

SARS-CoV-2 Omicron Variant

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Abstract:

The **Omicron variant** is a variant of SARS-CoV-2, the virus that causes COVID-19. As of December 2021, it is the newest variant. It was first reported to the World Health Organization (WHO) from South Africa on 24 November 2021. On 26 November 2021, the WHO designated it as a variant of concern and named it "Omicron", the fifteenth letter in the Greek alphabet

Background:

The variant has an unusually large number of mutations, several of which are novel and a significant number of which affect the spike protein targeted by most COVID-19 vaccines at the time of the discovery of the Omicron variant. This level of variation has led to concerns regarding its transmissibility, immune system evasion, and vaccine resistance, despite initial reports indicating that the variant causes less serious disease than previous strains. The variant was quickly designated as being "of concern", and travel restrictions were introduced by several countries in an attempt to slow its international spread.

Compared to previous variants of concern, Omicron is believed to be far more contagious (spreading much quicker), and spreads around 70 times faster than any previous variants in the bronchi (lung airways), but it is less able to penetrate deep lung tissue, and perhaps for this reason there is a considerable reduction in the risk of severe disease requiring hospitalisation. However, the extremely high rate of spread, combined with its ability to evade both double vaccination and the body's immune system, means the total number of patients requiring hospital care at any given time is still of great concern.

The new variant was first detected on 22 November 2021 in laboratories in Botswana and South Africa based on samples collected on 11–16 November. The first known sample was collected in South Africa on 8 November. In other continents, the first known cases were a person arriving in Hong Kong from South Africa via Qatar on 11 November, and another person who arrived in Belgium from Egypt via Turkey on the same date. As of 16 December 2021, the variant has been confirmed in more than 80 countries. The World Health Organization estimated that by mid-December, Omicron likely was in most countries, whether they had detected it or not.

Classification:

Nomenclature:

On 26 November, the WHO's Technical Advisory Group on SARS-CoV-2 Virus Evolution declared PANGO lineage B.1.1.529 a variant of concern and designated it with the Greek letter omicron. Greek letters are used to identify variants of SARS-CoV-2. The WHO skipped the preceding letters nu and xi in the Greek alphabet to avoid confusion with the similarities of the English word "new" and the Chinese surname Xi. The previous designation was for the "variant of interest" mu.^{[18][19][3]}

Possibly due to a lack of familiarity with the Greek alphabet among some English speakers and the relative frequency of the Latin prefix "omni" in other common



speech, the name of the variant has also occasionally been mispronounced and misspelled as "Omicron".

The GISAID project has assigned it the clade identifier GR/484A, and the Nextstrain project has assigned it the clade identifier 21K.

Mutations:

The variant has many mutations, some of which have concerned scientists. The Omicron variant has a total of 60 mutations compared to the reference / ancestral variant: 50 nonsynonymous mutations, 8 synonymous mutations, and 2 non-coding mutations. Thirty-two mutations affect the spike protein, the main antigenic target of antibodies generated by infections and of many vaccines widely administered. Many of those mutations had not been observed in other strains. The variant is characterised by 30 amino acid changes, three small deletions, and one small insertion in the spike protein compared with the original virus, of which 15 are located in the receptor-binding domain (residues 319–541). It also carries a number of changes and deletions in other genomic regions. Additionally, the variant has three mutations at the furin cleavage site. The furin cleavage site increases SARS-CoV-2 infectivity.

- Spike protein: A67V, Δ69-70, T95I, G142D, Δ143-145, Δ211, L212I, ins214EPE, G339D, S371L, S373P, S375F, K417N, N440K, G446S, S477N, T478K, E484A, Q493R, G496S, Q498R, N501Y, Y505H, T547K, D614G, H655Y, N679K, P681H, N764K, D796Y, N856K, Q954H, N969K, L981F
 - Half (15) of these 30 changes are located in the receptor binding domain-RBD (residues 319–541)
- ORF1ab
 - nsp3: K38R, V1069I, Δ1265, L1266I, A1892T
 - nsp4: T492I
 - nsp5: P132H
 - nsp6: Δ105-107, A189V
 - nsp12: P323L
 - nsp14: I42V
- Envelope protein: T9I
- Membrane protein: D3G, Q19E, A63T
- Nucleocapsid protein: P13L, Δ31-33, R203K, G204R

A link with HIV infection may explain a large number of mutations in the sequence of the Omicron variant. Indeed, in order to be affected by such a high number of mutations, the virus must have been able to evolve a long time without killing its host, nor being eliminated. One such situation occurs in people with a weakened immune system but receiving enough medical care to survive. This is the case in HIV patients in South Africa, who represent more than 20% of the population. Due to lack of access to clinics, fear of stigmatisation and disrupted healthcare, millions living with HIV in the region are not on effective HIV therapy. HIV prevention could be key to reducing the risk of uncontrolled HIV driving the emergence of Covid variants.

In addition, it is believed that one of these many mutations, comprising a 9-nucleotide sequence, may have been acquired from another type of virus (known as HCoV-229E), responsible for the common cold. This is not entirely unexpected—at times, viruses within the body acquire and swap segments of genetic material from each other, and this is one common means of mutation.

Sublineages and stealth variant:

Researchers have established the existence of three sublineages of Omicron. The 'standard' sublineage is now referred to as BA.1 /B.1.1.529.1, and the two other sublineages are known as BA.2 /B.1.1.529.2 and BA.3/B.1.1.529.3.

All three can be detected by full sequencing, but BA.2 has been nicknamed 'Stealth Omicron' because it differs from the 'standard' variety by not having the characteristic S gene target failure (SGTF)-causing deletion (Δ69-70) by which many PCR tests are able to detect a case as an Omicron, or Alpha, variant. Thus, countries that primarily rely on SGTF for detection may overlook BA.2. Some countries, including Denmark, use a variant qPCR that tests for several mutations, including Δ69-70, E484K, L452R and N501Y. It can also distinguish Delta (the heavily dominant variant worldwide, prior to the spread of Omicron), which has L452R but not N501Y, and all Omicron sublineages, which have N501Y but not L452R. As of 19 December 2021, BA.2 appears to be very rare with about twenty known cases from half a dozen countries. The third sublineage, BA.3, is also very rare and it does not represent the same potential problem in detection since it has the SGTF deletion (Δ69-70), similar to BA.1.

Possible consequences:

The WHO is concerned that a large number of mutations may reduce immunity in people who were previously infected and in vaccinated people. It is also possible the omicron variant might be more infective in this regard than prior variants. The effects of the mutations, if any, are unknown as of late November 2021. The WHO warns that health services could be overwhelmed especially in nations with low vaccination rates where mortality and morbidity rates are likely to be much higher, and urges all nations to increase COVID-19 vaccinations.

Professor Paul Morgan, immunologist at Cardiff University, also recommends vaccination. Morgan said, "I think a blunting rather than a complete loss [of immunity] is the most likely outcome. The virus can't possibly lose every single epitope on its surface, because if it did that spike protein couldn't work anymore. So, while some of the antibodies and T cell clones made against earlier versions of the virus, or against the vaccines may not be effective, there will be others, which will remain effective. (...) If half, or two-thirds, or whatever it is, of the immune response is not going to be effective, and you're left with the residual half, then the more boosted that is the better."

Professor Francois Balloux of the Genetics Institute at University College London said, "From what we have learned so far, we can be fairly confident that – compared with other variants – Omicron tends to be better able to reinfect people who have been previously



infected and received some protection against COVID-19. That is pretty clear and was anticipated from the mutational changes we have pinpointed in its protein structure. These make it more difficult for antibodies to neutralise the virus."

On 15 December 2021, the European Centre for Disease Prevention and Control assessed that, even if the variant turns out to be milder than Delta, its spread will very likely increase hospitalizations and fatalities due the exponential growth in cases caused by increased transmissibility.

On 23 December 2021, *Nature* indicates that, though Omicron likely weakens vaccine protection, reasonable effectiveness against Omicron may be maintained with currently available vaccination and boosting approaches.

Signs and symptoms:

As of 28 November 2021, the World Health Organization's update states, "There is currently no information to suggest that symptoms associated with Omicron are different from ... other variants".

A study performed between 1 and 7 December by the Center for Disease Control found that: "The most commonly reported symptoms [were] cough, fatigue, and congestion or runny nose". Research published in London on 25 December 2021 suggested the most frequent symptoms stated by users of the Zoe Covid app were "a running nose, headaches, fatigue, sneezing and sore throats."

A unique reported symptom of the omicron variant is night sweats.

Characteristics:

Many of the mutations to the spike protein are present in other variants of concern and are related to increased infectivity and antibody evasion. Computational modeling suggests that the variant may also escape cell-mediated immunity. On 26 November, the ECDC wrote that an evaluation of the neutralizing capacity of convalescent sera and of vaccines is urgently needed to assess possible immune escape, saying these data are expected within two to three weeks.

Contagiousness:

It was not known in November 2021 how the variant would spread in populations with high levels of immunity. It was also not known if the omicron variant causes a milder or more severe COVID-19 infection. According to pharmaceutical companies, vaccines could be updated to combat the variant "in around 100 days" if necessary.

Relating to naturally acquired immunity, Anne von Gottberg, an expert at the National Institute for Communicable Diseases, believed at the beginning of December 2021 that immunity granted by previous variants would not protect against Omicron. On 15 December 2021 Jenny Harries, head of the UK Health Security Agency, told a parliamentary committee that the doubling time of COVID-19 in most regions of the UK was

now less than two days despite the country's high vaccination rate. She said that the Omicron variant of COVID-19 is "probably the most significant threat since the start of the pandemic", and that the number of cases in the next few days would be "quite staggering compared to the rate of growth that we've seen in cases for previous variants".

Virulence:

As of 28 November 2021, the World Health Organization's update states "There is currently no information to suggest that symptoms associated with Omicron are different from ... other variants". Increased rates of hospitalization in South Africa may be due to a higher number of cases, rather than any specific feature of the Omicron variant.

On 4 December 2021, the South African Medical Research Council reported that from 14 to 29 November 2021 at a hospital complex in Tshwane, inpatients were younger than in previous waves and the ICU and oxygen therapy rates were lower than in earlier waves. These observations are not definitive and the clinical profile could change over the following two weeks, allowing for more accurate conclusions about disease severity. Excess deaths nearly doubled in the week of 28 November, suggesting under-reporting, but the level was still much lower than that seen in the second wave in mid-January 2021. On 12 December, director-general of the World Health Organization Tedros Adhanom asserted that it was wrong for people to consider Omicron as mild. This is because high exposure to previous infections in South Africa likely affects the clinical course of the new infections.

On 20 December, a report by the Imperial College COVID-19 Response Team based on data from England, found that hospitalisation and asymptomatic infection indicators were not significantly associated with Omicron infection, suggesting at most limited changes in severity compared with Delta.^[60] On 22 December, the team reported an approximately 41% (95% CI, 37–45%) lower risk of a hospitalization requiring a stay of at least 1 night compared to the Delta variant, and that the data suggest that recipients of 2 doses of the Pfizer–BioNTech, the Moderna or the Oxford–AstraZeneca vaccine remain substantially protected from hospitalization.^[61]

Diagnosis

See also: COVID-19 testing:

The FDA has published guidelines on how PCR tests will be affected by Omicron.^[62] Tests that detect multiple gene targets will continue to identify the testee as positive for COVID-19. S-gene dropout or target failure has been proposed as a shorthand way of differentiating Omicron from Delta.

The variant may be identified by sequencing and genotyping.^[63] The BA.1 lineage, but not the BA.2 lineage, can be identified by S gene target failure (SGTF) of the TaqPath assay, a trait shared with subsets of SARS-CoV-2 Alpha variant.^[38] Several other commercial assays can also be used, though they test for different amino acid substitutions.^[a]



Prevention:

As with other variants, the WHO recommended that people continue to keep enclosed spaces well ventilated, avoid crowding and close contact, wear well-fitting masks, clean hands frequently, and get vaccinated.

On 26 November 2021, BioNTech said it would know in two weeks whether the current vaccine is effective against the variant and that an updated vaccine could be shipped in 100 days if necessary. AstraZeneca, Moderna and Johnson & Johnson were also studying the variant's impact on the effectiveness of their vaccines. On the same day, Novavax stated that it was developing an updated vaccine requiring two doses for the Omicron variant, which the company expected to be ready for testing and manufacturing within a few weeks. On 29 November 2021, The Gamaleya Institute said that Sputnik Light should be effective against the variant, that it would begin adapting Sputnik V, and that a modified version could be ready for mass production in 45 days. Sinovac said it could quickly mass-produce an inactivated vaccine against the variant and that it was monitoring studies and collecting samples of the variant to determine if a new vaccine is needed. On 7 December 2021, at a symposium in Brazil with its partner Instituto Butantan, Sinovac said it would update its vaccine to the new variant and make it available in three months. On December 2, the Finlay Institute was already developing a version of Soberana Plus against the variant.

On 29 November 2021, the WHO said cases and infections are expected among those vaccinated, albeit in a small and predictable proportion.

On 7 December 2021, preliminary results from a laboratory test conducted at the Africa Health Research Institute in Durban with 12 people who received the Pfizer-BioNTech vaccine found a 41-fold reduction in neutralizing antibody activity against the variant in some of the samples. This is a big reduction, but it does not mean that the variant can escape vaccines completely, so vaccination with current vaccines is still recommended. Neutralizing antibody activity against the variant was greater in those fully vaccinated after being infected about a year earlier. Effectiveness estimates will likely change as more data is collected, as antibodies generated by vaccination vary widely between individuals and the sample was small. On 8 December 2021, Pfizer and BioNTech reported that preliminary data indicated that a third dose of the vaccine would provide a similar level of neutralizing antibodies against the variant as seen against other variants after two doses.

On 10 December 2021, the UK Health Security Agency reported that early data indicated a 20- to 40-fold reduction in neutralizing activity for Omicron by sera from Pfizer 2-dose vaccinees relative to earlier strains and a 20-fold reduction relative to Delta. The reduction was greater in sera from AstraZeneca 2-dose vaccinees, falling below the detectable threshold. An mRNA booster dose produced a similar increase in neutralising activity regardless of the vaccine used for primary vaccination. After a booster dose (usually with an mRNA vaccine), vaccine effectiveness against symptomatic disease was at 70%–75%, and the effectiveness against severe disease was expected to be higher.

On 26 November 2021, the WHO asked nations to do the following:

- Enhance surveillance and sequencing efforts to better understand circulating SARS-CoV-2 variants.
- Submit complete genome sequences and associated metadata to a publicly available database, such as GISAID.
- Report initial cases/clusters associated with virus-of-concern infection to WHO through the IHR mechanism.
- Where capacity exists and in coordination with the international community, perform field investigations and laboratory assessments to improve understanding of the potential impacts of the virus of concern on COVID-19 epidemiology, severity, and the effectiveness of public health and social measures, diagnostic methods, immune responses, antibody neutralization, or other relevant characteristics.

Treatment:

Corticosteroids such as dexamethasone and IL6 receptor blockers such as tocilizumab (Actemra) are known to be effective for managing patients with the earlier strains of severe COVID-19. The impact on the effectiveness of other treatments was being assessed in 2021.

On 29 November 2021, Pfizer CEO Albert Bourla said that Pfizer had submitted an Emergency Use Authorization application to the FDA for development of the RNA virus antiviral drug Paxlovid, and the company was confident that it could treat the Omicron variant. Merck and Ridgeback were evaluating the anti-RNA virus drug molnupiravir for omicron treatment at the time.

Relating to monoclonal antibodies (mAbs) treatments, similar testing and research is ongoing. Preclinical data on in vitro pseudotyped virus data demonstrate that some mAbs designed to use highly conserved epitopes retain neutralizing activity against key mutations of Omicron substitutions. Similar results are confirmed by cryo-electron microscopy and X-ray data, also providing the structural approach and molecular basis for the evasion of humoral immunity exhibited by Omicron antigenic shift as well as the importance of targeting conserved epitopes for vaccine and therapeutics design. While 7 clinical mAbs or mAb cocktails experienced loss of neutralizing activity of 1-2 orders of magnitude or greater relative to the prototypic virus, the S309 mAb, the parent mAb of sotrovimab, neutralized Omicron with only 2-3-fold reduced potency. Further data suggest Omicron would cause significant humoral immune evasion, while neutralizing antibodies targeting the sarbecovirus conserved region remain most effective. Indeed, most receptor-binding motif (RBM)-directed monoclonal antibodies lost in vitro neutralizing activity against Omicron, with only 3 out of 29 mAbs examined in another study retaining unaltered potency. Furthermore, a fraction of broadly neutralizing sarbecovirus mAbs neutralized Omicron through recognition of antigenic sites outside the RBM, including sotrovimab (VIR-7831), S2X259 and S2H97.

Epidemiology:

On 26 November 2021, the South African National Institute for Communicable Diseases announced that 30,904 COVID-tests (in



one day) detected 2,828 new COVID infections (a 9.2% positivity rate). One week later, on 3 December 2021, the NICD announced that 65,990 COVID tests had found 16,055 new infections (5.7 times as many as seven days before; positive rate 24.3%) and that 72 percent of them were found in Gauteng. This province of South Africa is densely populated at about 850 inhabitants per km². Gauteng's capital Johannesburg is a megacity (about 5.5 million inhabitants in the city itself plus 9.5 million in the urban region). In November 2021 the transmissibility of the Omicron variant, as compared to the Delta variant or other variants of the COVID-19 virus, was still uncertain. Omicron is frequently able to infect previously Covid-positive people.

It has been estimated the Omicron variant diverged in late September or early October 2021, based on Omicron genome comparisons. Sequencing data suggests that Omicron had become the dominant variant in South Africa by November 2021, the same month where it had been first identified in the country. "Phylogeny suggests a recent emergence. Data from South Africa suggests that Omicron has a pronounced growth advantage there. However, this may be due to transmissibility or immune escape related, or both." Also the serial interval plays a role in the growth.

Detectable changes in levels of COVID-19 in wastewater samples from South Africa's Gauteng province were seen as early as 17–23 October (week 42). The National Institute for Communicable Diseases reports that children under the age of 2 make up 10% of total hospital admissions in the Omicron point of discovery Tshwane in South Africa. Data on the S gene target failure (SGTF) of sampled cases in South Africa indicates a growth of 21% per day relative to Delta, generating an increased reproduction number by a factor of 2.4. Omicron became the majority strain in South Africa around 10 November. Another analysis showed 32% growth per day in Gauteng, South Africa, having become dominant there around 6 November.

In the UK, the logarithmic growth rate of Omicron-associated S gene target failure (SGTF) cases over S gene target positive (SGTP) cases was estimated at 0.41 per day,^[c] which is exceptionally high. Furthermore, by 14 December it appears to have become the most dominant strain. Without presuming behavior change in response to the variant, a million infections per day by December 24 are projected for a 2.5 days doubling time. In Denmark, the growth rate has been roughly similar with a doubling time of about 2–3 days, it having become the most prevalent strain on 17 December. Switzerland is not far behind and neither is Germany. In Scotland, Omicron apparently became the most prevalent variant on 17 December. In the Canadian province of Ontario, it became the most prevalent strain on 13 December. In the US, the variant appears to have become the most prevalent strain on December 21, growing at 0.23 per day. In Portugal, Omicron had reached 61.5% of cases on 22 December. In Belgium, the strain has become the most prevalent on 25 December and, the Netherlands appears to be on a similar path. In Italy, it had reached 28% of cases on 20 December and was doubling every two days, while it became the dominant variant in Norway on 25 December. In France, it made up about 15% of COVID-19 cases in mid-December, but around 27 December it had increased to more than 60%. Many other countries may not have enough timely information, as they may

not use Thermo Fisher TaqPath Assay or equivalent for their PCR tests to indicate Omicron. Researchers recommend sampling at least 5% of COVID-19 patient samples in order to detect Omicron or other emerging variants.

History:

A December 2021 article in *Science* observes Omicron did not evolve from any other variant of note, but instead on a distinct track diverging in perhaps mid-2020. The article expounds on three theories that might explain this surprising genetic lineage:

1. The virus could have circulated and evolved in a population with little surveillance and sequencing.
2. It could have gestated in a chronically infected COVID-19 patient.
3. It might have evolved in a nonhuman species, from which it recently spilled back into people.

Market reactions:

Worry about the potential economic impact of the Omicron variant led to a drop in global markets on 26 November, including the worst drop of the Dow Jones Industrial Average in 2021, led by travel-related stocks. The price of Brent Crude and West Texas Intermediate oil fell 10% and 11.7%, respectively. Cryptocurrency markets were also routed. The South African rand has also hit an all-time low for 2021, trading at over 16 rand to the dollar, losing 6% of its value in November.

In early December 2021, the chairman of the Federal Reserve, Jerome Powell, testified before the U.S. Senate Committee on Banking that "The recent rise in COVID-19 cases and the emergence of the Omicron variant pose downside risks to employment and economic activity and increased uncertainty for inflation."

International response:

On 26 November, WHO advised countries not to impose new restrictions on travel, instead recommending a "risk-based and scientific" approach to travel measures. On the same day, the European Centre for Disease Prevention and Control (ECDC) reported modeling indicating that strict travel restrictions would delay the variant's impact on European countries by two weeks, possibly allowing countries to prepare for it.

After the WHO announcement, on the same day, several countries announced travel bans from southern Africa in response to the identification of the variant, including the United States, which banned travel from eight African countries, although it notably did not ban travel from any European countries, Israel, Canada, or Australia where cases were also detected at the time the bans were announced. Other countries that also implemented travel bans include Japan, Canada, the European Union, Israel, Australia, the United Kingdom, Singapore, Malaysia, Indonesia, Morocco, and New Zealand.

The Brazilian Health Regulatory Agency recommended flight restrictions regarding the new variant. The state of New York declared a state of emergency ahead of a potential Omicron spike, although no cases had yet been detected in the state or the



rest of the United States. On 27 November, Switzerland introduced obligatory tests and quarantine for all visitors arriving from countries where the variant was detected, which originally included Belgium and Israel.

In response to the various travel bans, South African Minister of Health Joe Phaahla defended his country's handling of the pandemic and said that travel bans went against the "norms and standards" of the World Health Organization.

Some speculate that travel bans could have a significant impact on South Africa's economy by limiting tourism and could lead to other countries with economies that are reliant on tourism to hide the discovery of new variants of concern. Low vaccine coverage in less-developed nations could create opportunities for the emergence of new variants, and these nations also struggle to gain intellectual property to develop and produce vaccines locally. At the same time, inoculation has slowed in South Africa due to vaccine hesitancy and apathy, with a nationwide vaccination rate of only 35% as of November 2021.

On 29 November 2021, the WHO warned countries that the variant poses a very high global risk with severe consequences and that they should prepare by accelerating vaccination of high-priority groups and strengthening health systems. WHO director-general Tedros Adhanom described the global situation as dangerous and precarious and called for a new agreement on the handling of pandemics, as the current system disincentivizes countries from alerting others to threats that will inevitably land on their shores. CEPI CEO Richard Hatchett said that the variant fulfilled predictions that transmission of the virus in low-vaccination areas would accelerate its evolution.

In preparation for the Omicron variant arriving in the United States, president Joe Biden has stated that the variant is "cause for concern, not panic" and reiterated that the government is prepared for the variant and will have it under control. He also stated that large-scale lockdowns, similar to the ones in 2020 near the beginning of the pandemic, are "off the table for now."

In mid-December 2021, multiple Canadian provinces reinstated restrictions on gatherings and events such as sports tournaments, and tightened enforcement of proof of vaccination orders. British Columbia expressly prohibited any non-seated "organized New Year's Eve event", while Quebec announced a partial lockdown on 20 December, ordering the closure of all bars, casinos, gyms, schools, and theatres, as well as imposing restrictions on the capacity and operating hours of restaurants, and the prohibition of spectators at professional sporting events.

On 18 December 2021, the Netherlands government announced a lockdown intended to prevent spread of the variant during the holiday period.

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