, "Key Criteria for the Ethical Acceptability of COVID-19 Human Challenge Studies" (WHO, 2020). https://www.who.int/ethics/publications/key-criteria-ethical-acceptability-of-covid-19-human-challenge/en/. Accessed 26 October 2020.
7 1 DaySooner, "What is the potential impact of accelerating vaccine development?" and "FAQs." https://1daysooner.org/. Accessed 10 August 2020.
8 N. Eyal, Why challenge trials of SARS-CoV-2 vaccines could be ethical despite risk of severe adverse events. *Ethics Hum. Res.* **42**, 24–34 (2020).
9 B. Bambery, M. Selgelid, C. Weijer, J. Savulescu, A. J. Pollard, Ethical criteria for human challenge studies in infectious diseases. *Public Health Ethics* **9**, 92–103 (2016).
10 S. K. Shah *et al.*, *Ethical Considerations for Zika Virus Human Challenge Trials* (National Institute of Allergy and Infectious Diseases, 2017).
11 J. Corum, S.-L. Wee, C. Zimmer, Coronavirus vaccine tracker. *The New York Times*, 2020. https://www.nytimes.com/interactive/2020/science/coronavirus-vaccine-tracker.html. Accessed 13 September 2020.
12 M. E. Deming, N. L. Michael, M. Robb, M. S. Cohen, K. M. Neuzil, Accelerating development of SARS-CoV-2 vaccines–the role for controlled human infection models. *N. Engl. J. Med.* **383**, e63 (2020).
13 W. H. Chen *et al.*, Single-dose live oral cholera vaccine CVD 103-HgR protects against human experimental infection with vibrio cholerae O1 El Tor. *Clin. Infect. Dis.* **62**, 1329–1335 (2016).
14 U.S. Food and Drug Administration, "Development and licensure of vaccines to prevent COVID-19: Guidance for industry" (Docket FDA-2020-D-1137, FDA, June 2020; https://www.fda.gov/regulatory-information/search-fda-guidance-documents/development-and-licensure-vaccines-prevent-covid-19).
15 M. Webb Hooper, A. M. Nápoles, E. J. Pérez-Stable, COVID-19 and racial/ethnic disparities. *JAMA* **323**, 2466–2467. (2020).
16 N. Eyal, M. Lipsitch, P. G. Smith, Human challenge studies to accelerate coronavirus vaccine licensure. *J. Infect. Dis.* **221**, 1752–1756 (2020).
17 S. A. Plotkin, A. Caplan, Extraordinary diseases require extraordinary solutions. *Vaccine* **38**, 3987–3988. (2020).
18 E. Jamrozik, M. J. Selgelid, COVID-19 human challenge studies: ethical issues. *Lancet Infect. Dis.* **20**, e198–e203. (2020).
19 C. Grady *et al.*, So much at stake: Ethical tradeoffs in accelerating SARSCoV-2 vaccine development. *Vaccine* **38**, 6381–6387 (2020).

20 N. G. Evans, Human infection challenge studies: A test for the social value criterion of research ethics. *mSphere*, 10.1128/mSphere.00669-20 (2020).
21 W. Cornwall, Just 50% of Americans plan to get a COVID-19 vaccine: Here's how to win over the rest. *Science*, **30** June 2020. https://www.sciencemag.org/news/2020/06/just-50-americans-plan-get-covid-19-vaccine-here-s-how-win-over-rest. Accessed 12 August 2020.
22 CDC, Symptom duration and risk factors for delayed return to usual health among outpatients with COVID-19 in a multi-state healthcare systems network—United States, March–June 2020. *MMWR Weekly* **69**, 993–998 (2020).
23 S. Rajpal, *Cardiovascular magnetic resonance findings in competitive athletes recovering from COVID-19 infection*. *JAMA Cardol*, 10.1001/jamacardio.2020.4916 (2020).
24 G. A. G. Crameri *et al*., Reduced maximal aerobic capacity after COVID-19 in young adult recruits, Switzerland, May 2020. *Euro Surveill*. **25**, 10.2807/1560-7917.ES.2020.25.36.2001542. (2020).
25 H. Fernandez Lynch *et al*., Ethical payment to participants in human infection challenge studies, with a focus on SARS-CoV-2: Report and recommendations. *SSRN*, 10.2139/ssrn.3674548 (2020).
26 S. Holm, Controlled human infection with SARS-CoV-2 to study COVID-19 vaccines and treatments: bioethics in Utopia. *J. Med. Ethics* **46**, 569–573 (2020).
27 A. J. London, J. Kimmelman, Against pandemic research exceptionalism. *Science* **368**, 476–477 (2020).
28 L. Abbo *et al*., Letter to Stephen Hahn, Commissioner, Food and Drug Administration. https://cspinet.org/sites/default/files/COVID_Vaccine_Letter_to_FDA_8.5.2020.pdf. Accessed 12 August 2020.
29 K. Thomas, 9 drug companies pledge to 'stand with science' on coronavirus vaccines. *The New York Times*, 8 September 2020. https://www.nytimes.com/2020/09/08/health/9-drug-companies-pledge-coronavirus-vaccine.html. Accessed 12 August 2020.