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How bad is Omicron? What scientists know so far

COVID researchers are working at breakneck speed to learn about the variant's transmissibility, severity and ability to evade vaccines.

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South Africa is dealing with a large uptick in COVID cases, driven by a new, heavily mutated variant called Omicron. Credit: Guillem Sartorio/AFP/Getty

Barely a week has elapsed since scientists in Botswana and South Africa alerted the world to a fast-spreading SARS-CoV-2 variant now known as Omicron. Researchers worldwide are racing to understand the threat that the variant — now confirmed in more than 20 countries — poses to the world. Yet it might take scientists weeks to paint a more complete picture of Omicron, and to gain an understanding of its transmissibility and severity, as well as its potential to evade vaccines and cause reinfections.

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"Wherever I go, everyone says: tell us more about Omicron," says Senjuti Saha, a molecular microbiologist and director of the Child Health Research

Heavily mutated Omicron variant puts scientists on alert

Foundation in Dhaka, Bangladesh. "There is so little understanding of what's going on, and that's true, even for scientists."

Nature rounds up what scientists know so far about the Omicron variant.

How fast is Omicron spreading?

Omicron's rapid rise in South Africa is what worries researchers most, because it suggests the variant could spark explosive increases in COVID-19 cases elsewhere. On 1 December, South Africa recorded 8,561 cases, up from the 3,402 reported on 26 November and several hundred per day in mid-November, with much of the growth occurring in Gauteng Province, home to Johannesburg.

Epidemiologists measure an epidemic's growth using *R*, the average number of new cases spawned by each infection. In late November, South Africa's National Institute for Communicable Diseases (NICD) in Johannesburg determined that *R* was above 2 in Gauteng. That level of growth was last observed in the early days of the pandemic, Richard Lessels, an infectious-disease physician at KwaZulu-Natal University in Durban, South Africa, told a press briefing last week.

Gauteng's *R* value was well below 1 in September — when Delta was the predominant variant and cases were falling — suggesting that Omicron has the potential to spread much faster and infect vastly more people than Delta, says Tom Wenseleers, an evolutionary biologist at the Catholic University of Leuven in Belgium. Based on the rise in COVID-19 cases and on sequencing data, Wenseleers estimates that Omicron can infect three to six times as many people as Delta, over the same time period. "That's a huge advantage for the virus — but not for us," he adds.

Researchers will be watching how Omicron spreads in other parts of South Africa and globally to get a better read on its transmissibility, says Christian Althaus, a computational epidemiologist at the University of Bern, Switzerland. Heightened surveillance in South Africa could cause researchers to overestimate Omicron's fast growth. But if this pattern is repeated in other countries, it would be very strong evidence that Omicron has a transmission advantage, adds Althaus. "If it doesn't happen, for example, in European countries, it means things are a bit more complex and strongly depend on the immunological landscape. So we have to wait."

Although genome sequencing is needed to confirm Omicron cases, some PCR tests can pick up a hallmark of the variant that distinguishes it from Delta. On the basis of this signal, there are preliminary indications that cases, although extremely low in number, are rising in the United Kingdom. "That's certainly not what we want to see right now and suggests that Omicron could indeed also have a transmission advantage in the UK," Althaus adds.

Can Omicron overcome immunity from vaccines or infection?

The variant's swift rise in South Africa hints that it has some capacity to evade immunity. Around one-quarter of South Africans are fully vaccinated, and it's likely that a large fraction of the population was infected with SARS-CoV-2 in earlier waves, says Wenseleers, based on heightened death rates since the start of the pandemic.

In this context, Omicron's success in southern Africa might be due largely to its capacity to infect people who recovered from COVID-19 caused by Delta and other variants, as well as those who've been vaccinated. A 2 December preprint[1] from researchers at the NICD found that reinfections in South Africa have increased as Omicron has spread. "Unfortunately, this is the perfect environment for immune-escape variants to develop," says Althaus.

How well the variant spreads elsewhere might depend on factors such as vaccination and previous infection rates, says Aris Katzourakis, who researches viral evolution at the University of Oxford, UK. "If you throw it into the mix in a highly vaccinated population that has given up on other control measures, it might have the edge there."

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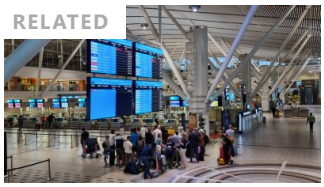

Omicron-variant border bans ignore the evidence, say scientists

Researchers want to measure Omicron's ability to evade immune responses and the protection they offer. For instance, a team led by Penny Moore, a virologist at the NICD and the University of the Witwatersrand in Johannesburg, is measuring the ability of neutralizing, or virus-blocking, antibodies triggered by previous infection and vaccination to stop Omicron from infecting cells. To test this in the laboratory, her team is making 'pseudovirus' particles — an engineered version of HIV that uses SARS-CoV-2's spike protein to infect cells — that match Omicron, which harbours as many as 32 changes to spike.

Another South Africa-based team, led by virologist Alex Sigal at the Africa Health Research Institute in Durban, is conducting similar tests of virus-neutralizing antibodies using infectious SARS-CoV-2 particles. So is a team led by Pei-Yong Shi, a virologist at the University of Texas Medical Branch in Galveston, who is collaborating with the makers of the Pfizer–BioNTech vaccine to determine how it holds up against Omicron. "I was really very concerned when I saw the constellation of mutations in the spike," he says. "We just have to wait for the results."

Previous studies of Omicron's spike mutations — particularly in the region that recognizes receptors on human cells — suggest that the variant will blunt the potency of neutralizing antibodies. For instance, in a September 2021 *Nature* paper[2], a team co-led by Paul Bieniasz, a virologist at Rockefeller University in New York City, engineered a highly mutated version of spike — in a virus incapable of causing COVID-19 — that shares numerous mutations with Omicron. The 'polymutant spike' proved fully resistant to neutralizing antibodies from most of the people they tested, who had either received two doses of an mRNA vaccine or recovered from COVID-19. With Omicron, "we expect there to be a significant hit", says Bieniasz.

People wait to be inoculated at a vaccination centre

Vaccines' potency against the Omicron variant could be blunted, early analyses suggest. Credit: Horacio Villalobos/Corbis/Getty

How will vaccines fare against Omicron?

If Omicron can dodge neutralizing antibodies, it does not mean that immune responses triggered by vaccination and prior infection will offer no protection against the variant. Immunity studies suggest that modest levels of neutralizing antibodies may protect people from severe forms of COVID-19, says Miles Davenport, an immunologist at the University of New South Wales in Sydney, Australia.

Other aspects of the immune system, particularly T cells, may be less affected by Omicron's mutations than are antibody responses. Researchers in South Africa plan to measure the activity of T cells and another immune player called natural killer cells, which might be especially important for protection against severe COVID-19, says Shabir Madhi, a vaccinologist at the University of the Witwatersrand.

Madhi, who has led COVID-19 vaccine trials in South Africa, is also part of efforts to conduct epidemiological studies of vaccines' effectiveness against Omicron. There are anecdotal reports of breakthrough infections involving all three vaccines that have been administered in South Africa — Johnson & Johnson, Pfizer–BioNTech and Oxford–AstraZeneca. But Madhi says researchers will want to quantify the level of protection against Omicron provided by vaccines, as well as by previous infection.

He suspects that the results will be reminiscent of how the AstraZeneca–Oxford vaccine performed against the Beta variant, an immune-evading variant that was identified in South Africa in late 2020. A trial led by Madhi found that the vaccine offered little protection against mild and moderate disease, while a real-world analysis in Canada showed greater than 80% protection against hospitalization.

If Omicron behaves similarly, Madhi says, "we're going to see a surge of cases. We're going to see lots of breakthrough infections, lots of reinfections. But there's going to be this unhinging of the case rate in the community compared to the hospitalization rate". Early reports suggest that most breakthrough infections with Omicron have been mild, says Madhi. "For me, that is a positive signal."

Will current boosters improve protection against Omicron?

The threat of Omicron has prompted some rich countries, such as the United Kingdom, to accelerate and broaden the roll-out of COVID vaccine booster doses. But it's not yet clear how effective these doses will be against this variant.

Third doses supercharge neutralizing-antibody levels, and it's likely that this will provide a bulwark against Omicron's ability to evade these antibodies, says Bieniasz. His team's work on the polymutant spike found that people who had recovered from COVID-19 months before receiving their jabs had antibodies capable of blocking the mutant spike. To Bieniasz, those results suggest that people with repeated exposure to SARS-CoV-2's spike protein, be it through infection or a booster dose, are "quite likely to have neutralizing activity against Omicron".

Does Omicron cause milder or more severe disease than previous variants?

Early reports linked Omicron with mild disease, raising hopes that the variant might be less severe than some of its predecessors. But these reports — which are often based on anecdotes or scant scraps of data — can be misleading, cautions Müge Çevik, an infectious-disease specialist at the University of St Andrews, UK. "Everyone is trying to find some data that could guide us," she says. "But it's very difficult at the moment."

A major challenge when assessing a variant's severity is how to control for the many confounding variables that can influence the course of disease, particularly when outbreaks are geographically localized. For example, reports of mild disease from Omicron infection in South Africa could reflect the fact that the country has a relatively young population, many of whom have already been exposed to SARS-CoV-2.

During the early days of the Delta outbreak, there were reports that the variant was causing more serious illness in children than did other variants — an association that dissolved once more data were collected, Çevik says.

Researchers will be looking for data on Omicron infections in other countries. This geographical spread, and a larger sample size as cases accrue, will give researchers a better idea of how generalizable the early reports of mild disease might be. Ultimately, researchers will want to conduct case-controlled studies, in which two groups of participants are matched in terms of important factors such as age, vaccination status and health conditions. Data from both groups will need to be collected at the same time, because the number of hospitalizations can be influenced by overall hospital capacity in a region.

And, crucially, researchers will need to control for the level of economic deprivation. A rapidly spreading new variant may reach vulnerable groups more rapidly, Çevik says, by nature of their work or living conditions. And such groups often experience more severe disease.

All of this will take time. "I think the severity question will be one of the last bits that we'll be able to untangle," she says. "That's how it happened with Delta."

Where has Omicron spread and how are scientists tracking it?

More countries are detecting the Omicron variant, but the capacity to rapidly sequence viruses from positive COVID-19 tests is concentrated in wealthy countries, meaning that early data on Omicron's spread will be skewed.

Surveillance efforts in Brazil and some other countries are taking advantage of a distinctive result on a particular PCR test that could allow them to pinpoint potential Omicron cases for sequencing, says virologist Renato Santana at the Federal University of Minas Gerais in Brazil. The test looks for segments of three viral genes, one of which is the gene that encodes for the spike protein. Mutations in Omicron's spike gene prevent its detection in the test, meaning that samples containing the variant will test positive for only two of the genes.

Even so, not everyone uses that test and it could take some time before Omicron's spread is fully mapped. Despite some guidelines urging countries to sequence 5% of their samples that test positive for SARS-CoV-2, few can afford to do so, says computational virologist Anderson Brito at the All for Health Institute in São Paulo, Brazil. And Brito worries that the travel bans enacted by some countries against South Africa, and other southern African nations, in the wake of its Omicron discovery could discourage governments from sharing genomic surveillance data. "We are punishing those who did a good job," he says.

In Bangladesh, which sequences about 0.2% of positive coronavirus samples, researchers would be eager to ramp up sequencing to keep tabs on Omicron and other emerging variants, says Saha. But resources are limited. Bangladesh is recovering from a large dengue outbreak, she adds. "In the global south, we are all worried about COVID, but let's not forget our endemic diseases," Saha says. "We can only do so many."

doi: https://doi.org/10.1038/d41586-021-03614-z

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