Human Challenges to Accelerate SARS-CoV-2 Vaccine Development

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Is it ethical to intentionally infect volunteers with the coronavirus to test the effectiveness of vaccines? Yes, argues our expert Dr. Stanley A. Plotkin. In this special report, he gives an overview of the advantages, risks and ethical questions of human challenge studies about COVID-19.

(7 Minute Read)

The SARS-CoV-2 virus is epidemic throughout the world, causing death and disruption on a catastrophic scale. Prevention of SARS-CoV-2 infections is therefore both a medical and societal priority. Vaccine development normally takes years from conception to licensure, and current estimates for SARS-CoV-2 vaccines require at least 12 to 18 months. There are over 70 vaccine candidates that will require clinical trials including placebo-controlled phase 3 efficacy trials. Large populations will be required, and it may be demanding to find places where the incidence is high enough given recommendations for social distancing. Such trials may take six months or more, with thousands of deaths occurring meanwhile.

A strategy that could eliminate these difficulties is to use human challenge studies, in which well-informed volunteers are randomized to receive vaccine or placebo and then challenged or exposed to SARS-CoV-2 virus. Vaccines that demonstrate protection against the challenge could lead to rapid emergency use. Human challenges have been used in studies of influenza and cholera despite risks to the subjects. In order to minimize risk in studies of SARS-CoV-2 vaccines, only young healthy volunteers would be enrolled. An important additional advantage of human challenge studies is the identification of correlates of protection, which could then be used to infer the likely efficacy or lack of efficacy of the many candidates. Those candidates shown to induce the inferred protective immune response could then be deployed based on demonstration of safety without the requirement of large efficacy trials.

Challenge Virus

The choice of a challenge virus could be based on the following criteria: isolation from a patient with a serious SARS-CoV-2 illness; typical genetic sequence; growth to high titer in cell culture such as Vero cells; causing typical infection in monkeys; and free of any contaminating agents. The route of administration would be intranasal, starting with very low dosage to establish the lowest dose that causes consistent infection.

Volunteers and Physical Setting

Numerous people have already been moved to volunteer. One Day Sooner, an organization representing potential volunteers, reported at least 3,900 volunteers for SARS-CoV-2 challenge studies. The ideal volunteer would be individuals in good health aged 21 to 29, who would receive education about COVID-19, including full disclosure of all potential risks, and would sign detailed permission forms. They would be screened for coronavirus antibodies to identify those who have not been infected, and would be housed in a facility guaranteeing isolation with intensive care medical facilities for those who develop symptoms. Such facilities would have access to Remdesivir, convalescent serum, or other modalities potentially effective against SARS-CoV-2.

Sequence and Timing

The first challenges would be done on seropositive individuals, those with evidence of a previous SARS-CoV-2 infection. If seropositive individuals are resistant to challenge infection the next step would be to challenge seronegative volunteers with a low dose, increasing to a higher dose if infection was not obtained. If seropositives become infected, the study would end as protection might not be feasible.

Assuming that we establish that seropositives are resistant to challenge and seronegatives are not, the next step would be to challenge vaccinees. Note that vaccination could start simultaneously with the earlier challenges to ensure readiness. The choice of vaccines that would be given to volunteers would depend on the results of phase 1 tests now being conducted, with an effort to choose different types of vaccines. This will make it feasible to identify the responses that correlate with protection and perhaps the level of response that is protective.

Clearly the time required to determine if a vaccine can protect will vary according to how much time it takes to produce the challenge virus and how much time it takes to establish the right challenge dose. Considering that standard vaccine development should allow experimental use of vaccines within six months, the results of challenge experiments should be available by four months from start.

Limitations and Advantages

Obviously, the human challenge situation does not completely mimic natural SARS-CoV-2 infection, but it should be possible to determine whether prior infection is protective and to establish what immune responses lead to that protection. There are two major risks: one is that of a serious and potentially fatal disease in the volunteers, and the other that protection will not be mimicked in real-life exposure. Although it is certainly possible that real-life exposure to SARS-CoV-2 will be more of a challenge than our artificial challenge, it is unlikely that there will be no protection at all from immune responses demonstrated to protect against artificial challenge. Thus, a positive result would allow emergency extension of vaccination to those at high risk of natural exposure, such as health care workers. A license could be granted eventually to specific vaccines after accumulation of data on safety and efficacy in large-scale use.

Ethical Issues

Historically, challenge studies have been approved and carried out even with the risk of death (see *COVID-19 in Numbers* below). In assessing proposed vaccine challenge trials and deciding how much risk can be permitted for young volunteers to undertake, it is important to keep in mind the risks that many individuals (HCWs, first responders, cleaning personnel) face from the virus until a safe and efficacious vaccine protects them.

Death from COVID-19 occurs, even in the 20-29 age group described above. But the latest numbers put short-term fatality in this age group at roughly the same level as short-term fatality among live kidney donors (1 in 3000). In fact, in *healthy* volunteers of that age, fatality following SARS-CoV-2 exposure should be substantially lower than 1 in 3000.

Live kidney donation is permissible thanks to its benefit to others and the volunteer's altruistic free and informed consent. Likewise, SARS-CoV-2 human challenge trials should be deemed permissible given the benefits to many, many others and the participants' altruistic free and informed consent (per the recommendation above).

Selecting challenge volunteers exclusively from areas with expected high SARS-CoV-2 transmission during and after the challenge should make challenge trials even easier to justify. First, participants would be at high probability of being exposed outside the trial. Second, because trial participation would guarantee access to any necessary critical care (see above), participants would be better off in the worst-case scenario of severe COVID-19 than by relying on potentially clogged services in (high-transmission areas of) the field. All in all, the trial would carry a lower net-risk for participants than the risks of a live kidney donor, and potentially, a standard efficacy trial (where any enhanced severity takes place outside a controlled medical environment), or if they decline to join any trial (and must rely on overburdened care systems).

If great care is taken to ensure the informed consent of volunteers, correct participant selection and trial procedures, and the competency of research teams, challenge studies should achieve approval by sponsors and research review committees.

Register Now for the Global COVID Lab Meeting

Second Global COVID Lab Meeting With Dr. Bette Korber May 21st at 10 am EST

Much attention has been paid to Dr. Bette Korber's new study suggesting a more transmissible form of SARS-CoV-2 is emerging due to mutations of the Spike (S) protein. These findings have important implications for SARS-CoV-2 transmission, pathogenesis and immune interventions, and have been widely and sometimes not accurately reported in the press. Dr. Korber will present her findings on May 21st at 10 am EST.

If you haven't registered for the webinar yet, you can still do so using the link below. The Global COVID Lab Meeting is open to everybody who is interested in the research:

REGISTER FOR THE WEBINAR HERE

The Global COVID Lab Meeting is a bi-weekly webinar series, presented by the Human Vaccines Project. Last week more than 850 people from every continent registered to hear Dr. James E. Crowe, Jr. present his lab's latest advances on the development of monoclonal antibody interventions for COVID-19, which progressing toward the clinic in record time. If you missed the first webinar, you can watch it here.

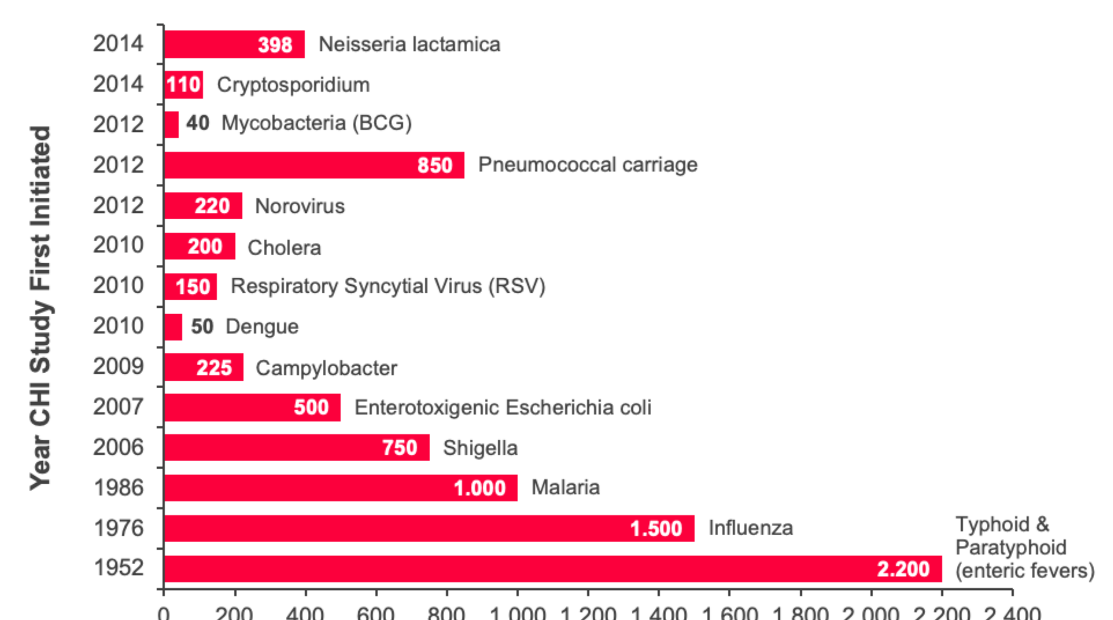
Must Read

The following articles cover important research around controlled human infection studies and COVID-19.

- Shah et al. describe an ethical framework for controlled human infection (CHI) studies for SARS-CoV-2 vaccines. They outline ethical conditions for conducting CHIs, including whether the potential social value justifies the risk, and provide guidance for various research stakeholders who are considering CHIs.
- Eyal et al. write in the Journal of Infectious Diseases that CHI trials could speed testing and rollout of an efficacious SARS-CoV-2 vaccine by several months and the net risk could be acceptable if certain conditions are met.
- The World Health Organization offers guidance to various research stakeholders on CHI studies by outlining necessary study criteria to ensure CHI's for SARS-CoV-2 vaccines are ethically acceptable.
- AVAC and TAG released a statement in response to the WHO guidelines that argue ethical CHI studies may not be possible in the absence of well-understood pathogenesis and approved treatment. They call for a standing committee of research stakeholders, including community representatives, to address the ethics of SARS-CoV-2 challenge trials and review protocols.
- STAT News points out the myriad issues involved in CHI studies, including observations that the time needed to develop the challenge model may negate anticipated acceleration.
- The outcome of a pre-COVID Welcome Trust sponsored meeting on controlled human infection studies offers a framework for considering benefits and barriers to the conduct of CHI studies in low and middle income country settings.

COVID-19 in Numbers

A History of Controlled Human Infection Studies



References for many of these studies are included in the comprehensive review by Darton (2015). Design, recruitment, and microbiological considerations in human challenge studies.
// https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5627502/