Human challenge trials are being pushed to develop a vaccine against the coronavirus

Benjamin Mateus
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Without much fanfare, news reports on vaccines against the coronavirus have been focusing on ways to expedite vaccine development through human challenge trials. In a nutshell, such trials would deliberately infect healthy volunteers with the coronavirus after they received the experimental vaccine, to determine its efficacy.

Democratic Representative Bill Foster of Illinois, leading the effort with 34 other members of the House of Representatives, sent a letter to the Food and Drug Administration, stating, "A more risk-tolerant development process is likely appropriate in the case of COVID-19 vaccine. The enormous human cost of the COVID-19 epidemic alters the optimization of the risk/benefit analysis."

Josh Morrison, a member of a supposed grass-roots effort, 1 Day Sooner, told *Nature* magazine, "We want to recruit as many people as possible who want to do this, and pre-qualify them as likely to be able to participate in challenge trials would they occur. At the same time, we feel that the public policy decisions around challenge trials will be better informed if they highlight the voice of people interested in participating in such trials." According to the group, thousands from over 50 countries have volunteered.

Vaccine trials are notoriously lengthy, with optimistic estimates of 12 to 18 months to vaccine rollout. Much of the time in vaccine trials is spent in testing the safety and efficacy of a vaccine. These placebo-controlled phase-three trials, in which one group receives the vaccine and another a placebo, typically involve several thousands of participants who are followed long enough to assess differences in disease incidence.

Human challenge trials have been conducted over hundreds of years but are trials of last resort and conducted under special circumstances and much oversight. In the case of COVID-19, they were first raised in late March in a proposal published in the *Journal of Infectious Diseases* by authors Nir Eyal, Marc Lipstich, and Peter G. Smith. They wrote in their abstract, "By replacing conventional phase-three testing of vaccine candidates [with human challenge trials], such trials may subtract months from the licensure process, making efficacious vaccines available more quickly."

The role of vaccines in global health cannot be understated. Smallpox was eradicated in 1977, the last case occurring in Somalia. Polio was eliminated in the United States in 1979. After a global campaign launched in 1994 by the United Nations Food and Agriculture Organization, rinderpest, a viral infection of cattle and domestic buffalo with near 100 percent lethality to livestock, was last confirmed in 2001 and declared eradicated in June 2011.

Measles, a virus for which only humans act as a host, killed 7 million to 8 million children annually until a decade of work led eventually to the development of a vaccine in 1963. Still, and despite an effective vaccine being available, measles infects more than half a million people across the globe, killing more than 140,000 people annually, mostly children under five years of age. Countries with the highest incidence include the Democratic Republic of Congo, Liberia, Madagascar, Somalia, and Ukraine—these five account for almost half of all cases worldwide.

The vaccination program in the United States, according to the CDC, has prevented more than 21 million hospitalizations and 732,000 deaths among children born in the last 20 years. Besides the morbidity and mortality associated with vaccinations, the economic benefits translate to $295 billion in direct costs and $1.38 trillion in total societal costs.

Efforts have been underway to develop a vaccine against the SARS-CoV-2 virus. Many see a vaccine as the only solution to the pandemic. With no pharmaceutical treatments that have shown clear mortality benefits, the present public health measures and supportive medical care remain essentially the only means by which to address the coronavirus and its impact on human populations.

According to the World Health Organization (WHO), there are currently six human trials in the race to develop a vaccine against SARS-CoV-2. Moderna, working in association with the NIAID, and INOVIO Pharmaceuticals are US-based trials, both in phase I. Moderna was the first to begin testing on humans in mid-March, building on its previous work on other coronaviruses. The University of Oxford, in Britain, is in phase I/II trial using a nonreplicating viral vector. The study is being led by Dr. Sarah Gilbert, who previously led work on "Disease X," a hypothetical pathogen with pandemic potential adopted by the WHO on their shortlist of blueprint priority diseases.

The other three trials are from China—CANSINO Biological, SINOVAC, and Beijing Institute of Biological Products. Seventy-seven other trials are in the preclinical evaluation stage.

In October 2016, the World Health Organization issued a statement on regulatory considerations for vaccine trials that pursue human challenge trials to expedite the development of these critical preventative treatments. They write, "It is essential that challenge studies be conducted within an ethical framework in which truly informed consent is given. When conducted, human challenge studies should be undertaken with abundant forethought, caution, and oversight. The information to be gained should clearly justify the risks to human subjects."

The WHO notes that if a pathogen has a high case fatality rate and there are no existing therapies to prevent or diminish the impact of the disease and preclude death, then it would not be appropriate to consider such trials. Based on reports, they are planning to publish a response to proposed COVID-19 human challenge trials soon.

Authors Eyal et al., in regard to concerns about a human challenge trial for COVID-19, admit that it could be possible that any protection demonstrated from a vaccine in a human challenge study may not be replicated when the vaccine is used in the population at large.

Additionally, there is no attenuated SARS-CoV-2 virus that can help participants avoid the hazards associated with COVID-19, as was indicated in the WHO's guidance, nor is there a therapeutic that could safely reduce the mortality risk after the participants are infected. More concerning, they write, is that "some vaccine constructs against coronavirus may induce more severe disease following infection, as has been reported in animal models of both SARS and MERS vaccine candidates." For this reason, they recommend challenging small groups sequentially to address this issue.

In support of the proposal, they state that these volunteers will have voluntarily consented to take these risks. They write, "In the present case, the study would involve multiple tests of comprehension of all risks so that the decision is deeply informed and voluntary." These participants would be isolated in treatment facilities and given the best care possible.

They also justified the conduct of the trial on the grounds that 1) the study will only recruit healthy participants, 2) the vaccine likely will benefit some of those in the trial, 3) in the absence of a vaccine they are likely to be infected anyway, 4) only people with a high baseline risk of getting exposed should be recruited, 5) participants would be afforded the best available care, and 6) potentially some therapeutics may be available to ameliorate morbidity or mortality.

Dr. Beth Kirkpatrick, professor and chair of the Department of Microbiology and Molecular Genetics at the University of Vermont, who runs a human challenge trial unit, explained to STAT that human challenge models for COVID-19 do not exist. She said it would take upwards of two years to design and approve one, given all the ethical and regulatory constraints that they entail.

One of the primary considerations with such a human challenge trial is to establish appropriate endpoints for symptoms—flu-like illness or pneumonia—and their implications for the efficacy of the vaccine. As yet, scientists are still puzzled over why some people become ill while others do not, and why symptomatic patients have a constellation of symptoms as compared to others. Additional concerns raised include if the data from such a study will translate to efficacy in all age categories, since the population being tested is young and healthy. Information about vaccine safety would also be compromised in these smaller trials.

The working class must treat with a great deal of skepticism the claimed benefits of such treatments and how such studies are being conducted, especially in the face of a pandemic with a novel coronavirus that at every turn has surprised and baffled scientists and researchers. Given the despair and upheavals caused by this pandemic, volunteers for these trials will likely come from among workers who are at the highest risk for contracting the infection because of the "essential" nature of their work.

That these human challenge trials are being vigorously supported by the political establishment is deeply concerning. The normal sentiments of mistrust, caution, and vigilance to protect the individuals involved seem absent. Ultimately, the race for vaccine development is rooted in capitalist relations which provide a tremendous profit incentive to the corporations that manufacture them, in addition to the general concern in ruling circles about promoting a back-to-work policy. The human challenge trials become a facilitator for both purposes.

The attempt to cut corners and expedite trials have already led to abject failures, which in the long run only delay the need to determine which therapeutics and vaccines will work and are inherently safe and which present adverse profiles. In the face of the frenzy and despair that is igniting social tensions, it becomes even more necessary to adhere rigorously to scientific principles. Even in desperate times, these principles will save time, life, and resources.