‘Challenge studies’: Should we be testing COVID vaccines by intentionally infecting volunteers?

To those who’ve never thought about volunteering to be intentionally infected to test a vaccine, the idea may at first seem a bit bonkers. But such “challenge” studies not only have a rich history, but nearly 40,000 people have already checked the box “I am interested in being exposed to the coronavirus to speed up vaccine development” at 1daysooner, a website and non-profit organization that launched in April.

Challenge studies go by other names: “controlled human infection models,” “human viral challenge,” and “purposeful infection.” Dripping virus-tainted saltwater into a volunteer’s nostrils enables researchers to track infection, and the immune system’s response to it, right from the start. The approach complements phase 3 clinical “field” trials of efficacy that await natural infection in the community.

A bioethical quandary

A challenge study can speed discovery of whether or not a vaccine works. That’s important because a vaccine hastens the herd immunity that builds from natural infection. But the risk of possible harm to a recipient of an experimental vaccine may be greater with intentional infection than with community exposure, simply because it’s more likely to happen.

Use of a placebo group is another matter.

A placebo is the gold standard in a conventional clinical trial collecting initial data. But it isn’t necessarily needed for a challenge trial when phase 3 results are forthcoming, as is the case for COVID-19.

Exposure to SARS-CoV-2 after taking an experimental vaccine is scary enough — it’s riskier if the “vaccine” is really a placebo. Philosopher Kent A. Peacock and psychologist John R. Vokey, both of the University of Lethbridge, argued against placebos in COVID challenge trials in STAT News.

Seema Shah, JD, professor of Medical Ethics at the Northwestern University Feinberg School of Medicine, explained the nuances of using placebos:

“If you are testing whether vaccines or treatments work, a placebo is usually necessary. Challenge studies can create a reliable model of infection where researchers learn what dose is needed to infect all volunteers but not make them too sick, and then you wouldn’t use a placebo. Models are also used to investigate transmission and learn about the early stages of infection, and those don’t require placebo.”
Several prominent bioethicists who’ve given the matter of COVID challenge trials much thought support the idea.

Bioethicists Stanley A. Plotkin from the University of Pennsylvania and Arthur Caplan from New York University call developing and distributing an efficacious COVID-19 vaccine a “moral imperative for the world” in the journal Vaccine, calling for immediate discussion of beginning challenge studies. Those conversations are now well underway.

A challenge study isn’t a new idea

Considering the design of COVID challenge trials might benefit from a look back at the history of protection of research subjects that led to the founding of the field of bioethics in 1970.

The National Research Act of 1974 inspired the Belmont Report of 1979 that established three requirements for people who volunteer for experiments, including clinical trials: respect for autonomy (ability to make decisions); beneficence (benefit); and justice (anyone who meets criteria can volunteer).

More recent renditions of participant protection expanded the definition of ethical research to embrace non-maleficence (“do no harm”) and, vital for vaccine testing, utilitarianism, which justifies actions if they benefit a majority. Even more on target, in 2014 an international group of ethicists interpreted utilitarianism to include “maximization of public health.”

Should we potentially harm a few to possibly save many? That’s the risk of challenge trials. With thousands still dying of COVID-19 every week, demonstrating efficacy another way, to complement the phase 3 trials, would save lives. Overlapping phases and early production of vaccine candidates will surely speed the conventional trajectory, but it isn’t enough.

Even challenge trials with coronaviruses aren’t novel. In 1967 researchers reported in the British Medical Journal experiments that dripped a new respiratory virus “surrounded by a fringe of club-shaped projections” collected from six students with colds into the noses of 26 healthy volunteers. Would they come down with the sniffles? Counting the number of handkerchiefs soiled daily revealed that half of them did. The culprit? Seasonal coronavirus 229-E.

Challenge studies sped development of an improved cholera vaccine in Baltimore from 1977 through 1995, using volunteers and strict quarantine protocols in a hospital to manage symptoms. Most participants who became ill suffered only mild, brief fever and diarrhea.
Over the years challenge studies have been deployed against a list of horrors: dengue, shigella, typhoid fever, giardia, tuberculosis, rhinovirus, norovirus, and most commonly, malaria and influenza. It was considered for Zika virus infection but never done because the epidemic abated, and led to approval of an Ebola vaccine in 2019 in a mere 10 months.

In December 2019, Ricardo Palacios from the University of São Paulo in Brazil and Shah wrote a prescient commentary in the journal *Trials*: “When could human challenge trials be deployed to combat emerging infectious diseases? Lessons from the case of a Zika virus human challenge trial.”

They couldn’t have known a novel virus was about to unfurl on the world.

**Volunteering, not coercion**

Challenge studies have a checkered past. [Doctors in Nazi Germany](https://en.wikipedia.org/wiki/Doktor_mit院子里) did it, but without consent.

So did Werner Henle, a virologist at the University of Pennsylvania, who tested an influenza vaccine on prisoners and intellectually disabled children in a state facility. Jonas Salk, of polio vaccine fame, tested flu vaccines on mental patients and prisoners in Michigan.
The huge difference between then and now is the word “forced.” Participants in challenge studies for COVID-19 vaccines will follow an informed consent process that ensures that they understand and accept the risks — including the unknown and the possibility of receiving a placebo, if that’s part of a particular plan.

It’s especially important for potential participants to read the consent forms carefully, because regulations have loosened a bit, in a way that may maximize the information gleaned from a challenge trial. Health and Human Services (HHS) updated the “Common Rule” from 1981 that stated that benefits to the participant and to society must outweigh risks to the subject. The amendment in 2018 stated that risks to the subject might be “reasonable,” not zero.

That regulatory flexibility is appreciated now. Jerry Menikoff, MD, JD, Director of the Office for Human Research Protections at HHS, points out that unlike challenge studies for malaria, cholera, and influenza, COVID-19 is riskier because we know less about it. Plus, there’s no “rescue” treatment if an experimental treatment harms someone.

The flip side of potential risk is potential benefit. In a challenge study, investigators can track the nuances of the immune response and degree of viral shedding from the precise start of infection, something not possible in the community, where conventional vaccines are tested. What we can learn from challenge studies may outweigh the concerns. Protocols can be designed to compare vaccines using the fewest volunteers possible, such as by using one placebo group for multiple vaccine candidates.
Bioethicist Nir Eyal, PhD, and epidemiologists Marc Lipsitch, PhD, and Peter G. Smith, DSc, added perspective in an article in *The Journal of Infectious Diseases*. They compare the sacrifice of a challenge study participant to those of volunteer firefighters, participants in drug trials, members of the military, and living organ donors.

**How challenge studies will unfold**

In June, the Advisory Group on Human Challenge Studies from the World Health Organization (WHO) released a draft of an 81-page “technically valid roadmap” to guide discussion among bioethicists, public health experts, epidemiologists, and physicians. It’s currently open for public comment. The report is more specific than a similar guide published in 2001 from NIH researchers.

The WHO document begins with “factors that warrant special caution” when conducting a challenge study for COVID-19: severity, high transmissibility, deaths of young healthy individuals, activity of the virus on surfaces for hours, lack of rescue treatment, and the surprises that the evolving pandemic brings. These are the factors that give pause to thoughts of including placebo arms. Then the document lists steps.

First is creation of “challenge strains” of the virus for the volunteers. Four strains are being considered because they represent the distribution of SARS-CoV-2 around the world.
Genetic modification of the challenge strains can insert telltale DNA “tags” that enable tracking of distinct viruses, and other tweaks can render the viruses milder than the predominant natural strains. If a vaccine fails to protect, a person wouldn’t get too sick.

The WHO group decided that participants should be between ages 18 and 25, who are less likely to develop severe symptoms, if any.

Next, the test virus, or placebo, is placed in the nostrils using a pipette, rather than a nasal spray that can shoot virus deep into the lungs. Experiments have shown that three doses are needed to infect most, if not all, participants.

The volunteers then will spend up to 3 weeks in single rooms on isolation units in facilities that have constant monitoring from a nursing station and presence of an expert physician, availability of ICU equipment, and existing treatments like remdesivir and steroids, until PCR tests are negative. The protocol also includes mental health screening for ability to tolerate the isolation. Some of these places were developed for influenza studies.

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Researchers can analyze mounting viral load as well as the unfolding immune response in real time in participants who’ve been infected, categorizing T cells, identifying the viral antigens that different antibodies attack, and charting inflammatory markers in blood. They’ll also be on the lookout for “disease enhancement,” which is when a vaccine worsens an infection.

No challenge trial for a COVID-19 vaccine has yet to begin, and details are still being worked out. The 19 members of the Advisory Group agreed on using young people, four viral strains, and existing treatments, but were split on three other issues: whether studies should proceed even if no better rescue treatments come along; whether a vaccine that protects young people will work on older people or those with pre-existing conditions; and whether the study should or will accelerate regulatory approval, including emergency use authorization. Perhaps comments from the public will help to flesh out these issues.

Where are we now?

Interest in challenge trials for COVID-19 has been building.

Seema Shah and her colleagues published a framework and analysis in Science in May that included “developing a challenge strain, drafting consensus protocols that address ethical concerns, and engaging stakeholders to enhance their social value, minimize risks, and build public trust.”

By midsummer, Adrian Hill, MD, PhD, director of Oxford University’s Jenner Institute, made the media rounds to discuss their candidate vaccine, the adenovirus-based ChAdOx1 nCoV-19, noting:
We’re hoping to be doing challenge trials by the end of the year. This might be in parallel or might be after the phase three trial is completed. They’re not competing options, they’re complementary.

Phase 3 trials of the vaccine are ongoing or about to begin in the UK, Brazil, South Africa, Japan, Russia, and the US, but were temporarily paused on September 8 due to a participant becoming ill.

Even if challenge trials start soon, making sense of findings will take time. Cautioned Meagan E. Deming, MD, PhD, of the Center for Vaccine Development and Global Health, University of Maryland and colleagues in the September 3 New England Journal of Medicine, developing “a robust challenge model for testing SARS-CoV-2 vaccines” may take a year or two. “Investigators at potential sites should begin soon to engage stakeholders in the scientific, regulatory, public health, and local communities.”

Bioethicists Plotkin and Caplan eloquently sum up the challenge of challenge studies:

“Deliberately causing disease in humans is normally abhorrent, but asking volunteers to take risks without pressure or coercion is not exploitation but benefitting from altruism. As Shakespeare put it, ‘Desperate diseases by desperate measures are relieved.’”

Those who volunteer to receive an experimental vaccine and then be infected with a potentially lethal viral pathogen exemplify selflessness. They are the polar opposite of the people who flagrantly ignore public health recommendations to prevent spread of COVID-19.

Ricki Lewis has a PhD in genetics and is a genetics counselor, science writer and author of Human Genetics: The Basics. Follow her at her website or Twitter @rickilewis