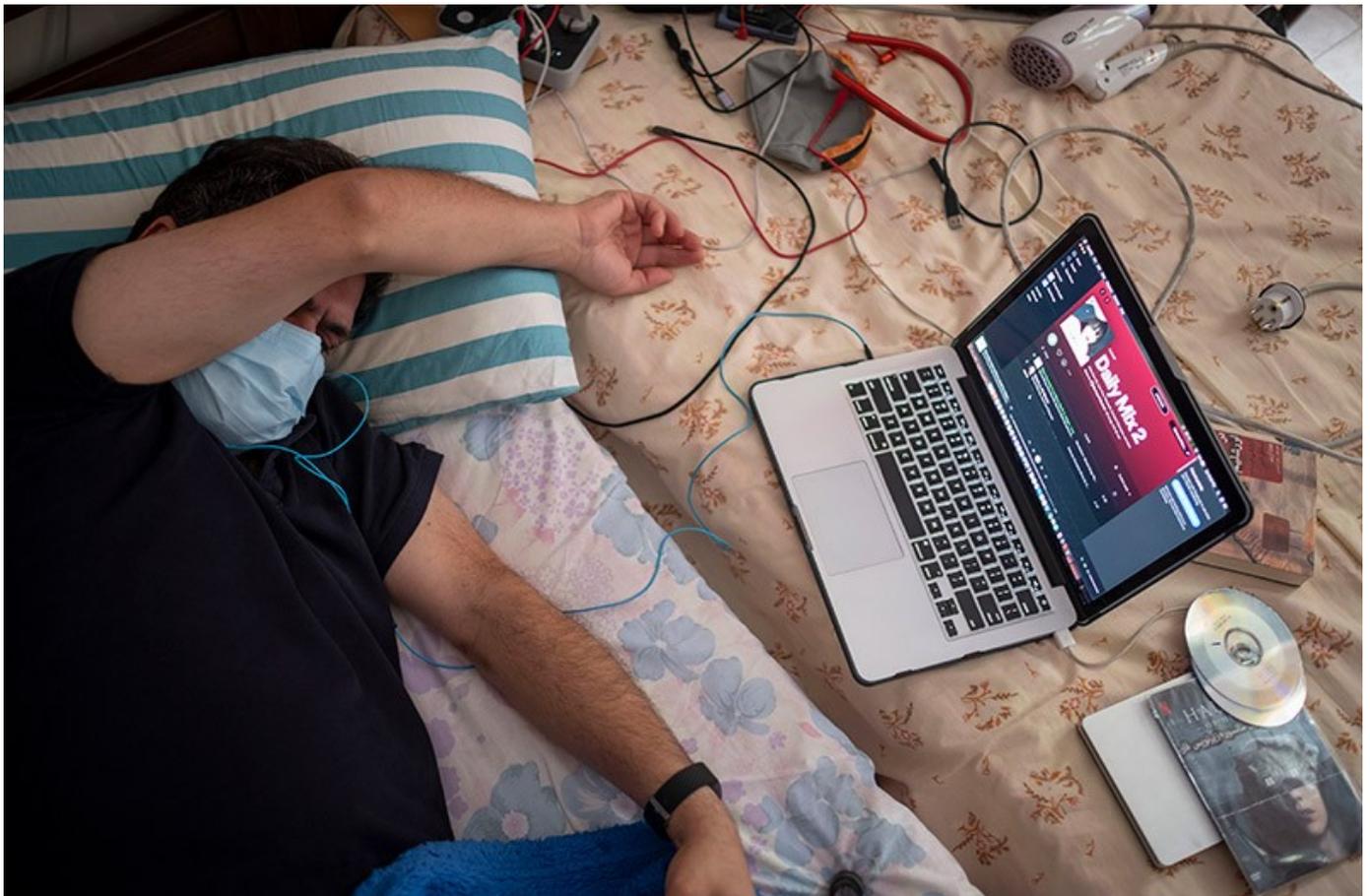


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Scientists deliberately gave people COVID — here's what they learnt

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

Ewen Callaway



Study participants reported symptoms typical of other respiratory infections, such as runny noses and sore throats. Fevers were less common. Credit: Morteza Nikoubazl/NurPhoto via Getty

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 The results were posted¹ on 1 February on the preprint server Research Square and have not been peer reviewed.

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 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 numerous 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.

 **View of researchers at work in the hVIVO Lab.**

The challenge trial was conducted in London. Credit: hVIVO

The trial, led by researchers at Imperial College London and a Dublin-based commercial clinical-research organization called Open Orphan and its London-based subsidiary hVIVO, 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 two 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 incredibly 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, on average. That contrasts with the roughly five-day ‘incubation period’ that real-world epidemiological studies have documented between a probable exposure and symptoms. High viral levels persisted for an average of 9 days, and 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 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 uninfected participants had very low levels of virus for short periods of time, 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. "We're trying to understand the fundamentals of why people are protected even though they've not been exposed to a virus like this before," Chiu adds.

Transmission electron micrograph of SARS-CoV-2 virus particles (gold) within an infected nasal Olfactory Epithelial Cell.

A micrograph of SARS-CoV-2 virus particles (gold). Credit: NIAID ([CC BY 2.0](#))

His 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 to involve at-risk groups, such as older people, 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, not just SARS-CoV-2, he adds.

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 viral 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 problems with smell or taste that lasted, in some cases, for more than six months, 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.”

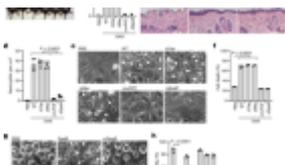
doi: <https://doi.org/10.1038/d41586-022-00319-9>

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