

News in focus



MORTEZA NIKOUBAZL/NURPHOTO VIA GETTY

Study participants reported symptoms typical of other respiratory infections, such as runny noses and sore throats. Fevers were less common.

SCIENTISTS DELIBERATELY GAVE PEOPLE COVID — HERE'S WHAT THEY LEARNT

Only half of participants who were exposed to the coronavirus developed infections, most with mild symptoms.

By Ewen Callaway

Healthy, young people who were intentionally exposed to the coronavirus SARS-CoV-2 developed mild symptoms — if any — in a first-of-its-kind COVID-19 human-challenge study.

Such trials present a unique opportunity to study viral infections in detail from start to finish, but are controversial because of the risks they pose to participants.

The UK study of 34 individuals, aged 18–30 years, shows that such trials can be done safely, say scientists, and lays the

groundwork for more in-depth studies of vaccines, antivirals and immune responses to SARS-CoV-2 infection. The results were posted on 1 February on the preprint server Research Square and have not been peer reviewed (B. Killingley *et al.* Preprint at Research Square <https://doi.org/hfsc; 2022>).

Nearly half of the participants who received a low dose of virus did not become infected, and some of those who became infected had no symptoms. Participants who did develop COVID-19 reported mild-to-moderate symptoms, including sore throats, runny noses and loss of smell and taste.

“It presents a potentially important advance in how to assess future vaccine and drug efficacy,” says Miles Davenport, an immunologist at the University of New South Wales in Sydney, Australia. “This opens a number of important possibilities to study immunity in a controlled environment.”

However, some researchers question whether the insights yielded by the study so far are important enough to justify the risks to participants, such as the potential for long-term side effects. “In my mind, it’s still not entirely clear whether these studies are ethically justified, and I’m waiting to see what else

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they've found," says Seema Shah, a bioethicist at Northwestern University in Chicago, Illinois.

Finding the dose

Human-challenge studies have been used for decades to study influenza, malaria and other infectious diseases. Some researchers argued in favour of conducting such trials with SARS-CoV-2 in the early months of the pandemic, as a way to accelerate the development of vaccines. But others saw challenge trials as too dangerous to be acceptable, when so little was known about the virus and few, if any, effective treatments were available.

The trial was led by researchers at Imperial College London together with a Dublin-based commercial clinical-research organization called Open Orphan and its London-based subsidiary hVIVO. It was announced in October 2020, and the first participants were exposed to the virus in early 2021. Volunteers received £4,565 (US\$6,200) for their participation, which involved at least 2 weeks of quarantine in a high-level isolation unit at the Royal Free Hospital in London.

The first participants received a very low dose – roughly equivalent to the amount of virus in a single droplet of nasal fluid – of a virus strain that circulated in the United Kingdom in early 2020. Researchers anticipated that a higher dose would be needed to infect a majority of participants, says Andrew Catchpole, chief scientific officer of hVIVO. But the starting dose successfully infected more than half of the participants.

The virus replicated rapidly in those who became infected. On average, people developed their first symptoms and tested positive, using sensitive PCR tests, less than two days after exposure. That contrasts with the roughly five-day 'incubation period' that real-world epidemiological studies have documented between a probable exposure and symptoms. High virus levels persisted for an average of 9 days, and for up to 12 days.

The most common symptoms were typical of other respiratory infections: sore throats, runny noses and sneezing. Fever was less common, and no one developed the persistent cough that had been used as a hallmark of COVID-19, says Catchpole. Around 70% of infected participants lost their senses of smell or taste – another COVID-19 signature – to varying degrees. Such problems persisted for more than six months in five participants and for more than nine months in one. Some people developed no symptoms at all, but had as much virus in their upper airways as did participants who exhibited symptoms, and their infections lasted for as long.

Researchers involved in the study want to understand why so many people did not become infected, despite being exposed to SARS-CoV-2. Some participants had very low levels of virus for short periods of time, but did



The challenge trial took place in London.

not develop infections, suggesting that their immune systems were actively fighting the virus, says Christopher Chiu, a physician-scientist at Imperial College London, who led the study.

Future studies of the challenge-trial participants will attempt to explain why. Previous research has suggested that coronaviruses that cause the common cold might confer protection against COVID-19 in some people. Another possibility is that some people have potent innate immune responses that don't require a previous encounter with a particular pathogen or a closely related virus.

Chiu's team plans to launch another challenge trial that will expose vaccinated people to the Delta variant of SARS-CoV-2. That study will attempt to identify immune factors that protect people from 'breakthrough' infections after vaccination. For the time being,

human-challenge trials for SARS-CoV-2 will probably enrol only people at very low risk of severe disease, says Catchpole. But as researchers gain experience running these challenge trials safely, it might be possible to expand them, Chiu adds.

Concerns linger

The study looked safe and well conducted, says Matthew Memoli, an infectious-disease physician and virologist at the US National Institute of Allergy and Infectious Diseases in Bethesda, Maryland.

It should make some people more comfortable with doing more human-challenge trials for SARS-CoV-2, he adds. Such trials could prove useful in the development of vaccines that protect against a broad range of coronaviruses.

Meagan Deming, a vaccine scientist and virologist at the University of Maryland in Baltimore, says the study confirms insights gained from other COVID-19 studies, such as the swift rise in virus levels. But it has not eliminated her concerns about exposing people to a strain of SARS-CoV-2 that hasn't been weakened. More than two-thirds of participants who became infected had long-lasting problems with smell or taste, she notes.

"It sounds like this is the most serious risk that materialized. This is the one to keep an eye on," adds Shah. Moreover, she questions whether the insights gleaned from the study so far justify such risks. "This study reads like a promissory note that ultimately, in conjunction with the other research they're doing, there will eventually be substantial scientific and social benefits. But we're not really seeing that yet."

DOES THE WORLD NEED AN OMICRON VACCINE? WHAT RESEARCHERS SAY

Public-health specialists are debating the need for a shot targeting the concerning variant.

By Emily Waltz

After the Omicron variant of SARS-CoV-2 was first identified in November, vaccine makers quickly began developing shots against the highly mutated and transmissible virus. Last week, pharmaceutical firm Pfizer and biotechnology company Moderna both announced that they had initiated clinical trials in which they are dosing people with Omicron-based vaccines. But whether rolling out these shots is

necessary, or even practical, is unclear, according to public-health authorities and infectious-disease specialists interviewed by *Nature*.

For those faced with making the complicated decision, debates have begun. Some think it might not be worthwhile, because Omicron cases could plummet before manufacturers can finalize the vaccines. Others point out that it's difficult to predict whether the next SARS-CoV-2 variant will be like Omicron. "We have a lot of confidence in the [current] vaccines, but we must now discuss