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SOAPBOX HEALTH & MEDICINE

Infecting people with COVID-19 could speed vaccine trials. Is it worth it?

Science News spoke with researchers on either side of the debate about human challenge trials

Human challenge trials, where volunteers who receive experimental vaccines are purposefully infected with a pathogen such as the coronavirus, could bring about a quicker end to the pandemic. But the risks and benefits of such trials are far from clear.

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By Jonathan Lambert

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The world waits with bated breath for a COVID-19 vaccine, which could effectively end the pandemic once it's widely available. Until then, more people will die from the disease, and economies will struggle to fully recover.

With such intense pressure to get a vaccine quickly, many experts are contemplating a controversial shortcut to the usual vaccine testing protocol: human challenge trials.

Instead of vaccinating hundreds to thousands of people and waiting to see if they naturally catch the virus, scientists would purposely infect a smaller number of vaccinated volunteers with COVID-19 in a controlled setting to see if a vaccine offered protection. If successful, such studies could fast-track vaccine evaluation, as well as our understanding of COVID-19 immunity.

However, doctors and researchers don't all agree on whether it's ethical to infect people with a disease that remains poorly understood, and for which there is currently no reliable treatment. That leaves it to those bioethicists, researchers and regulators to weigh the pros and cons.

If scientists stick to the usual playbook, a licensed vaccine is at least 12 to 18 months away, experts say. That's not because it takes long to develop possible vaccines — dozens are already in the testing stage (*SN: 5/20/20*) — but because of the time that it takes to be sure a vaccine is safe and actually works.

The final and most involved stage of this process, Phase III clinical trials, requires thousands of volunteers to get the vaccine or a placebo. Then, scientists track them over months to see whether vaccinated people are less likely to get sick compared with unvaccinated people.

And it could take longer now that lockdowns and social distancing have flattened the curve of new cases. "You can only test vaccine efficacy if incidence [of the disease] is high enough," says Helen McShane, a vaccine biologist at the University of Oxford. The less the disease is spreading, the longer traditional Phase III trials will take.

Challenge trials might shave months off the process. "Human challenge trials have been done for hundreds of years," says Seema Shah, a bioethicist at Northwestern University Medical School in Chicago. "They come with a lot of promise, but also with serious ethical concerns."

For example, in 1796, English physician Edward Jenner, an earlier popularizer of vaccination, demonstrated that inoculation with cowpox worked as a vaccine against smallpox by injecting his gardener's 8-year-old son with cowpox and then exposing him to the disease. "**Clearly**, that's problematic," Shah says.

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Nowadays, challenge trials are typically done on diseases about which scientists know a lot, and for which there are numerous treatment options, such as influenza or malaria. But there's currently no established drug safety net for COVID-19, though some drugs show promise (*SN: 4/29/20*). And much still remains unknown about the virus, including all the risk factors for severe disease (*SN: 4/22/20*). Consequently, most advocates are calling for such trials to be done only on young and healthy volunteers, who seem least at risk for serious illness.

Still, researchers, clinicians, bioethicists and policymakers are debating the ultimate utility of human challenge trials for COVID-19. The ethical calculus could change as we learn more about the virus and continue developing treatments, but some experts are already putting out rough plans for how to minimize risk to participants.

Here are two perspectives on the issue, from scientists weighing both the risks and potential benefits.

Human challenge trials could help us have a vaccine quicker and save lives.

"We face a worldwide epidemic with a high mortality, and the only thing likely to stop it is vaccination," says Stanley Plotkin, a vaccine developer at the University of Pennsylvania. Human challenge trials have the potential to get us an effective vaccine sooner and thus save lives, Plotkin says, and we should start planning how to do them ethically now.

"I would, of course, not want to subject anyone to harm, but the fact is that harm is accumulating all over now, and if we can reduce the total amount of harm, I think it's worth doing," Plotkin says. "Extraordinary circumstances require extraordinary solutions."

Human challenge trials could help scientists answer important unknowns about the virus more quickly than animal studies can, Plotkin says. "A human challenge trial could tell us whether prior infection is protective or not, as well as what sort of immune responses are protective," Plotkin

says. “Both of those have very large implications in terms of whether people with prior infection could take care of the sick,” as well as our ability to evaluate the efficacy of vaccine candidates outside of challenge trials.

Stanley Plotkin, a vaccine developer at the University of Pennsylvania, says that a COVID-19 vaccine could be accelerated by purposefully infecting humans with the coronavirus in what’s known as a human challenge trial.

S. PLOTKIN

Plotkin acknowledges the potential risks to participants. “Giving someone an infection can cause serious harm,” he says, “but the usual way of doing things also means that many people will become ill and possibly die.” To minimize risk, Plotkin says such trials should only be carried out on young, healthy people who understand the risks and give their full consent. “There are thousands of people willing to be volunteers for such studies on moral grounds, with knowledge of the risks.”

A vaccine shown to work in a challenge trial on young people may not work in older people, or may be less effective, Plotkin says. “But a challenge trial could allow us to more easily determine whether the immune responses we see in younger people are also seen in older people,” who get the experimental vaccine but aren’t subjected to a challenge virus. Even if the vaccine only worked in younger folks, “that could still protect older people simply because they wouldn’t be getting infected by younger [vaccinated] people,” he says.

While some have argued that challenge trials could replace Phase III clinical trials, Plotkin doesn’t see human challenge trials as a full substitute for normal safety trials. He also doesn’t expect them to result in regulators licensing a vaccine for widespread use. “But it could allow for emergency use among high-risk people or health care workers,” he says. “It could also help us determine which vaccine candidates show signs of working,” which could allow manufacturers to get a potentially lifesaving head start on mass production.

“This is not an exclusive pathway,” he says, “it’s a supplementary pathway to try to speed things up.” If normal vaccine trials revealed a candidate, or we learn more about the risks to volunteers,

Plotkin says challenge trials should be stopped. "But if we don't start planning human challenges now, they won't be available if we decide months from now that it would've been a good idea."

Human challenge trials are too risky, and may not end up being that helpful.

"I still haven't been persuaded that a human challenge trial would be informative enough to make a final decision about which vaccine is the right vaccine to roll out at scale," says Angela Rasmussen, a virologist at Columbia University.

The hallmark of any human challenge trial is fully informed consent from participants. But Rasmussen questions whether that's possible at this stage. "I don't know that we can actually inform them of all the risks because there's still so much that's just unknown about this virus," she says.

Angela Rasmussen, a virologist at Columbia University, says that there's still too much we don't know about the coronavirus behind COVID-19 to purposefully infect the virus into humans to speed along research.

A. RASMUSSEN

Evidence suggests that young, healthy people are least likely to suffer severely from COVID-19 infection, but "we're still learning about different types of disease that it may cause," Rasmussen says. Reports of young people suffering strokes, and taking damage to the kidneys, heart and other organs have emerged in recent months, making it difficult to quantify the actual risks. "I just don't see how a subject could provide their fully informed consent."

Accepting those risks may result in more harm than good, Rasmussen says. By design, any COVID-19 challenge trial would be done on a small, homogenous group. That could limit its broader applicability, she says, and "could miss issues with the vaccine that can only be caught in a larger, more diverse study population."

She **points** to previous examples, like the mid-2000s HIV vaccine candidate that actually increased risk of HIV infection in those who got the vaccine, or a "SARS classic" study in which older vaccinated mice experienced more severe disease after being infected.

"My concern is that you could have a major safety issue like that if you are doing only human challenge trials in young, healthy volunteers," Rasmussen says. A robust response in young people could mask harmful effects that emerge in older people or a different population, she says.

While a challenge trial could identify promising vaccine candidates more quickly, it might also prop up the wrong one based on limited results. If serious issues come up for other populations, the consequences could be dire, Rasmussen says. "And we'd have wasted resources that could have been devoted to standard Phase II and III trials."

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Other unknowns limit a challenge trial's potential utility, too, Rasmussen says. "We don't know the infectious dose for COVID-19," she says, meaning the amount of virus that someone must get to kick-start an infection. If a challenge trial got the dose or route of infection wrong, it might not be comparable to pathogenic SARS-CoV-2, the virus that causes COVID-19. "A vaccine would appear to work under those conditions, but it might not be applicable to how people actually need to be protected in the real world."

Rasmussen doesn't rule out that challenge trials could be helpful. "It's important to keep an open mind about anything that can speed our way to a vaccine, but we need to be cautious and be humble," Rasmussen says. "There's a lot more we don't know about this virus than what we do know. If a human challenge trial goes wrong, it could go catastrophically wrong, which could ultimately be harmful for all vaccine development efforts."

Who decides?

Exactly who gives the green light for a COVID-19 challenge trial remains unclear. Normally the decision to proceed with such a trial lies with the funder of the research (the U.S. National Institutes of Health, for example) and ethics boards at the research institutions or regions where the study will be done.

But given the extraordinary nature of the current situation, the World Health Organization, as well as leaders of the NIH, have called for an additional layer of review for any COVID-19 challenge trials, which could include an independent panel of ethicists, clinical trial researchers and vaccine development experts.

In the United States, the Food and Drug Administration would license a vaccine for widespread use, and they would have to decide whether results of a human challenge study would weigh on their ultimate decision. It's not a given that the agency would take those results into consideration.

Meanwhile, people are already volunteering to take part in COVID-19 human challenge trials, were they to happen. Already, over 20,000 people around the world have expressed interest in participating in COVID-19 challenge trials through "1 Day Sooner," a campaign to collect volunteers.

CITATIONS

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