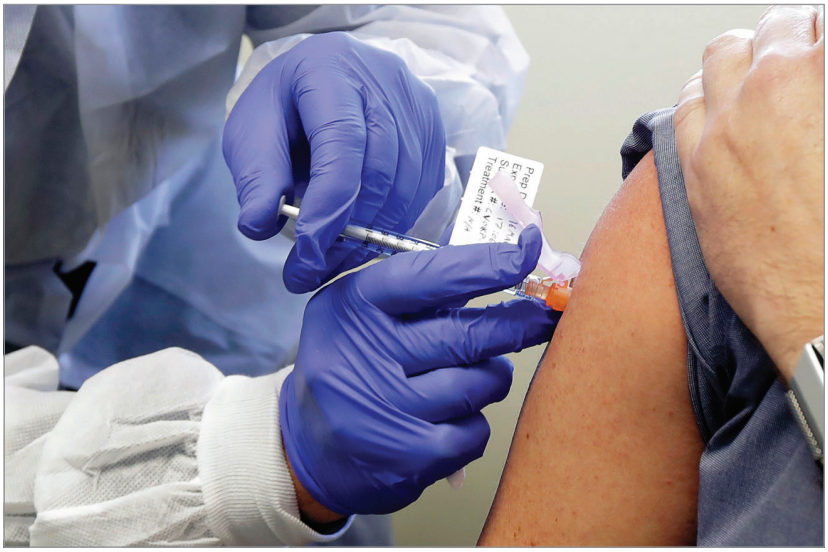
Medical News & Perspectives

Challenge Trials—Could Deliberate Coronavirus Exposure Hasten Vaccine Development?

Rita Rubin, MA



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Josh Morrison, JD, was so moved by a 2007 essay about one woman's desperate search for a kidney that he decided he wanted to donate one. "Okay, I can save someone's life," the self-described nonconformist told himself.

It took a few years, but in 2011 he donated a kidney to a stranger who'd been waiting 8 years. Then in 2014, Morrison, a Harvard Law School graduate, left corporate law and cofounded Waitlist Zero, whose mission is to make it easier for patients to ask for a kidney and donors to give one.

Living organ donation in the US has dropped because of the coronavirus disease 2019 (COVID-19) pandemic, Morrison said. After reading a March 31 article about how young, healthy individuals like himself could accelerate the development of a COVID-19 vaccine, he knew he had found another cause worthy of his passion for doing good.

This time, instead of getting donor kidneys to patients more quickly, the 34-year-old Morrison hopes to make a COVID-19 vaccine available at least 1 Day Sooner, which is the name of the organization he cofounded.

The group is signing up volunteers willing to enroll in randomized, placebo-controlled trials of candidate COVID-19 vaccines. These wouldn't be conventional clinical trials, though. After getting either the investigational vaccine or the placebo, volunteers would deliberately be exposed to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) instead of waiting for the virus to find them in the community.

"Anything that could get a vaccine sooner and get this over with sounds great to me," said Morrison, who coauthored a May 14 preprint article, which hasn't been peer reviewed. It describes scenarios in which human challenge trials, also called controlled human infection models, would be useful in accelerating COVID-19 vaccine development.

Human challenge trials have been used to test vaccines against a number of infectious diseases, including malaria and influenza. Participants in such studies remain quarantined in a clinical trials unit while researchers monitor their immune response and whether they develop symptoms.

But unlike malaria or influenza, COVID-19 has no known cure or, as yet, proven treatment, raising ethical concerns about challenge trials of a vaccine against it.

Bioethicist George Annas, JD, MPH, at the Boston University School of Public Health, questions how volunteers in such studies could truly provide informed consent.

"Well into this pandemic, we don't know a lot about this virus," Annas pointed out in an interview. "This is not the way out of the pandemic. If you want to be serious about science, you have to know how this disease works."

A "Necessary Evil"?

Despite the potential risks, more than 25 000 volunteers from 102 countries had signed up to participate in a challenge trial less than 6 weeks after the 1 Day Sooner website launched on April 17.

"I just want this to be solved already," a volunteer from Romania commented online.

Morrison and other proponents of challenge trials argue that exposing young, healthy people, a population that appears to have the lowest risk of dying from COVID-19, is no more dangerous than the accepted practice of allowing them to donate a kidney or liver lobe.

"It's not every day that doctors intentionally give a pathogen to study participants," acknowledged Rutgers University bioethicist Nir Eyal, DPhil. Eyal is part of an informal working group advocating for human challenge trials involving volunteers aged 20 to 29 years. Based on COVID-19 cases from February, a recent study estimated that 0.03% of people in that age group who were infected with SARS-CoV-2 died, and 1.1% were hospitalized. Rates were substantially higher in older age groups.

Eyal and 2 of his working group colleagues first raised the subject of human challenge studies for COVID-19 vaccine candidates in the article that sparked Morrison's interest. In it, they suggested that a global pandemic changes the ground rules for clinical trials. Given the circumstances, they wrote, challenge studies might be an acceptable way to bypass

phase 3 trials, the final stage of assessing safety and effectiveness before the US Food and Drug Administration (FDA) considers whether to approve a vaccine or drug. Phase 3 trials typically enroll several thousand people who must be observed long enough in the field to determine whether people in the vaccine group developed fewer infections than those in the control group, Eyal and his coauthors noted.

Challenge trial volunteers' net risk could be acceptable if they're healthy young adults with a high baseline risk of natural infection—residents of areas with high transmission rates, for example—who would receive frequent monitoring, and, if they become ill, would get the best available care, the authors wrote.

"I started thinking about them [challenge trials] as a necessary evil," Eyal said in an interview. "You really dislike doing something, but you have to do it because so much is at stake."

In a recent opinion piece, researchers from the Netherlands suggested that using historic controls from previous challenge studies, instead of a placebo group, could minimize cumulative risk to participants. However, that's obviously not an option for vaccines against SARS-CoV-2, a novel virus for which challenge trials have never been conducted.

In a May 19 article, 2 other members of the human challenge trial working group, New York University bioethicist Arthur Caplan, PhD, and Stanley Plotkin, MD, who in 1964 invented the rubella vaccine, wrote that regulators and ethicists should consider "the likelihood that control groups in typical phase 3 efficacy trials of SARS-2 vaccines will suffer more deaths than in carefully done human challenges, to say nothing about simultaneous deaths in people not in the studies exposed to circulating virus."

Gaining Momentum

Support for COVID-19 vaccine challenge trials seems to be growing.

At least 35 members of Congress, including former US Department of Health and Human Services (HHS) Secretary Donna Shalala, PhD, now a Democratic congresswoman from Florida, have endorsed COVID-19 vaccine challenge trials. They signed an April 20 letter to HHS Secretary Alex Azar and US Food and Drug Administration (FDA) Commissioner Stephen Hahn, MD, urging them to consider using challenge trials to assess candidate vaccines more quickly.

"Our situation in this pandemic is analogous to war, in which there is a long tradition of volunteers risking their health and lives on dangerous missions for which they understand the risks and are willing to do so in order to help save the lives of others," the members of Congress wrote.

In a statement in May, the FDA said human challenge studies to expedite a COVID-19 vaccine "raise a variety of potential scientific, feasibility, and ethical issues." However, the agency said it will help those interested in conducting such studies to evaluate these issues.

The World Health Organization (WHO) weighed in May 6 with guidance aimed at scientists, ethics committees, funders, policy makers, and regulators. As the WHO pointed out, challenge studies have a long history and have helped accelerate the development of vaccines against typhoid and cholera as well as determine correlates of immune protection against influenza.

However, as Albert Einstein College of Medicine emeritus bioethicist Ruth Macklin, PhD, noted in a blog post, the WHO does not list the availability of an accepted treatment among its ethical criteria for SARS-CoV-2 vaccine challenge studies.

"With several vaccines already in the pipeline, I conclude that a rush to begin human challenge studies for a grave disease lacking an effective treatment is ethically unjustifiable," Macklin wrote.

Science, but Maybe Not Speed

Whether challenge trials could help speed the development of a safe and effective COVID-19 vaccine is debatable. The first COVID-19 vaccine challenge trial will likely take months of preparation; meanwhile, clinical trials of several candidate vaccines have already begun.

"I think we can probably be faster by taking these vaccines forward and testing them in a conventional way," said Philip Dormitzer, MD, PhD, vice president and chief scientific officer, viral vaccines, at Pfizer Vaccines Research and Development, which has launched clinical trials of 4 candidate COVID-19 vaccines. Before joining Pfizer, Dormitzer led viral vaccine research at Novartis, where his team's work supported the development of 3 licensed vaccines against pandemic influenza A(H1N1) infection.

Despite what some proponents suggest, challenge studies can't replace phase 3 trials, said London-based Adrian Wildfire, MSc, project director for the infectious diseases human challenge unit at SGS Life Sciences.

"Because it's a small study, at most 120 people in it, you're never going to find a safety signal," Wildfire said of a challenge trial. However, challenge studies could help weed out less-promising candidate vaccines without having to invest first in large phase 3 trials, Wildfire added.

And if it turns out that COVID-19 occurs in waves, challenge trials would be useful in periods of lower SARS-CoV-2 prevalence in the community, he noted. The University of Oxford's Adrian Hill, PhD, who initially predicted an 80% chance that his lab's vaccine could be available by September, has become less optimistic. The reason? Declining cases in the community means phase 3 trial participants are less likely to be exposed to SARS-CoV-2, making it more difficult to assess the vaccine's effectiveness.

Preparation for potential COVID-19 vaccine challenge trials needs to begin now, said Matthew Memoli, MD, director of the laboratory of infectious diseases clinical studies unit at the National Institute of Allergy and Infectious Diseases.

"We should be planning for this option [challenge trials]," Memoli, who has conducted challenge trials of vaccines against such diseases as influenza and respiratory syncytial virus, said in an interview. "Whether it's something we should be doing at this moment, I'm sort of undecided. I think there are a number of practical obstacles."

Memoli coauthored an article May 7 about the ethics of challenge trials to study COVID-19 vaccines. Individual challenge trials could address multiple scientific questions, such as identifying correlates of protection against infection, the authors noted.

Dormitzer, who was not a coauthor, agreed that challenge studies represent "a very useful basic scientific tool" because researchers would know exactly when participants were exposed to SARS-CoV-2. Such trials could help elucidate the length of the incubation period as well as the end of viral shedding, he said.

The Challenge of a Challenge Agent

In a controlled human infection model of a vaccine to protect against a respiratory illness, be it COVID-19 or influenza, researchers don't simply ask an infected

individual to cough in the face of an immunized individual and then wait to see if the latter gets sick.

Instead, the trick is to create a challenge virus—in this case, a version of SARS-CoV-2—that will make people sick but not too sick. The challenge virus would be squirted into a volunteer's nose with a nasal atomizer attached to a syringe, which releases particles that are too big to go directly to the lungs but instead spread nicely in the nasopharynx, Memoli said.

Virus could be isolated from an infected person, but researchers would have to make sure it's not accompanied by anything else that could make challenge study participants sick, he said. Then it would have to be grown under good manufacturing practice guidelines. Normally, Memoli said, when he grows virus in the laboratory, he feeds cells with fetal bovine serum. However, he said, because prion disease could be transmitted via cow serum, researchers would instead have to use synthetic media, in which virus might not grow as well, for a human challenge agent.

"The optimal [challenge] virus would be one that didn't give you downstream sequelae but gave you all the symptoms you needed," Wildfire noted. "Personally, I'd like to grow a wildtype and an attenuated version" in case the wildtype challenge virus was too strong, he said.

The safety of the challenge virus could first be tested in ferrets and golden hamsters, which appear to be good COVID-19 animal models, Wildfire said. "If it just makes them slightly sick, then that's fine," he said.

But that's only the beginning, cautioned Dormitzer, who worked on controlled human infection models before coming to Pfizer. "Then you need to test in people very carefully to make sure that it's safe," he said. "Then you need to develop an infectious dose."

So although the same challenge virus could and would be used in studies of a variety of COVID-19 vaccines, the path to the first controlled human infection model will be time-consuming, Dormitzer said.

Meanwhile, Wildfire said, he has sought funding to develop SARS-CoV-2 challenge viruses from public agencies and private foundations, including the US National Institutes of Health and the UK's Wellcome Trust health research charity.

"Everybody wants to do challenge studies…but nobody wants to pay to make challenge agents," Wildfire said. "What I'm trying to do is set up a company that makes challenge agents for use by everybody…I don't care if they're academic. I don't care if they're commercial."

Defining Success

A COVID-19 vaccine challenge study would enroll people whose young age and good health put them at the lowest risk of severe illness. But how relevant would the findings be for the population at the highest risk, namely older individuals with comorbidities?

"If we take a vaccine, and we give it to young healthy people, and it protects them, that does not tell us it's going to protect an 80-year-old woman with COPD [congestive obstructive pulmonary disease]," Memoli said.

But challenge trials could help determine correlates of infection that could be applied to developing a vaccine for the highest-risk individuals, he said. For example, did the vaccine protect challenge trial participants because it induced neutralizing antibodies? If so, how could the vaccine induce those antibodies in older and sicker people? Perhaps by adding an adjuvant?

With influenza, "we knew that when you get older you don't have as strong a response to the vaccine as you do if you're younger," Memoli said. "If we didn't have the data on the young people…we wouldn't be able to figure that out."

Plus, he said, if a vaccine doesn't induce a protective response in a 25-year-old, researchers can be pretty certain it won't work in a child or an older person and should not be pursued.

Other Practical Issues

While creation of a challenge virus is key, controlled human infection studies of a potential COVID-19 vaccine face other hurdles as well.

"To do a COVID-19 challenge would be a very difficult task," Memoli said. "There are enormous numbers of practical issues in doing it."

One of the biggest obstacles is how long clinical trial units would have to isolate study participants, Memoli said. They can't go home until they stop shedding the virus—as determined by daily polymerase chain reaction (PCR) testing—and can no longer infect others.

With influenza vaccine challenges, he tells volunteers, "We expect you to go home in 10 days," although one of them recently set a record by having to remain in quarantine for 15 days.

With a COVID-19 vaccine challenge study, Memoli said, he might have to tell participants that they can expect to go home in 2 months, not 2 weeks, because people have tested positive for SARS-CoV-2 weeks after recovering from the infection.

Some observers have suggested that positive test results weeks after symptoms dissipate could simply be due to residual RNA, not live virus capable of infecting others. However, Memoli said he is skeptical because RNA isn't stable by itself. It might last 2 or 3 days after the virus disappears, but not 2 or 3 weeks or more, he said.

"If we can't overcome that hurdle in some way, then it reduces the benefit of doing the challenge," Memoli explained. "This is why I haven't decided if we should do it or not."

Compensation is another issue. Participants in 2-week influenza vaccine challenge studies typically receive $3000 or $4000, Memoli said. Because of the amount of time required, he said, COVID-19 vaccine challenge trials would have to pay participants "a very significant amount of money," probably well over $10 000 apiece.

Whether people would volunteer simply because they need the money, and not out of altruism, is a concern, Eyal said. "It shouldn't be a way for you to boost your income."

Despite all their obstacles and limitations, COVID-19 human challenge trials are worth considering, Dormitzer said. "I think we want all the tools we can get to both understand and to combat the virus," he said. "Can you do this safely and ethically? If you can, I think it's worth doing." ■

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