The next variant: three key questions about what's after Omicron

The number of SARS-CoV-2 infections is finally falling in some nations. But after two years of oscillating between pandemic surges and retreats, even people in these countries cannot help but wonder when the next blow will come — and what form it will take. Here are three key questions scientists would like to answer about the follow-up to Omicron.

When will the next variant of concern emerge?

There is no way to know for sure when a variant will become dominant, or whether it will become a 'variant of concern' — meaning that there are signs that it has picked up worrying new properties, such as more rapid spread.

The public is most familiar with the first dominant sub-variants of Omicron and Delta. But researchers have been tracking a host of others that are jockeying for dominance. In the United Kingdom, for example, a Delta variant called AY.4.2 was rapidly replacing one called AY.4 in late 2021. "And then Omicron came along and just blew up," says bioinformatician Andrew Page at the Quadram Institute in Norwich, UK.

The history of these viral dynamics suggests that a new variant will sweep through every few months, says Page. "They seem to happen quite regularly," he says. But whether that variant will become a variant of concern remains an open question. At present, the original BA.1 Omicron lineage is being replaced by one called BA.2. This lineage, although probably more transmissible than BA.1, does not seem to be a major change from the original one.

Such dynamics are probably common in viral pathogens. But the world has not followed a viral infection so closely before, says Page, and as a result, scientists have missed some details. The close scrutiny, however, is already diminishing: COVID-19 testing rates in the United Kingdom have declined, in part because Omicron tends to produce relatively mild disease. That means people are less likely to seek testing, and governments become less proactive in encouraging tests.

Eventually, this will weaken SARS-CoV-2 genomic surveillance efforts. When Omicron was discovered, the alarm was sounded very quickly, Page says, but in the future, it could take weeks longer. "There's no way that we can keep up the pace we've had so far," he says. "But if it's not causing severe disease, do you need to have such intense surveillance?"

Will the next variant cause severe disease?

Omicron is less likely to cause severe disease than previous variants of concern — a feature that has helped to temper the impact of its rampant spread.

That has fed speculation that the virus could be evolving towards a strain that induces milder disease, but SARS-CoV-2's evolutionary path remains unclear, says Andrew Rambaut, who studies viral evolution at the University of Edinburgh, UK. Thus far, new variants of concern have evolved not from the dominant preceding one, but from separate lineages. There is no guarantee that the next dominant variant will sprout from the 'mild' Omicron branch of the SARS-CoV-2 family tree. "It is possible that a later variant may be back to a Delta or Alpha lineage, with sufficient immune evasion to sweep Omicron away," says Rambaut.

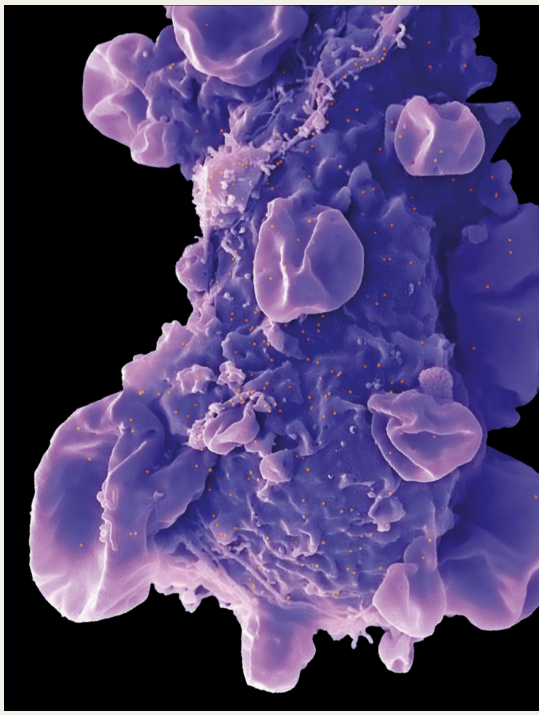
Researchers also still don't know the extent to which Omicron's relative mildness is due to the prevalence of immunity against SARS-CoV-2, rather than intrinsic properties of the virus itself. As more of the world's population becomes vaccinated, infected or both, immunity is likely to grow and so, too, will resilience against severe COVID-19.

But there are some differences in how Omicron behaves compared with previous variants, notes immunologist Wendy Burgers at the University of Cape Town in South Africa. Several animal studies, for example, have found that Omicron is less likely to affect the lungs[1]. "Will the next mutated variant have different properties?" she says. "I don't think there's any guarantee that those intrinsic differences might not be worse."

Will vaccines protect against new variants?

The 54 mutations in Omicron's genome — and particularly the 34 clustered in a key viral protein called spike — severely weakens the ability of COVID-19 vaccines to prevent infection. But protection against severe disease seems to have remained high, and probably contributed to the perceived mild disease caused by Omicron.

That bodes well for the resilience of vaccine-mediated immunity against future variants of concern, says Burgers. Although Omicron's spike mutations seem to weaken antibody defences, scientists have detected only slight declines in the ability of immune cells called T cells to recognize the virus. These cells are thought to be key to limiting the scope of a viral infection, killing off infected cells and limiting the virus's spread. "I really breathed a sigh of relief after Omicron," Burgers says. "I'm optimistic that the T-cell response will be quite resilient even if a new variant emerges."



Particles (orange; artificially coloured) of the SARS-CoV-2 Omicron variant bud from a cell.

STEVE GSCHMEISSNER/SPL

But Burgers notes that as antibodies become less relevant for immunity, T cells become more important, and a viral variant that can evade T-cell surveillance will have a key survival advantage. "The T-cell response is doing much more of the heavy lifting," she says. "So one thing we might start seeing is T-cell escape."

In viruses such as influenza, the ability to escape T-cell immunity develops gradually over the course of years. But it's hard to predict how quickly it will proceed in the middle of a pandemic, Burgers says.

It is also becoming more difficult for immunologists to anticipate how population

immunity will shape the course of the pandemic, as its drivers grow increasingly complex. People might have received one of several vaccines, or a combination of them, or been infected with one or more variants, with or without vaccination.

In general, this accumulation of exposures should boost immunity, says infectious-disease specialist Santiago Ávila Ríos at Mexico's National Institute of Respiratory Diseases in Mexico City. In a preprint, Ríos and his team reported that multiple exposures, either through vaccination or infection, amplified antibody responses, as well as responses by immune cells called B cells[2]. "Thus, as more persons become exposed to the virus through different mechanisms, the emergence of new variants of concern may impose a lower disease burden," he says.

But some types of exposure might be better than others for preparing the body to fight off new variants. One preprint[3] found that people who had been vaccinated and then became infected with Omicron had "whopping increases in antibodies", says co-author Penny Moore at the University of the Witwatersrand in Johannesburg, South Africa. Those antibodies could attach to and disarm multiple variants besides Omicron, a property called cross-reactivity.

But antibodies produced by people who have been infected with Omicron but not previously exposed to SARS-CoV-2 — either by vaccination or infection — were less robust in blocking other variants. "We can't assume that those people would be particularly well protected against incoming variants of concern," Moore says.

Ultimately, the data continue to point to the importance of vaccination, says Burgers. "We know that vaccines shore up our immunity and that immunity will be cross-reactive, when it comes to T cells, with another variant," she says. "There's a lot that we don't know, but there's a lot that's in our control."

By Heidi Ledford

1. Diamond, M. *et al*. Preprint at Research Square https://doi.org/10.21203/rs.3.rs-1211792/v1 (2021).
2. Bednarski, E. *et al*. Preprint at medRxiv https://doi.org/10.1101/2022.02.07.22270626 (2022).
3. Richardson, S.I. *et al*. Preprint at medRxiv https://doi.org/10.1101/2022.02.10.22270789 (2022).

News explainer

CALL TO SAFEGUARD 'CRISPR BABIES' SPARKS ETHICAL DEBATE

Fears of excessive interference cloud proposal for protecting children whose genomes were edited.

By Smriti Mallapaty

Two prominent bioethicists in China are calling on its government to set up a research centre dedicated to ensuring the well-being of the first children born with edited genomes. Scientists have welcomed the discussion, but many are concerned that the pair's approach would lead to unnecessary surveillance of the children.

The proposal comes ahead of the possibly imminent release from prison of He Jiankui, the researcher who in 2018 shocked the world by announcing the birth of babies whose genomes he had edited. He's actions were widely condemned by scientists around the world, who called for a global moratorium on editing embryos destined for implantation. Several ethics committees have since concluded that the technology should not be used to make changes that can be passed on.

Researchers say that the latest proposal, in a document by Qiu Renzong at the Chinese Academy of Social Science in Beijing and Lei Ruipeng at the Huazhong University of Science and Technology in Wuhan, is the first to discuss how to manage the children's unique situation. "It's an important document", and a welcome move by researchers in China, says Gaetan Burgio, a geneticist at the Australian National University in Canberra.

The document — which Qiu and Lei have shared with various scientists and several Chinese ministries, as well as with *Nature*, but which has not yet been published — states that the children need special protections because they're a "vulnerable group". Gene editing could have created errors in the children's genomes, which could be passed to their children. They recommend regular sequencing of the children's genomes to check for "abnormalities", including conducting genetic tests of their embryos in the future.

He Jiankui, jailed for editing embryos that he then implanted, could soon be released.

MARK SCHIEFELBEIN/AP/SHUTTERSTOCK

Qiu and Ruipeng also recommend that He contribute to the children's medical expenses, and take primary financial, moral and legal responsibility for their health and well-being, along with the Southern University of Science and Technology in Shenzhen, with which He was affiliated, and the government. Qiu says that he has submitted the document to the health, education, and science and technology ministries, and expects a positive response.

But Joy Zhang, a sociologist at the University of Kent in Canterbury, UK, says it is difficult for scientists to know what recommendations to make because there is almost no information about the children's current condition, and the circumstances of their conception. "China has kept everything so tight," she says.

Global shock

In 2018, the world learned that He had implanted embryos in which he had used CRISPR–Cas9 to edit a gene known as *CCR5*, which encodes an HIV co-receptor, with the goal of making them resistant to the virus. The implantation led to the birth of twins in 2018, and a third child was later born to separate parents. The parents had agreed to the treatment because the fathers were HIV-positive and the mothers were HIV-negative, and the couples were barred from access to alternative assisted-reproduction technologies in China.

In December 2019, He was sentenced to three years in prison. Sources close to him say that he should be released soon. Qiu says he might be assigned a research position.

Eben Kirksey, a medical anthropologist at Alfred Deakin Institute in Melbourne, Australia, who has written a book on human genome-editing, agrees that He should shoulder some responsibility for the children. He promised that they would receive health insurance for the first 18 years of their lives,