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Preliminary laboratory data hint at what makes Omicron the most superspreading variant yet

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Airline crew members arrive on the first day of a new rapid Covid-19 testing site for arriving international passengers at Los Angeles International Airport on December 3. *Mario Tama/Getty Images*

Omicron is now in 77 countries, and moving faster than any previous strain of the coronavirus. In the U.K., where Omicron cases are doubling every two days, scientists believe it is behind this week's record-setting surge in new infections. The new variant is already causing about 13% of cases in New York and Washington states, just two weeks after Omicron was first detected in the U.S. Nationwide, it is hovering around 3% of total cases, but Omicron is rapidly eating into Delta's dominance. And with insufficient testing and lag times in sequencing, it has likely gained even more ground than these numbers indicate.

But what exactly gives Omicron its competitive advantage has so far been unclear. Preliminary data, announced via press release Wednesday, which provide a first look at how Omicron may behave inside the human body, offers a clue to what might be behind its superspreading powers: more virus in people's airways, which could mean more virus in the air.

The new research comes from a Hong Kong University team led by public health professor Michael Chan Chi-wai and pathologist John Nicholls. Previously, the researchers pioneered a method for growing human tissues extracted from the lung and respiratory tract, which they used to study how SARS-CoV-2 invaded cells and replicated compared to other dangerous coronaviruses. Using this same system, they analyzed how live, replicating particles of Omicron infected the tissues. They found that over the first 24 hours, Omicron multiplied about 70 times faster inside respiratory-tract tissue than the Delta variant. When they ran the same experiments with the lung tissue, they found Omicron was actually worse at infecting those cells than either Delta or the original strain of the virus that originated in Wuhan.

That seemingly helps explain the variant's infectiousness, and also why it may not be causing as severe sickness as previous variants of the coronavirus — as early data suggest.

"That basically tells us it's inherently more transmissible," said Müge Çevik, a clinical lecturer in infectious diseases and medical virology at the University of St. Andrews School of Medicine in Scotland. "The reason Omicron is spreading so fast is not just because of immune evasion" — its ability to elude antibodies from vaccines or infection with earlier variants — "but a combination of that with intrinsic enhanced infectiousness."

How much more infectious still remains to be seen, Çevik said. This finding, from tissue studied in the lab, suggests that Omicron's mutations have turbo-boosted its ability to enter human cells and replicate inside them. But until scientists have collected and analyzed samples from inside patients' noses and throats, they won't know if the variant actually leads to substantially higher viral loads, which has been the key to Delta's own enhanced infectiousness over previous strains. These tissues were studied in isolation, without the presence of immune cells, which studies have shown should still slow down Omicron's self-copying sprint.

The University of Hong Kong results haven't been peer-reviewed or published as a preprint. And STAT was unable to reach anyone on the research team. But the findings support another study with SARS-CoV-2 pseudoviruses, published as a preprint Tuesday, by scientists at the Ragon Institute of Massachusetts General Hospital. They found that Omicron's heavily mutated spike protein outmuscled both Delta and the original coronavirus at attaching to ACE2 — the receptor that the virus uses to enter human cells. "We find Omicron pseudovirus is more infectious than any other variant tested," they wrote.

Together, these early lab findings reflect the epidemiological data coming in, said Çevik. In particular, she pointed to reports of recent superspreading events; a holiday party at a restaurant in Norway where more than half of the 120 attendees, all vaccinated and who had taken a rapid test the day before, contracted the virus; a night club at the center

of Australia's Omicron outbreak where more than 200 people got infected; a wedding in Wisconsin that left a dozen vaccinated (and some boosted) health care workers positive for the new variant. While only anecdotes, they're difficult to explain unless Omicron is, in fact, spreading more efficiently through the air.

While the Hong Kong team analyzed tissue of the bronchi — the big tubes that move air from the nose and mouth into the lungs — the types of cells that Omicron infected, and replicated rapidly inside, are found higher up in the airway as well. "This suggests much increased potential for aerosol generation during breathing," said Don Milton, an aerobiologist at the University of Maryland, who has studied the physical dynamics of respiratory viruses for decades.

Breathing, he explained, is essentially the process of opening and closing your airways. When they close, they become covered in a thin liquid film, which acts kind of like the surface of a bubble. When you breathe in and your airways open, the bubble bursts, creating tiny particles known as aerosols, which you then breathe out and can hang around in the air and be breathed in by other people.

Studies going back to the 1970s have shown that when people are infected with a respiratory virus or bacteria, those microorganisms tend to concentrate on the thinnest part of the bubble. The result is that the tiniest particles, the ones that can stay aloft the longest and travel the farthest distances, tend to have higher concentrations of disease-causing pathogens than the larger particles you generate when coughing or sneezing. Despite much scientific debate early on in the pandemic, the evidence now suggests that SARS-CoV-2 is primarily spread through infectious aerosols that people breathe in.

As part of a $15 million project funded by the National Institutes of Health, Milton's lab in Maryland has been measuring the amount of SARS-CoV-2 inside the breath of infected college students and staff,

using a medieval-looking device he invented called the Gesundheit II. Although his team hasn't yet used it on anyone with Omicron, when they get their first cases, he expects to find more copies of the virus than with any previous variant. "Those early versions spreading in 2020 were not nearly as good at generating aerosols as the Alpha variant," Milton said. "Alpha was more transmissible, and then came Delta, which was more transmissible than Alpha, and Omicron is upping the game even more. So, I'm worried."

He recommended upgrading to more tight-fitting masks better at filtering out aerosols, like a KF94 or N95, and wearing them in indoor public spaces, and stressed the importance of ventilation and air filtration.

Çevik isn't so sure these types of interventions can alter Omicron's meteoric trajectory at this point. "There's just not enough time," she said. That's why she thinks the best strategy is to get boosted immediately with an additional dose of a Covid vaccine. Studies have shown that Omicron has an easier time than previous variants at infecting vaccinated people, but that booster shots restore immune protection. "We're all going to get infected with Omicron. At this moment, what's important is whether you're vaccinated or not when you're exposed to the virus."

SARS-CoV-2 often attacks first via the respiratory tract. People experience a sore throat, a stuffy nose, a loss of smell. If unchecked by the immune system, the virus then makes its way down into the lungs, where it can lead to pneumonia and kick off life-threatening inflammation known as a cytokine storm. Vaccines injected into the arm have been highly effective at preventing this progression to severe disease and death. But they don't generate the kind of first-line defense in the nasal passages you'd need to block all infection (which has been behind the argument for developing intranasal vaccines).

If Omicron's mysterious evolutionary journey proves to truly have given it a preference for airways over the lungs that could be a really good thing, said Stanley Perlman, a longtime coronavirus researcher at the University of Iowa. "If your lungs don't work, then your heart has to work harder, your kidneys have to work harder; there's a big difference between pneumonia and an upper respiratory tract infection," he said.

But that's all a big if, right now, while we wait for more clinical data that can illuminate what Omicron is really doing inside the bodies of people it infects. "It all hints that this virus could be going in the right way, that it's slowly turning into a common cold-causing coronavirus, like we're all hoping for," said Perlman. "But right now, it's really just hints."

SARS-CoV-2 transitioning into a virus that's always around but doesn't trigger tsunamis of health care system-crashing illness, becoming endemic, like a handful of other human coronaviruses before it, has been seen by many scientists as the most likely scenario for how the pandemic ends. But predicting when exactly that will happen has been anyone's guess.

Çevik had put the odds on that day coming years into the future. Now Omicron seems to be speeding up that timeline. "I didn't think it would happen this quickly, but this variant has the potential to expedite that process of the virus becoming endemic."

Jeremy Kamil, a virologist at Louisiana State University Health Shreveport, said it's too soon to say whether Omicron will be the force that pushes the pandemic into a seasonal settle-down. "This virus has always defied projections," he said. While the most likely scenario remains an endemic transition — the virus won't keep evolving into more threatening versions forever — it also won't be going away anytime soon, he said. "I think people are really desperate for answers, everyone's exhausted, so we want to hear something encouraging, but it's important not to make that leap without the data."

For now, even if Omicron does prove to cause milder disease in most people, there's still real cause for alarm because of its potential to infect unprecedented numbers in the population all at once. "The resulting surge will cause so many infections that they accumulate into a risk to health care," Bill Hanage, an epidemiologist at Harvard's T.H. Chan School of Public Health told STAT via email. "That is what matters."

After two years of caring for Covid-19 patients around the clock, including the latest Delta-inflicted surges, hospital systems are already stretched dangerously thin. Health care workers are quitting in droves — at least 18% have left the workforce since the pandemic began, leading to shortages of nurses nationwide. And while there are now potent new drugs and monoclonal antibodies to treat Covid patients, without enough staff to put IVs in arms, things could get ugly quickly. In South Africa earlier this month, 20% of hospital staff got sidelined with Omicron infections. If that happened here, it could push hospital systems beyond the point of recognizability.

Scientists expect more data on Omicron to help answer some of the lingering questions about how it spreads and how much harm it can do. But by then, we may be in the middle of the biggest wave yet. "Right now we're seeing England's numbers literally jumping off the chart," said Kamil. "And we expect to see this soon everywhere."

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