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Severe Acute Respiratory Syndrome Coronavirus 2 Human Challenge Trials: Too Risky, Too Soon

To the Editor—Eyal et al [1] have recently argued that researchers should consider conducting severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) human challenge studies to hasten vaccine development. We have conducted (J. L.) and overseen (L. D.) human challenge studies and agree that they can be useful in developing anti-infective agents. We also agree that adults can autonomously choose to undergo risks with no prospect of direct benefit to themselves. However, we disagree that SARS-CoV-2 challenge studies are ethically appropriate at this time, for 3 reasons: (1) current scientific knowledge of SARS-CoV-2 infection is insufficient to manage risks; (2) autonomous decision making, while necessary, does not override concerns about risk; and (3) undertaking challenge studies now would imperil confidence in the research enterprise, potentially undermining the global response to the coronavirus disease 2019 (COVID-19) pandemic.

Current scientific knowledge is insufficient to manage the risks of severe disease or death among volunteers in SARS-CoV-2 human challenge studies, especially in terms of selecting low-risk volunteers [2]. New risks of COVID-19 continue to emerge, such as unexpected cardiovascular events [3] and strokes in otherwise healthy, young people [4]. Selecting a proper dose for a challenge study while protecting volunteers would be difficult given the high variability in patient responses [5]. There are no highly effective treatments, nor is there information about long-term health consequences of infection.

Eyal et al [1] allude to other research involving risks of severe disease or death, including human challenge studies for other diseases. But such studies—for example, malaria challenge trials—minimize and manage risks to volunteers by using well-characterized pathogens with known clinical sequelae in painstakingly defined subpopulations [6]. Malaria treatment with Food and Drug Administration–approved drugs is readily available, and decades of research enable selection of low-risk volunteers. Even so, unexpected events can happen: a genetic polymorphism affecting metabolism of the malaria treatment primaquine was found in a challenge study [7]. Had the disease been poorly understood, the results could have been catastrophic.

It is not obvious that the possible benefits of developing a successful vaccine in less time justify the risks SARS-CoV-2 challenge studies, as Eyal and colleagues suggest [1]. There is no guarantee that any trial, or series of trials, will produce a viable vaccine: consider vaccine research for human immunodeficiency virus or hepatitis C. There is also little precedent for the Food and Drug Administration to license a vaccine primarily based on evidence from challenge studies (recent approval of a cholera vaccine is an exceptional case [8]). Even promising results in challenge studies may not correlate with population-level effects [9], and additional field trials would be needed. If a vaccine is proved effective, obstacles to production and distribution might limit how many lives it saves [10].

Autonomous authorization (informed consent) is essential for protecting research volunteers' rights, and Eyal et al emphasize the legitimacy of a mature person's choice to accept risk [1]. However, people often make decisions in irrational or idiosyncratic ways—in life generally [11], and in research. Volunteers often believe that unproven experimental treatments will medically benefit them (therapeutic misconception [12]) or that unproven vaccines will protect against infection (preventive misconception [13]). Altruistic volunteers who sign up for potential challenge studies [14] amidst the global COVID-19 pandemic may also suffer from a misconception—an overconfidence that the research will provide substantial societal benefit [15]. Given the inherent uncertainty in vaccine development, this kind of optimistic bias could lead people to take risks without seeing the associated benefits, in conflict with their core values and interests. Furthermore, volunteers who have a change of heart after being infected with SARS-CoV-2 would have no opportunity to withdraw from the study that would reduce risk [16].

Beyond concerns about decision making, SARS-CoV-2 human challenge studies have the potential to be exploitative. There are disparities in power, information, and control between researchers and volunteers [17]. Economically disadvantaged people are often willing to join trials despite discomforts and risks because financial compensation is offered [18]. Thus, vulnerable members of the public

might bear a disproportionate burden of risks that are unjustifiably high.

Eyal et al [1] compare volunteering in a SARS-CoV-2 human challenge study to firefighting and living kidney donation, activities that are permissible despite their risks [19]. However, there are important differences between research and nonresearch activities. Clinical research is a complex, fragile enterprise based on shared understanding of risks, burdens, benefits, and values among diverse stakeholders [20]. In addition to rigorous research oversight, the research enterprise depends on stakeholders' mutual trust and willingness to adhere to certain expectations, including that researchers will prioritize the safety of study volunteers [21]. The fragility of the enterprise is due in part to issues noted: idiosyncrasies of human decision making, uncertain risks and benefits, and potential exploitation.

When study volunteers die or suffer serious harm at the hands of researchers, investigators themselves become complicit, potentially undermining the stakeholders' confidence in the research enterprise. One very bad outcome not only harms the individual volunteer, it harms the whole research process [22], and public trust is likely to plummet [23]. Violations of public trust have ripple effects on research, public health efforts, and clinical care.

The current landscape facing the research and public health communities is fraught. Mistrust of research and of vaccines in particular is rampant; conspiracy theories, misinformation, and anti-science attitudes are spreading. Bad outcomes in a SARS-CoV-2 human challenge study could be devastating, as recent experience demonstrates that mistrust interferes with public health efforts in epidemic conditions [24].

Although SARS-CoV-2 human challenge studies are not ethically acceptable at present, this may change if the following conditions are met: (1) better characterization of factors leading to severe disease and death in SARS-CoV-2 infection, to definitively screen out high-risk volunteers; (2) availability of proved effective treatment to prevent severe disease and disease; (3) a clearer understanding of protective effects of immunity and the elucidation of the goal of a vaccine to guide dosing and end-point selection; and (4) a public engagement strategy to address the challenge study and the risks to participants. We agree that solutions to the COVID-19 pandemic must be expedited, and we advocate for efficient research and regulatory processes to support that goal. However, conducting SARS-CoV-2 human challenge trials now unjustifiably threatens both the well-being of volunteers and confidence in the research enterprise.

Notes

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Response to Dawson et al

To the Editor—Dawson et al [1] raise 3 concerns about human challenge trials to assess the efficacy of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines. First, that current scientific understanding is insufficient to know all the risks to volunteers, including potential long-term effects. However, assuming that the effects of artificial infection resemble those of natural infection, there is substantial evidence that, so long as only young and healthy people are recruited [2–5], the risk of death is comparable to that of live kidney donation [6–8]. Known and unknown nonlethal complications following infection are also possible, but based on the evidence to date, among young people, complications within the duration of follow-up that has been possible in the first months of this pandemic are likely to remain rare. It would be imperative that volunteers in challenge studies have a clear understanding of the known risks and of the possibility of yet unrecognized risks. That includes long-term risks whose frequency is unknowable, a familiar complication inherent in all first-in-human trials—including any phase III trials of novel SARS-Cov-2 vaccines.

Second, Dawson et al [1] question whether autonomous decision making by volunteers overrides concerns about risk, given that "people often make decisions in irrational or idiosyncratic ways," suggesting that irrational decisions are likelier in this case than elsewhere. We note that >28 000 individuals have already declared willingness to participate in SARS-Cov-2 challenge trials [9] and we think it unlikely that all of these are acting irrationally. Of course, not all may be suitable for a challenge trial, and a thorough informed consent process should make a determination on each selected candidate. Procedures for obtaining fully comprehending consent, familiar to research ethics since the 1980s, have been well established for novel interventions, including those for which risks are ill defined. Dawson et al note, "Given the inherent uncertainty in vaccine development, this kind of optimistic bias could lead people to take risks without seeing the associated benefits" [1]. However, this concern could apply to first-in-human vaccine trials, and even in phase 3 SARS-Cov-2 vaccine trials, there is, for example, an uncertain risk of the vaccine inducing enhancing coronavirus disease 2019 (COVID-19) disease [10].

Third, Dawson et al consider that the conduct of challenge studies would imperil public confidence in the COVID-19 research enterprise, potentially undermining the global response to the COVID-19 pandemic [1]. This we question. So long as investigators are open about the possibility of rare events occurring and this is made public knowledge, if these events do occur rarely (as might also happen in conventional vaccine trials), we think it unlikely that COVID-19 research or public health response would be affected, even if a rare volunteer did experience serious disease or death as a result of participation.

We recognize that challenge trials would raise fewer ethical worries if it were possible to exclude all volunteers at high