SARS-CoV-2 Human Challenge Trials: Too Risky, Too Soon

KEY WORDS: SARS-CoV-2, COVID-19, coronavirus, vaccines, human challenge studies, risk-taking, public trust, ethics

DISCLAIMER: Material has been reviewed by the Walter Reed Army Institute of Research and the Uniformed Services University of the Health Sciences. There is no objection to its presentation and/or publication. The opinions or assertions contained herein are the private views of the authors, and are not to be construed as official, or as reflecting true views of the Department of the Army or the Department of Defense.

FINANCIAL SUPPORT: No specific funding was provided for this preparation of this letter.

POTENTIAL CONFLICTS OF INTEREST: None.

AUTHORS:

Liza Dawson, PhD, MA
Chief of Bioethics
Institutional Review Board Chair
Research Integrity Officer
Walter Reed Army Institute of Research
503 Robert Grant Avenue
Silver Spring, MD 20910
(301) 319-7504
liza.dawson.civ@mail.mil

Jake Earl, PhD
Bioethicist
Walter Reed Army Institute of Research
503 Robert Grant Avenue
Silver Spring, MD 20910
(404) 702-6453
jacob.c.earl.ctr@mail.mil

Jeffrey Livezey, MD, MSc, LTC, MC, USA
Assistant Professor, Dept of Pediatrics
Deputy Director, Clinical Pharmacology
Program Director, Clinical Pharmacology Fellowship
USUHS
(301) 319-9872
jeffrey.r.livezey.mil@mail.mil

Eyal et al. have recently argued that researchers should consider conducting SARS-CoV-2 human challenge studies to hasten vaccine development [1]. We have conducted (JL) and overseen (LD) 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 three 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 COVID-19 pandemic.

Current scientific knowledge is insufficient to manage the risks of severe disease or death of 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. 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 sub-populations [6]. Malaria treatment with FDA-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. There is no guarantee that any trial, or series of trials, will produce a viable vaccine: consider vaccine research for HIV or hepatitis C. There is also little precedent for FDA 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 proven 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. 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. Further, 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. compare volunteering in a SARS-CoV-2 human challenge study to firefighting and living kidney donation, activities that are permissible despite their risks [19]. But there are important differences between research and non-research 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 mortality in SARS-CoV-2 infection to definitively screen out high-risk volunteers.
2. Availability of proven effective treatment to prevent severe morbidity and mortality.
3. Clearer understanding of protective effects of immunity and the elucidation of the goal of a vaccine to guide dosing and endpoint selection.

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 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.

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