The Economist

Menu

Briefing

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The wonky-spiked variant

Omicron looks ominous. How bad is it likely to be?

Much has been learnt about how to treat covid-19 and how to live with it

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VIROLOGISTS WILL tell you that predicting how a new virus might evolve is a fool's errand. Predicting that it will evolve, though, is money in the bank. The virus that causes covid-19, SARS-COV-2, is no exception. Since the first copy of its

genome was published on January 10th 2020, sequenced from a sample collected in Wuhan days earlier, some 5.6m SARS-CoV-2 genomes have been added to GISAID, a database. They have been arranged into 23 clades—groupings with a distinct

common ancestor which differ from the original sequence and from all the others in at least one particular. Each clade has had the chance to outcompete the other versions, and almost all have failed. Most differences do not make much of a difference. Then again, some do—spectacularly so.

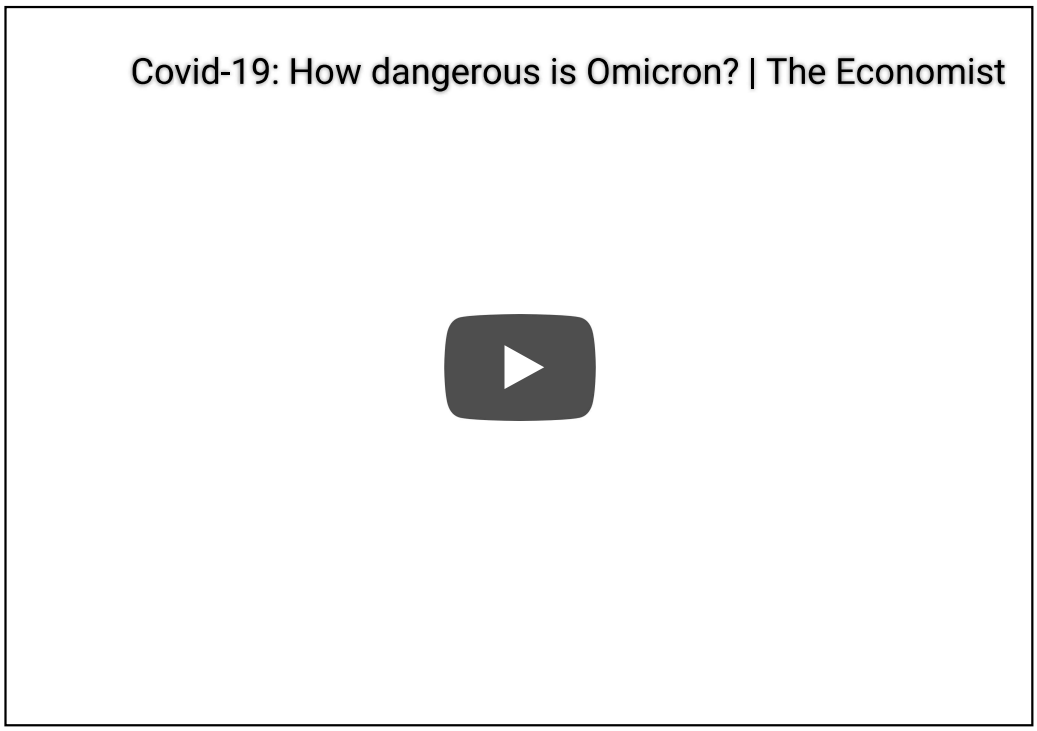
Between November 15th and 25th the number of new cases of covid in South Africa jumped from fewer than 400 a day to more than 2,000. Sequencing showed that a large number of these were down to a variant initially known as B.1.1.529, and subsequently designated Omicron. In genomic terms, Omicron is wildly different from any other variant seen to date.

The nature of its differences suggested, in theory, that it might be better at getting into human cells than its relatives were. It might also be better at avoiding the attentions of antibodies from vaccination or an earlier infection. Virologists had long thought that a variant which combined both those advantages "would be a pretty dangerous thing", according to Noubar Afeyan, a co-founder of Moderna, one of the manufacturers of mRNA vaccines against SARS-CoV-2. But they also thought it was unlikely. Now "Omicron is exactly that", Mr Afeyan says. Its mutations and its apparently rapid spread added up to something potentially scary.

On November 26th the World Health Organisation (WHO) accordingly labelled

Omicron a "variant of concern", the fifth version of the virus to be thus marked out. Stockmarkets around the world fell sharply on the news. Companies sensitive to covid restrictions, such as airlines and hotel chains, were hit hard. The dollar, a safe-haven investment in times of uncertainty, has strengthened. But this was not a shock on anything like the scale of that seen during the initial spread of the disease.

The WHO has warned that the new strain carries a "very high" risk of causing surges in infection all around the world. As yet, though, such a surge has been seen only in South Africa, and things may stay that way. It is possible that the surge had other causes and that any variant around at the time would have spread. Or some factor which favours the variant in South Africa may be absent everywhere else.



There is precedent for this. Southern Africa suffered a wave of the Beta variant at the end of 2020, but it never became established elsewhere. Alpha swept across Europe but never became established in southern Africa. The reasons a variant spreads in one place and not another are, like much of the rest of evolution, thought to be largely environmental. For SARS-CoV-2 a crucial part of the environment is the immune system, and immune systems are different all over the world. How different genes, endemic infections, general levels of health, microbiomes and more end up stopping one variant from displacing another is

largely uncharted territory.

But not all variants stay local. First detected in India roughly a year ago, Delta displayed a level of transmissibility which saw it outcompete other strains almost everywhere, establishing itself as the dominant strain and often causing new waves of disease as it did so.

The Economist

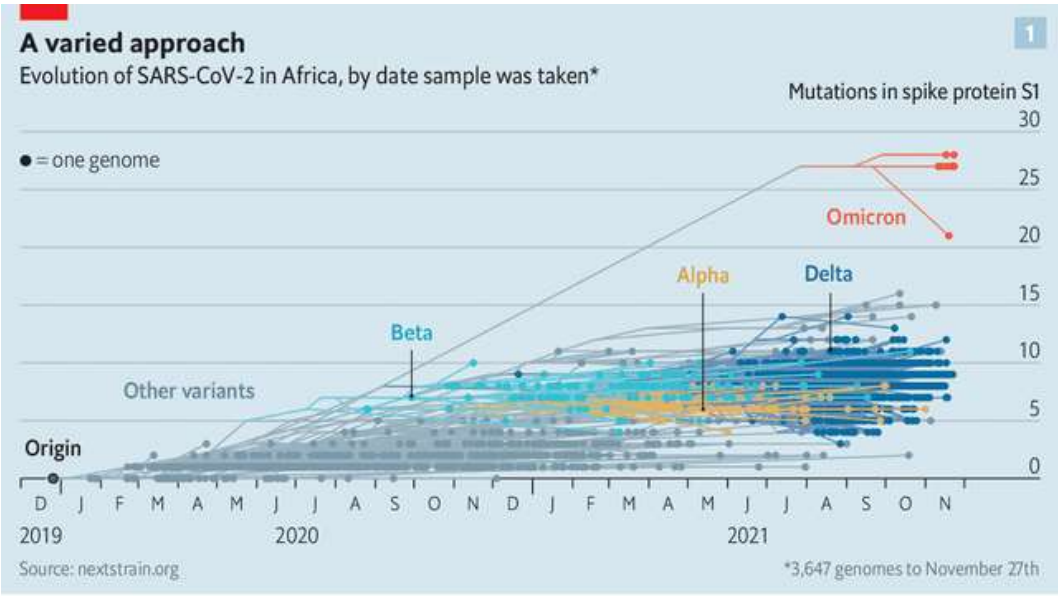
It is the possibility that Omicron might now outcompete Delta—either through being inherently more transmissible, by being better at overcoming prior immunity, or a bit of both—that has the world on edge and may yet see markets lose their cool. Many countries have banned or restricted travel from southern Africa. Some, like Israel and Japan, have banned all foreigners from coming in. Despite this, by December 2nd over two dozen countries had reported the presence of the Omicron variant within their borders (see map). That seems to suggest the cat is already out of the bag; if Omicron has the ability to displace Delta, it is probably already in a position to do so.

Delaying the inevitable can still provide real benefits, because health systems are sensitive to the rate at which viral waves grow and peak: slow is better, fast is worse. European countries, already struggling with a winter wave of the Delta variant and worried about the risk of flu, are tightening measures like mask-wearing and restrictions on mingling. There is ever more talk of vaccine mandates. The prospect of renewed distancing, working from home and even lockdowns is

adding to a range of other economic worries around the world.

Western countries where double vaccination is common are providing more booster shots. That makes sense even if it turns out that the antibodies the immune system generates in response to existing vaccines are not as well-tailored to Omicron as they were to earlier variants. The boosters will not make better antibodies, but they will spur the body into making more of them, at least for a while. Studies have found that the quantity of antibodies against SARS-CoV-2 matters even if the antibodies are not specific to the variant. Vaccine-makers are looking at how to change their offerings to deal with the newcomer more effectively—and trying to work out whether they actually need to.

At the genetic level, Omicron differs from the original Wuhan version in more than 50 places. But it is also very different from other recent versions of the virus (see chart 1). Its closest relatives are versions of the virus first spotted at least a year ago and rarely sequenced since. There are three possible explanations for this.



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One is that Omicron's ancestor managed to circulate for almost a year without being detected by the genomic-surveillance apparatus, and while picking up many more mutations than any other variant has. This seems unlikely. Another is that Omicron's ancestor jumped into and out of an animal population over the past year, picking up its large number of mutations there. Many of the mutations are

completely new, not seen before in any variant, lending some credence to this hypothesis.

But it is the third possibility which seems most likely, not least because similar things have been documented before. This is for the ancestral SARS-CoV-2 to have infected someone with a compromised immune system. Because such people are unable to get rid of it, the virus can evolve inside them for months, accumulating mutations as it does so. Their bodies provide what Sharon Peacock of Cambridge University calls an "evolutionary gym" on which variants can both build up their strength and learn some new tricks.

Omicron you're so fine

The most worrying of Omicron's mutations are in the gene that describes the spike protein. This is the tool the virus uses to bind itself to cells and enter them. Delta probably owes its greater transmissibility in part to the fact that it sticks better to cells. Its mutations produce a spike in which nine of the amino acids in the 1,273-amino-acid-long chain from which the protein is made are distinctively different. The mutations in an unnamed variant called C.1.2, which boasted one of the most mutated spike ever seen until the past few weeks, changed 14 of the amino acids. Omicron's mutations change 35; ten of the mutations have never been seen in any of the variants of concern to date.

Almost half of the 35 changes are in the receptor-binding domain, the business end of the protein when it comes to entering cells and also the part targeted by the most effective antibodies. By changing the shape of this part of the protein, the mutations could make Omicron better at getting into cells and also less easily recognised by antibodies that work against a different version of the spike.

A mutated spike is not necessarily a better spike. C.1.2 derived no benefit from having more mutations there than any other variant—it never spread all that far and may now be extinct. But the locations of Omicron's mutations make it worrying. "If you look at the sequence on paper, because of the number of mutations and where they are, it is very concerning because of the impact on neutralising antibodies," says Susanna Dunachie, an immunologist at the University of Oxford.

Some other mutations are worrying, too. After binding to a cell, the spike breaks in

two at a juncture called the furin cleavage site, allowing the viral genome to get inside. Ravindra Gupta of Cambridge worries that Omicron's three mutations close to this site will give it an advantage in replication similar to that enjoyed by Delta. Another mutation may allow it to confuse the way in which the immune system uses a chemical messenger called interferon.

Computer modelling using AlphaFold, a program developed by DeepMind, a British artificial-intelligence research company owned by Alphabet, to predict the shape of Omicron's spike also suggests that antibodies will stick to it at least a bit less well, says Colby Ford, a computational biologist at the University of North Carolina at Charlotte. Experimental approaches that compare the effect of the individual mutations involved tend to agree—but the complexity of protein-folding means that the effects of different mutations are not strictly additive; some will reinforce each other, others will cancel each other out. The experiments that should provide a clear idea of what is going on will be those which pit a wide range of antibodies against the whole protein as found on virus particles. Such work is going on all over the world, nowhere more urgently than in the laboratories of the various vaccine-developers.

Ugur Sahin, the boss of BioNTech, one of the two companies that have developed mRNA vaccines against the virus, accepts that because the vaccines get cells to make spike proteins according to the recipe used in the earliest genomes to be sequenced, the neutralising effect of vaccine-elicited antibodies will be lower for Omicron. But he adds that it is not clear how great the reduction will be, and points out that immunological protection is not provided by antibodies alone.

Vaccines engage the immune system's T-cells as well. These are lymphocytes that respond not just to finished proteins, as antibodies do; they also recognise protein fragments. Because 97% of Omicron sequences are identical to the original virus found in Wuhan, Dr Sahin says, these T-cell responses should still work. He expects that most fully vaccinated people with boosters should at worst fall only moderately ill if infected with Omicron. Alessandro Sette, an immunologist at the La Jolla Institute for Immunology and his colleagues have shown that T-cells preserve 93-97% of their targeting capacity when faced with a new variant.

Nonetheless, BioNTech is working on a vaccine using mRNA that describes the

Omicron spike. So is Moderna. Both companies have been down this road before, developing tailored vaccines against Beta and Delta. They did not go into production because they did not, in the end, prove necessary; the original vaccines held up well. Whether the same looks likely to be true for Omicron should be known, the companies say, in a matter of weeks.

The makers of vaccines that use other approaches to their trade are also exploring the possibilities of doing something specific to Omicron; but the mRNA technology is inherently quicker to work with, and being first on the market would be a huge advantage. Morgan Stanley, a bank, reckons that both firms could make about 6bn booster shots next year.

When studying vaccines against Beta and Delta, both firms worked to develop procedures that would allow modified versions of their jabs to be approved quickly by regulators. Dr Sahin says that if a new vaccine does turn out to be needed, his firm could deliver it within 100 days: the estimate includes regulatory approval. The time taken to change production procedures, though, would make it unlikely that substantial quantities of an Omicron-targeting vaccine could be produced before the middle of 2022. Changing a production line from one vaccine to another also means a halt to vaccine output on that line.

Economic immunity

The fact that old vaccines will still work to at least some extent and new ones are possible is reassuring. But if, through a mixture of high transmissibility and immune evasion, Omicron does prove better at infecting, and reinfecting, the world, then some bumpy months could lie ahead, not least for the economy. Jerome Powell, the chairman of America's Federal Reserve, has suggested that if people became scared of the variant they might drop out of the labour force. That could worsen labour shortages and lead to wage growth. If it were to hit Vietnam, or even China, hard, the supply-chain crunch could worsen.

But though many wonks are cutting their global-growth forecasts by a few tenths of a percentage point none of them is extending the y-axis below zero, as they had to back in March 2020. According to a straw poll conducted by Deutsche Bank on November 29th, just 10% of participants in the financial markets thought that the new variant would be the "biggest topic in financial markets at year-end". This is

because the economy has evolved a level of tolerance to the disease; it no longer disrupts life as much as it used to, and so given levels of covid cases, hospital admissions and even deaths have less of an economic impact than they once did.

Analysis by Goldman Sachs, a bank, combines data on mandated social-distancing measures and the amount of adherence they meet with into an "effective-lockdown index". The previous two significant variants, Alpha and Delta, caused lockdowns to tighten, but to a significantly lower level than in early 2020 (see chart 2). In the past nine months only a handful of countries have locked down as stringently as they did in 2020.

The Economist

Developed-world governments are less willing to impose forceful measures, in part because vaccines have substantially weakened the link between cases and hospital admissions and death. Better drugs and treatments have also helped, and new antiviral pills from Merck and Pfizer should improve things further—though existing therapies based on mass-produced antibodies may be less effective when faced with Omicron's spike.

They have also found that some measures, including curfews and school closures, bring few benefits at a high cost; they are thus no longer part of the toolkit. More policymakers also acknowledge that covid is becoming endemic, raising the bar for interventions. In America many state governors have promised never to

implement lockdowns again. On November 30th the British government resisted suggestions from their medical advisers that people should limit social contacts.

Public compliance with restrictions has also faded. People are less scared of the virus or more resigned to their fate. The Netherlands and Austria are technically in lockdown, but people are about twice as mobile as they were at the beginning of 2021, according to an analysis of Google mobility data on visits to sites of retail and recreation, workplaces and public-trans port stops carried out by *The Economist*.

And what social distancing still goes on, either because of rules or choices, has less economic cost than it used to. People can work more efficiently from home because they have invested in technologies that enable them to improve their virtual office. Businesses are also better able to cope with lockdowns. Retailers have improved their online offerings, whereas restaurants and bars do more takeaway. In the middle of 2020 a ten-point tightening in Goldman's index provoked a 6% decline in GDP. But the effect weakened in subsequent months; it now sits at about 2%.

In the coming days and weeks Omicron will show its true colours. It could prove to be extremely dangerous. But in the two years since people in Wuhan started to come down with a strange new disease, much has been learned about SARS-COV-2, how to treat it and how to live with it. That, at least, should be some comfort. ■

This article appeared in the Briefing section of the print edition under the headline "Watchful waiting"

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