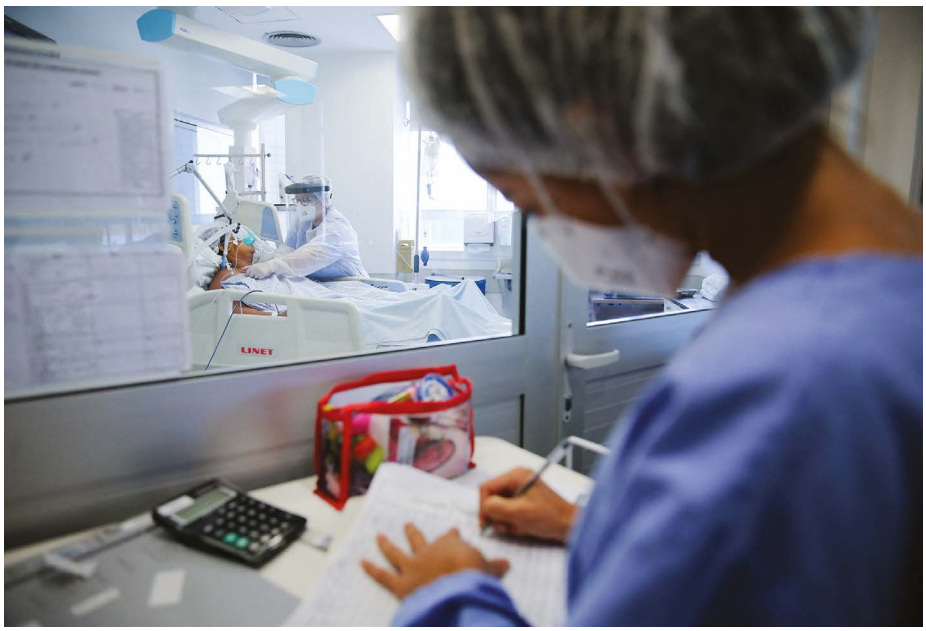

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Researchers are studying the long-term effects of drugs given to people with COVID-19.

CAN DRUGS CUT THE RISK OF LONG COVID? WHAT SCIENTISTS KNOW SO FAR

Researchers investigate whether existing vaccines and treatments can prevent lasting symptoms.

By Heidi Ledford

In the early days of the COVID-19 pandemic, urologist and clinical epidemiologist Kari Tikkinen found his schedule full of cancelled surgeries, so he had some time to kill. "Do whatever you feel is most useful," his boss at the University of Helsinki advised him. So Tikkinen threw himself into running clinical trials for COVID-19 therapies.

From the start — before the world learnt of long COVID — Tikkinen saw a need to follow study participants for months after their recovery. He wanted to monitor long-term side effects of the medicines. "Very soon, it became clear: it's not only about safety," he says.

Now, Tikkinen and a handful of others are hoping to learn more about whether treatments given during the acute phase of COVID-19 can reduce the risk of experiencing symptoms months later. "It's an urgent and pressing health need that people need to start focusing on," says intensive-care specialist Charlotte Summers at the University of Cambridge, UK.

Debilitating symptoms

Research into long COVID — which is also known as post-acute sequelae of COVID-19, and is usually defined as COVID-19 symptoms that last longer than three months — has lagged behind studies of the acute phase of infection. People who experience long COVID live with a wide array of symptoms, ranging from mild to severely debilitating. Researchers have proposed a variety of causes for the condition — from lingering viral reservoirs, to autoimmunity, to tiny blood clots. Many think that a mix of these factors is to blame. "It took a while to get going on any serious mechanistic long-COVID research," says immunologist Danny Altmann at Imperial College London. "It's hard to piece the big picture together."

Thus far, vaccines are the best way to prevent long COVID. COVID-19 vaccines reduce the risk of SARS-CoV-2 infection, and they might lessen the risk of long COVID after a breakthrough infection in someone who has been vaccinated.

Several studies have looked at this question: although they yielded divergent results, the overall trend suggests that vaccination could reduce the risk of long COVID by about half among those who become infected despite being vaccinated. For example, one study that has not yet been peer reviewed found that vaccination reduced the chances of developing long-COVID symptoms by about 41% in more than 3,000 double-vaccinated participants who later became infected with SARS-CoV-2 (D. Ayoubkhani *et al*. Preprint at medRxiv https://doi.org/hnwx; 2022).

But that still leaves too many people at risk of getting long COVID, says Altmann. "Half is not as good as I thought it would be," he says. "I was thinking and hoping that long COVID would be a thing of the past."

Early treatment

Beyond vaccination, it's unclear whether any existing COVID-19 therapy has an effect on long-COVID risk. A drug that reduces disease severity might reduce the severity of long-term symptoms, says Altmann. But long COVID is not always associated with acute illness. "There are loads of people out there who are really destroyed by long COVID and had asymptomatic or near asymptomatic infections," he says. "It's really hard to grapple with."

Nevertheless, some studies plan to look at the impact of early treatment with antiviral drugs on long COVID. A clinical trial called PANORAMIC has been testing the effects of the oral antiviral molnupiravir, developed by Merck in Kenilworth, New Jersey, and Ridgeback Biotherapeutics in Miami, Florida, on COVID-19 severity. Although it is not the primary goal of the study, researchers will gather data from participants at three and six months after treatment — which could determine whether the drug affects long-COVID risk. Similarly, two trials of Paxlovid, an antiviral drug developed by Pfizer in New York City, will include a six-month follow-up of participants.

These antiviral drugs are typically used to treat people with relatively mild COVID symptoms. Tikkinen and his colleagues hope to learn more about the long-term impact of treatments received by those who were hospitalized with COVID-19. His team is following up with participants in the University of Helsinki's arm of the World Health Organization's international COVID-19 treatment trial, called SOLIDARITY. In the next few weeks, he hopes to have the results of a one-year follow-up study of participants who were hospitalized with COVID-19 and treated with the antiviral drug remdesivir.

His team will also follow up with participants in two other arms of the SOLIDARITY trial, one that tested an immune-suppressing drug called infliximab and another that tested imatinib, a drug that could help to reduce inflammation in blood vessels.

But, Tikkinen cautions, none of these studies had enough participants to give clear-cut answers on long COVID. His team went to extraordinary measures to contact participants months after their remdesivir treatment and to encourage them to fill in a survey about their symptoms. They got a 95% response rate, which Tikkinen says is unusually high for such long-term studies. But because the original

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study included only about 350 people, it is probably still too small to provide a definitive conclusion.

Small-scale trials

Researchers are hoping to find out whether more treatments can reduce the risk of long COVID. A large UK-based trial called HEAL-COVID is testing two drugs that target the cardiovascular system in people who have been hospitalized with COVID-19. One, called apixaban, is an anticoagulant. The other, atorvastatin, is a cholesterol-lowering medication thought to reduce inflammation in blood vessels.

The study will investigate whether either treatment reduces hospitalizations and deaths in the year after people are first discharged from hospital. Nearly one-third of people who are discharged after treatment for COVID-19 are re-admitted within six months, and 12% die within six months of their initial discharge. "And when we looked at what was most plausibly leading to death after hospitalization, it was probably the cardiopulmonary effects," says Summers, who is leading the study.

At the University of Chicago in Illinois, pulmonologist and critical-care physician Ayodeji Adegunsoye has observed a possible increase in the accumulation of scar tissue, called fibrosis, in the lungs well after the acute infection in people who were hospitalized with COVID-19 and required supplemental oxygen. He is now testing a drug called sirolimus — an immune-suppressing drug that is sometimes given to organ-transplant recipients — in such people, in the hope that it will prevent the migration of cells that promote fibrosis in the lung.

By their nature, long-COVID studies require patience: one commonly accepted definition of long COVID is the persistence of certain symptoms for more than 12 weeks after the acute infection. Altmann is optimistic that this year will yield advances, but cautions against reading too much into small trials that might not yield statistically meaningful results. "There's such pressure," he says. "There's this incredibly pressing and desperate need — we all feel that anxiety."

DOZENS OF UNIDENTIFIED BAT SPECIES COULD HOST NEW VIRUSES

Study suggests some 40% of horseshoe bats in Asia have yet to be formally described.

By Smriti Mallapaty

A genomic analysis suggests that there are probably dozens of unknown species of horseshoe bat in southeast Asia[1].

Horseshoe bats (*Rhinolophidae*) are considered the reservoir of many zoonotic viruses — which jump from animals to people — including the close relatives of the viruses that caused severe acute respiratory syndrome and COVID-19. Identifying bat species correctly might help pinpoint areas with a high risk of zoonotic disease, says Shi Zhengli, a virologist at the Wuhan Institute of Virology in China. "This work is important," she says.

The study was published in *Frontiers in Ecology and Evolution* on 29 March.

Better identification of unknown bat species could also support the search for the origins of SARS-CoV-2 by narrowing down where to look for bats that may harbour close relatives of the virus, says study co-author Alice Hughes, a conservation biologist at the University of Hong Kong. The closest known relatives of SARS-CoV-2 have been found in *Rhinolophus affinis* bats in southwestern China[2], and in three species of horseshoe bat in Laos[3].

Hughes wanted to better understand the diversity of bats in southeast Asia and find standardized ways of identifying them. So she and her colleagues captured bats in southern China and southeast Asia between 2015 and 2020. They took measurements and photographs of the bats' wings and noseleaf — "the funky set of tissue around their nose", as Hughes describes it — and recorded their echolocation calls. They also collected a tiny bit of tissue from the bats' wings to extract genetic data.

CHIEN LEE/NATURE PICTURE LIBRARY

There could be more species of horseshoe bat than previously thought.

To map the bats' genetic diversity, the team used mitochondrial DNA sequences from 205 of their captured animals, and another 655 sequences from online databases — representing a total of 11 species of Rhinolophidae. As a general rule, the greater the difference between two bats' genomes, the more likely it is that the animals represent genetically distinct groups, and therefore different species.

The researchers found that each of the 11 species were probably multiple species, possibly including dozens of hidden species across the whole sample. Hidden, or 'cryptic', species are animals that seem to belong to the same species but are actually genetically distinct. For example, the genetic diversity of *Rhinolophus sinicus* suggests that the group could be six separate species. Overall, the authors estimated that some 40% of the species in Asia have not been formally described.

"It's a sobering number, but not terribly surprising," says Nancy Simmons, a curator at the American Museum of Natural History in New York City. Rhinolophid bats are a complex group and there has been only a limited sampling of the animals, she says.

However, relying on mitochondrial DNA could mean that the number of hidden species is an overestimate. That is because mitochondrial DNA is inherited only from the mother, so could be missing important genetic information, says Simmons. Still, the study could lead to a burst of research into naming new bat species in the region, she says.

The findings corroborate other genetic research suggesting that there are many cryptic species in southeast Asia, says Charles Francis, a biologist at the Canadian Wildlife Service, Environment and Climate Change Canada, in Ottawa. But, he says, the estimates are based on a small number of samples.

Hughes' team used the morphological and acoustic data to do a more detailed analysis of 190 bats found in southern China and Vietnam and found that it supported their finding that many species had not been identified in those regions. The study makes a strong argument for "the use of multiple lines of evidence when delineating species", says Simmons.

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2. Zhou, P. *et al. Nature* **579**, 270–273 (2020).
3. Temmam, S. *et al. Nature* https://doi.org/10.1038/s41586-022-04532-4 (2022).

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