NIH) that describe work on what are known as enhanced potential pandemic pathogens (ePPPs). Two years later, *Science* reported (see go.nature.com/3kykntg) that the advisory panel quietly approved two experiments to manipulate avian-influenza viruses similar to those that set off the original uproar, prompting fresh calls for reform.

Although the scope of the NSABB's new review of risky pathogen research remains similar to the one it had planned for 2020, the COVID-19 pandemic will undoubtedly have an influence. The NIH, in particular, has been scrutinized during the pandemic for funding potentially risky coronavirus research.

In 2014, the WIV received funding from the NIH, through a subcontract with the New York-based research organization EcoHealth Alliance, to manipulate bat coronaviruses. Some of the funding came during the federal moratorium on gain-of-function research. But the NIH says it approved the funding because the experiments didn't meet its definition of ePPP research, a stance that has been contested by some US policymakers.

In response, Republican lawmakers have introduced draft legislation that would again place a moratorium on the funding of gain-of-function research. This move has alarmed some researchers, including those who attended the 27 April listening session. Felicia Goodrum Sterling, president of the American Society of Virology, based in Ann Arbor, Michigan, pointed out that rapid advances in COVID-19 therapeutics and vaccines were made possible, in part, by manipulating viruses. For example, to create the Johnson & Johnson and Oxford–AstraZeneca COVID-19 vaccines, scientists modified adenoviruses to produce the SARS-CoV-2 spike protein.

Policy reform wanted

Many at the listening session pushed for stricter oversight of risky pathogen research, however. Some suggested that the HHS advisory-panel approach be extended to other US entities. Gregory Koblentz, a biosecurity-policy specialist at George Mason University in Arlington, Virginia, pointed out that pharmaceutical firms, philanthropic institutions and federal agencies, including the Department of Energy, also conduct research on potentially risky pathogens. They should adhere to the same guidelines, he said.

In a nod to concerns about the WIV, others thought that the US government should consider more carefully how it funds gain-of-function research abroad, and should encourage other countries to adopt a similar ePPP review process.

Some are also calling for changes to the HHS ePPP review panel itself. Lipsitch would like the identities of the advisers on the panel to be revealed and their comments on research grants to be published (these details are currently confidential). Others worry that if this were to happen, advisers might decline to participate over concerns about harassment. Scientists have reported an uptick in harassment during the pandemic, particularly those who discuss the origins of SARS-CoV-2.

Still, the US government could be more transparent when it comes to biosecurity research, experts said. Tom Inglesby, director of the Johns Hopkins Center for Health Security in Baltimore, Maryland, called for the risks and benefits of funded experiments to be shared openly, the specific criteria used to evaluate projects to be disclosed and for better guidance in communicating results to the public. This would go a long way to improving public trust in science and the NIH, which has declined during the pandemic, he said.

The fact that policies governing ePPPs continue to be tweaked more than a decade after the controversial avian-influenza experiments shows that the issue is extremely nuanced, Koblentz told *Nature*. He acknowledges the benefits of risky pathogen research, but he worries that researchers will become complacent about the inherent risk if stricter policies aren't put in place — especially given that the number of laboratories equipped to handle dangerous pathogens is increasing worldwide.

The NIH plans to host more listening sessions and a public stakeholder meeting before the NSABB finalizes its draft report.

ARE COVID SURGES BECOMING MORE PREDICTABLE?

New Omicron relatives BA.4 and BA.5 offer hints about the future of SARS-CoV-2.

By Ewen Callaway

Here we go again. Nearly six months after researchers in South Africa identified the Omicron coronavirus variant, two offshoots of the game-changing lineage are once again driving a surge in COVID-19 cases there.

Several studies released in the past week show that the variants — known as BA.4 and BA.5 — are slightly more transmissible than earlier forms of Omicron[1], and can dodge some of the immune protection conferred by previous infection and by vaccination[2,3].

"We're definitely entering a resurgence in South Africa, and it seems to be driven entirely by BA.4 and BA.5," says Penny Moore, a virologist at the University of the Witwatersrand

SHIRAAZ MOHAMED/AP/SHUTTERSTOCK

Infections with new variants of Omicron are rising in South Africa and Europe.

in Johannesburg, South Africa, whose team is studying the variants. "We're seeing crazy numbers of infections."

However, scientists say it is not yet clear whether BA.4 and BA.5 will cause much of a spike in hospitalizations in South Africa or elsewhere. High levels of population immunity — provided by previous waves of Omicron infection and by vaccination — might blunt much of the damage previously associated with new SARS-CoV-2 variants.

Moreover, the rise of BA.4 and BA.5 — as well as that of another Omicron offshoot in North America — could mean that SARS-CoV-2 waves are beginning to settle into predictable patterns, with new waves periodically emerging from circulating strains (see 'Omicron's new identities'). "These are the first signs that the virus is evolving differently" compared with the first two years of the pandemic, when variants seemed to appear out of nowhere, says Tulio de Oliveira, a bioinformatician at Stellenbosch University in South Africa, who led one of the studies.

Transmission advantage

By analysing viral genomes from clinical samples, de Oliveira and his colleagues found[1] that BA.4 and BA.5 emerged in mid-December 2021 and early January 2022, respectively. The lineages have been rising in prevalence since then, and currently account for 60–75% of COVID-19 cases in South Africa. Researchers have also identified the variants in more than a dozen other countries, mostly in Europe.

On the basis of the growth in BA.4 and BA.5 case numbers in South Africa — which now average nearly 5,000 per day, from a low of around 1,200 in March — de Oliveira's team estimates that the variants are spreading slightly faster than did the BA.2 sub-lineage of Omicron (which itself was a bit more transmissible than the first Omicron variant, BA.1). The study was posted on the medRxiv preprint server and has not yet been peer reviewed.

The boost in transmissibility is "quite an advantage", and similar in magnitude to the advantages that some other fast-spreading SARS-CoV-2 variants had over their predecessors, says Tom Wenseleers, an evolutionary biologist at the Catholic University of Leuven in Belgium. "Taking everything together and looking at all the data, it seems a sizeable new infection wave is certain to come."

Jesse Bloom, a viral evolutionary biologist at Fred Hutch, a research centre in Seattle, Washington, agrees that BA.4 and BA.5 are spreading faster than other Omicron lineages. "What is still unclear is why they are more transmissible," he says. "One possibility is that they are just inherently better at transmitting." The other is that the variants are better at eluding immune responses such as antibodies, allowing them to infect people with prior immunity.

Both are closely related to BA.2 — although exactly how is not clear, Bloom adds. BA.4 and BA.5 both carry a key mutation called F486V in their spike proteins — the viral protein responsible for infection and the prime target of immune responses. Bloom's team has previously found that this mutation could help variants to dodge virus-blocking antibodies.

Further studies suggest that BA.4 and BA.5 are spreading, at least in part, because of their ability to evade immune responses. A team led by virologist Alex Sigal at the Africa Health Research Institute in Durban, South Africa, analysed blood samples from 39 people who had been infected during the first Omicron wave, 15 of whom had been vaccinated[2].

> **"Looking at all the data, it seems a sizeable new infection wave is certain to come."**

In lab experiments, antibodies in the samples were several times less effective at preventing cells from being infected by BA.4 or BA.5 than at keeping out the original Omicron. But antibodies from vaccinated people were more potent against the new variants than were those from unvaccinated people. The study was posted on medRxiv.

Another paper, posted on the ResearchSquare preprint server and led by virologist Xiaoliang Xie at Peking University in Beijing, found that antibodies triggered by BA.1 infection were less potent against BA.4 and BA.5. Moore says the results chime with her unpublished experiments, too.

BA.4 and BA.5's capacity to escape immunity, although not dramatic, "is enough to cause trouble and lead to an infection wave" — but the variants are not likely to cause disease much more severe than was seen during the previous wave, especially in vaccinated people, Sigal said on Twitter. "They clearly have an advantage in antibody escape, which is one contributing factor in why they are spreading," says Bloom.

Hospitalizations are slowly ticking up in South Africa — from a low of just under 2,000 people in early April — but researchers say it's too soon to tell whether BA.4 and BA.5 will put much pressure on health-care systems.

The next wave

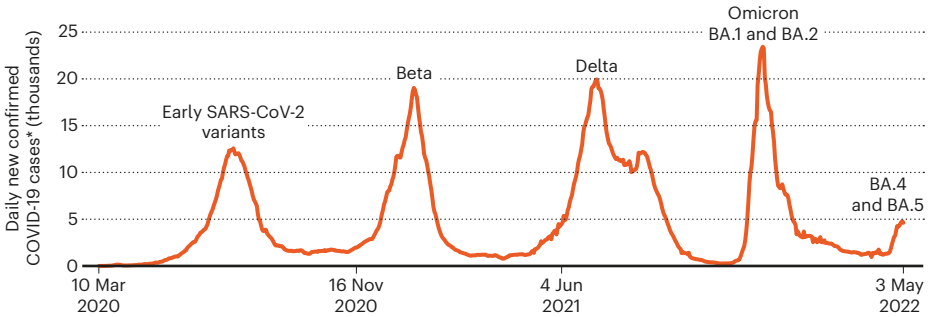
Although BA.4 and BA.5 have been detected in several European countries and in North America, the variants might not set off a fresh COVID-19 wave there — at least right away. The closely related BA.2 variant has just swept through Europe, so the population's immunity could still be high, says Wenseleers. "It gives hope that maybe in Europe it will have a smaller advantage and will cause a smaller wave."

Some parts of North America are also seeing the rise of other Omicron sub-lineages that have spike-protein mutations in some of the same places as in BA.4 and BA.5. Variant BA.2.12.1 also has the capacity to evade antibodies triggered by a previous Omicron infection and vaccination, according to Xie's study[3].

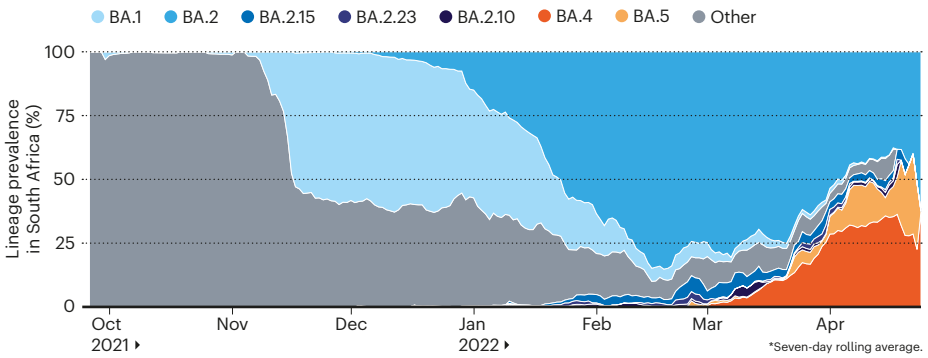
The emergence of these strains suggests that the Omicron lineage is continuing to make

OMICRON'S NEW IDENTITIES

Cases of COVID-19 are rising again in South Africa, after the emergence of Omicron variants called BA.4 and BA.5.



BA.4 and BA.5 spread faster than previous Omicron variants and are accounting for a growing proportion of COVID-19 cases in South Africa.



SOURCE: TOP, OUR WORLD IN DATA; BOTTOM, OUTBREAK.INFO

gains by eroding immunity, says David Ho, a virologist at Columbia University in New York City. "It's pretty clear that there are a few holes in Omicron that are gradually being filled up by these new sub-variants."

If SARS-CoV-2 continues on this path, its evolution could come to resemble that of other respiratory infections, such as influenza. Immune-evading mutations in circulating variants, such as Omicron, could combine with dips in population-wide immunity to become the key drivers of periodic waves of infection. "It is probably what we should expect to see more and more of in the future," says Moore.

Previous variants, including Alpha, Delta and Omicron, differed widely from their immediate predecessors, and all emerged from distant branches of the SARS-CoV-2 family tree.

Wenseleers and other scientists say we shouldn't rule out more such surprises from SARS-CoV-2. For instance, Delta hasn't completely vanished and, as global immunity to Omicron and its family increases, a Delta descendant could mount a comeback. Whatever their source, new variants seem to emerge roughly every six months, notes Wenseleers, and he wonders whether this is the structure that COVID-19 epidemics will settle into.

"That is one way to read the patterns that have been observed so far," says Bloom. "But I think we should be cautious in extrapolating general rules from a fairly short observation time frame."

1. Tegally, H. *et al*. Preprint at medRxiv https://doi.org/10.1101/2022.05.01.22274406 (2022).
2. Khan, K. *et al*. Preprint at medRxiv https://doi.org/10.1101/2022.04.29.22274477 (2022).
3. Xie, X. *et al*. Preprint at ResearchSquare https://doi.org/10.21203/rs.3.rs-1611421/v1 (2022).

TRUE COVID DEATH TOLL COULD BE MORE THAN DOUBLE OFFICIAL COUNT

The World Health Organization's long-awaited estimate is in line with other studies.

By David Adam

Some 15 million people died during the first two years of the COVID-19 pandemic, new figures from the World Health Organization (WHO) suggest. That's about 2.7 times the toll officially reported to the agency by individual countries. The difference is based on estimates of 'excess mortality', which include deaths missed by national reporting systems.

The figures, released last week, are the latest in a series of estimates of the global pandemic death toll, which epidemiologists and public-health experts say are necessary to assess decisions taken and plan more effectively for future events.

"These sobering data not only point to the impact of the pandemic but also to the need for all countries to invest in more resilient health systems that can sustain essential health services during crises, including stronger health information systems," WHO director-general Tedros Adhanom Ghebreyesus said in a press statement.

The WHO's estimates of total deaths broadly agree with previous studies. Its numbers have already proved controversial, however. India has publicly disputed the organization's estimate of excess deaths there, and argued that the process is flawed.

Official pandemic death statistics are lower than excess-deaths estimates because of delayed and incomplete reporting and a lack of data in dozens of countries. To fill in these gaps, statisticians and data scientists look at overall death figures for the pandemic period and compare them with those of pre-pandemic years. Even these baseline mortality data are not available for many countries, so global estimates of excess deaths also rely on computer models to estimate COVID-19 fatalities.

The WHO's global excess-deaths estimate for 2020 and 2021 is 14.9 million (see 'COVID's true toll'). Most of these deaths (84%) are concentrated in southeast Asia, Europe and the Americas, with more than two-thirds (68%) occurring in just 10 countries.

"The work by the WHO is applaudable, and I know a huge effort has gone into it. Broadly speaking, they lend credence to the estimates of the pandemic's true death toll," says Sondre Solstad, who leads modelling work at *The Economist* magazine in London to estimate excess pandemic deaths.

The Economist estimated excess deaths at between 12.3 million and 21.3 million in 2020 and 2021. A third effort, by the Institute for Health Metrics and Evaluation in Seattle, Washington, put excess deaths for the period at between 17.1 million and 19.6 million. The models use varying data sets and techniques, which produce different results.

"This model is a live model, and these are just the latest results, but we plan on updating it with more data for existing and additional countries, which will improve it," says Ariel Karlinsky, an economist at the Hebrew University of Jerusalem in Israel who worked on the WHO project.

"It's high time for reliable global, regional, national and local all-cause-mortality surveillance," Karlinksy adds. "It will help us better know the toll of other disasters and might even alert us to the next possible pandemic."

Haggling over figures

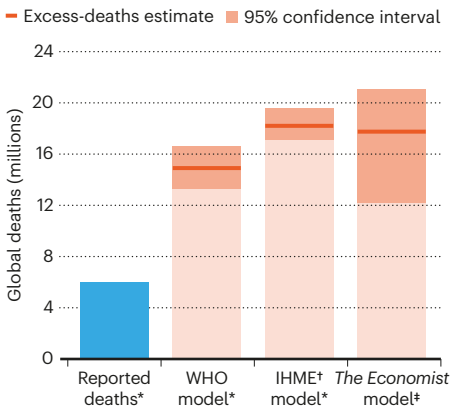
India remains a sticking point in the death figures. The WHO estimates that pandemic deaths in the country in 2020 and 2021 were between 3.3 million and 6.5 million – around 10 times India's official COVID-19 death toll of 481,000 for the same period. India shared its national data for 2020 with the WHO only on 4 May, and has been haggling over the figures for months, according to a source involved in the WHO work who wished to remain anonymous because of political sensitivity. "They're basically trying to derail the whole thing."

In a public statement, India's Ministry of Health and Family Welfare said that it had "concerns with the methodology" of the estimates and had been in "regular and in-depth technical exchange with WHO on the issue".

Shahid Jameel, a virologist and former chair of India's COVID-19 genome-sequencing committee, says that he trusts the WHO's estimates more than the government's figures. "The ballpark figure that India has produced so far, of about 500,000, is certainly very low. Those of us who were there and who have experienced it know that it is very low," he says. "And now there are studies to support that."

COVID'S TRUE TOLL

The number of confirmed deaths (blue bar) caused by COVID-19 is much smaller than tallies of 'excess deaths' (pink bars), which are deaths above what is expected during the pandemic.



*Up to 31 December 2021; †Institute for Health Metrics and Evaluation; ‡up to 27 December 2021.

SOURCES: OUR WORLD IN DATA/THE ECONOMIST/IHME/WHO