News in focus

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South Africa is dealing with a large uptick in COVID-19 cases, driven by a new, heavily mutated variant called Omicron.

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.

By Ewen Callaway & Heidi Ledford

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 30 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.

"There is so little understanding of what's going on, and that's true even for scientists," says Senjuti Saha, a molecular microbiologist and director of the Child Health Research Foundation in Dhaka, Bangladesh.

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 that the variant could spark explosive increases in COVID-19 cases elsewhere. On 1 December, South Africa recorded 8,561 cases, up from 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 Lessells, an infectious-disease physician at the University of KwaZulu-Natal 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. 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."

Vaccines' potency against the Omicron variant could be blunted, early analyses suggest.

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 proportion of the population was infected with SARS-CoV-2 in earlier waves, says Wenseleers.

In this context, Omicron's success in southern Africa might be due largely to its capacity to infect people who have recovered from COVID-19 caused by Delta and other variants, as well as those who've been vaccinated. A 2 December preprint from researchers at the NICD found that reinfections in South Africa have increased as Omicron has spread (J. R. C. Pulliam *et al.* Preprint at medRxiv https://doi.org/g8gj; 2021). "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."

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 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 spike changes.

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 paper, a team co-led by Paul Bieniasz, a virologist at the 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 (F. Schmidt *et al.* *Nature* https://doi.org/gmvn4z; 2021). The 'polymutant spike' proved fully resistant to neutralizing antibodies from most of the people the team 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.

"This is the perfect environment for immune-escape variants to develop."

How will vaccines fare against Omicron?

If Omicron can dodge neutralizing antibodies, it does not mean that immune responses triggered by vaccination and previous infection will offer no protection against the variant. Immunity studies suggest that modest levels of neutralizing antibodies might 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, might be less affected by Omicron's mutations than are antibody responses. Researchers in South Africa plan to measure the activity of T cells and other immune players called natural killer cells, which might be 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, but 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

HORACIO VILLALOBOS/CORBIS/GETTY

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."

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.

A challenge when assessing a variant's severity is how to control for the confounding variables that can influence the course of disease, particularly when outbreaks are 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.

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 age, vaccination status and health conditions.

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," says Çevik.

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.

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 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 in the wake of the Omicron discovery could discourage governments from sharing genomic surveillance data. "We are punishing those who did a good job," he says.

News analysis

Omicron border bans ignore the evidence, say scientists

Researchers say travel restrictions are too late and might even slow studies of Omicron.

More than 50 countries have stepped up border controls to keep out Omicron, a highly mutated SARS-CoV-2 variant of concern that is sweeping through South Africa. But researchers say restrictions targeting only travellers from a handful of countries are unlikely to work, and come at significant cost.

Scientists in some affected countries also say that travel bans risk slowing down urgent research on Omicron, by limiting the arrival of imported lab supplies.

"I'm not that optimistic that the way in which these measures are being rolled out right now will have an impact," says Karen Grépin, a health economist at the University of Hong Kong.

"It's too late. The variant is circulating globally," agrees Kelley Lee, who studies global health at Simon Fraser University in Burnaby, Canada.

Many travel bans target South Africa, which raised the alarm about Omicron on 24 November, as well as Botswana, Lesotho, Eswatini, Zimbabwe and Namibia.

In South Africa's most populous province, Gauteng, Omicron accounts for the majority of virus samples sequenced in the past few weeks. The World Health Organization (WHO) designated it a variant of concern because it has many mutations in its spike protein, which could make it more infectious or improve its ability to evade antibodies.

Researchers say border restrictions might deter nations from alerting the world to variants in future. They will also slow down urgent research, because few planes carrying cargo — including lab supplies needed for sequencing — are now arriving in South Africa. Researchers are racing to understand how Omicron's transmissibility and ability to evade immunity created by vaccines differ from those of pre-existing SARS-CoV-2 variants. They're also investigating the relative severity of the illness Omicron causes.

Travel bans "affect the speed at which scientists are able to investigate", says Shabir Madhi, a vaccinologist at the University of the Witwatersrand in Johannesburg, South Africa. Researchers might also struggle to share samples with global collaborators.

Tulio de Oliveira, a bioinformatician at the University of KwaZulu-Natal in Durban, South Africa, says the slashing of commercial flights could threaten crucial genomic surveillance efforts by a network of institutions in the country. "By next week, if nothing changes, we will run out of sequencing reagents," he says.

Last week, the WHO published guidance that recommended against travel bans to control viral spread. The advice includes specific recommendations for measures that would be useful, including quarantining new arrivals, and testing travellers for SARS-CoV-2 before and after journeys.

The WHO guidance represents a clear shift in researchers' understanding of the effectiveness of travel restrictions over the course of the pandemic. Before COVID-19, scattered data led many public-health agencies to denounce border restrictions — although almost every country imposed them in early 2020. But the pandemic has revealed that restrictions can be useful in certain contexts (K. A. Grépin *et al*. *BMJ Glob. Health* **6**, e004537; 2021), especially for relatively geographically isolated nations such as Australia and New Zealand.

One lesson has been that restrictions are most effective when implemented rapidly, but the Omicron-related border closures were too late, says Grépin. The variant has now been detected on every populated continent and in more than 20 countries and territories. "As soon as countries start looking for it, they're finding it, so the advantage of time is probably gone," she says.

Restrictions are also probably most effective at slowing the number of initial cases in a country when they reduce the total volume of arrivals, rather than when they focus on specific countries, says Lee.

For such measures to be effective, they also need to be comprehensive, including regular testing and at least a week of quarantine (B. Yang *et al*. *Lancet Reg. Health West. Pac*. **13**, 100184; 2021) for travellers who do arrive, says Catherine Worsnop, who studies international cooperation during global health emergencies at the University of Maryland in College Park. But this, she says, is something "most countries have not done".

By Smriti Mallapaty