NUS National University of Singapore | Saw Swee Hock School of Public Health

10 Dec 2021

Rapid Review 2.0

OMICRON (B.1.1.529) VARIANT

The following rapid review summarises the emerging information around Omicron and expert opinion where evidence has yet to develop.

Updates from the last version are highlighted in purple. The cut-off date for new information included in the rapid review was Wednesday 8 Dec, 2021. Note that the evidence is evolving rapidly and even a few days may mean significant changes. Many international studies are underway to characterise Omicron.[1,2]

CONTENTS

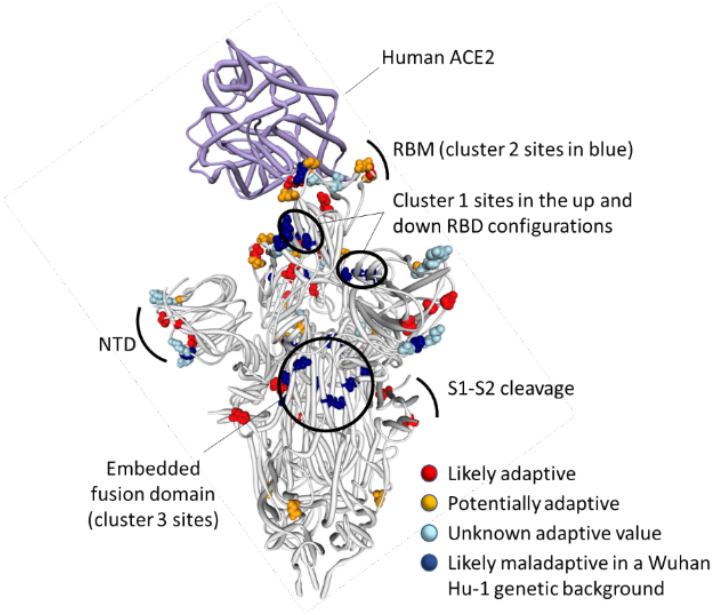
EVIDENCE SUMMARY

The evidence summary should be read alongside the full rapid-review report. The characterisation of Omicron is still very uncertain and so the following summary is likely to be subject to significant change over coming weeks.

	Confidence	Assessment
Transmissibility	**Low**	**At least as transmissible as currently circulating variants.** Preliminary modelling based on limited data suggest a central projection for Omicron growth rate of 0.1 to 0.4 per day with a doubling time of between two and three days.
Infection severity	**Low**	**Insufficient data at this time.** Initial reports suggested that Omicron may be milder, but there are increasing hospitalisations in South Africa. Due to confounding factors and the lagging indicators of hospitalisation and death, the infection severity will not be known for a while, there is no certainty in data yet.
Naturally acquired immunity	**Low**	**Mutations suggestive of reduced protection from natural immunity.** There is some limited supporting epidemiological evidence. Data is insufficient at this time.
Vaccine acquired immunity	**Low**	**Mutations suggestive of reduced protection from vaccine derived immunity.** Preliminary small-scale lab neutralising studies have reported around a 30-40 fold reduction in neutralising antibodies. This might lead to increased symptomatic infection in vaccinated individuals and an increased risk of hospitalisation. Computer modelling studies also predict significant evasion of existing vaccine-derived neutralising antibodies.
Therapeutics	**Low**	**Most therapeutics may remain effective.** Lab data suggests reduced effectiveness of a monoclonal antibody treatment.

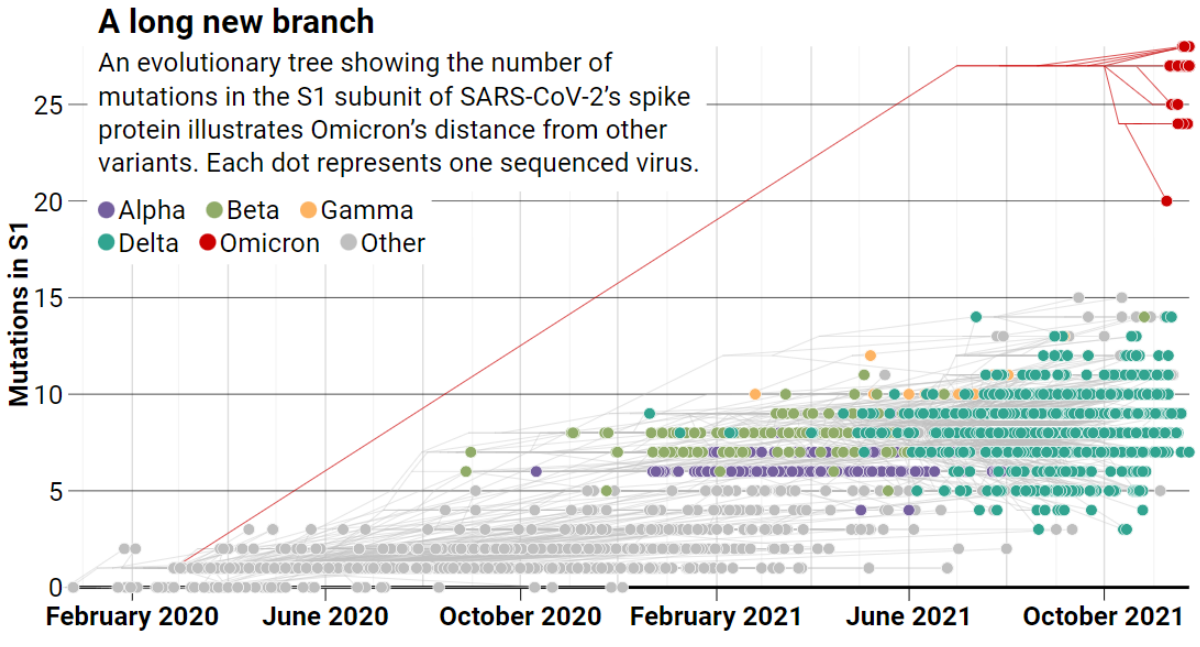
EMERGENCE, SEQUENCING AND PREVALENCE

The Omicron variant's genome has accumulated 53 mutations relative to the original reference strain, with 30 non-synonymous substitutions in the Spike encoding S gene alone, the part that interacts with human cells before cell entry and that has been the primary target for current vaccines.[4,5]



Distribution of Omicron amino acid replacements on the three dimensional SARS-CoV-2 Spike trimer (RBD – receptor binding domain).

Most studies focus on the receptor binding domain (RBD) of the Spike protein. However, some studies suggest that the Spike N terminal domain (NTD) may have a role in facilitating virus entry via sialic-acid receptor binding. A recent analysis of the Omicron variant suggests the variant may have increased sialic acid binding energy, compared to previous variants, which may contribute to increased transmission.[6]



NEXTSTRAIN.ORG, ADAPTED BY N. DESAI/*SCIENCE*

Science.Org.[7]

Omicron genomes have been uploaded to international sites and whilst many have the defining mutations of Omicron, some do not have the full set and/or have their own unique mutations.

There is a proposal to expand the breadth of the B.1.1.529 (Omicron) lineage to include variants that are similar to Omicron (BA.1.). A cousin lineage to Omicron has been proposed (BA.2), this is just taxonomy changing to encompass the full phylogeny. Both sub-lineages carry almost all the same mutations, but BA.2 does not carry the spike:69/70del deletion and will therefore **not** be detectable by S-gene target failure.[8]

The closest sequences are over a year ago.[9] Expert opinion based on analysis of genomic lineages suggests a median estimate of a common ancestor at Oct 7 (95% CI between Sept 19 and Oct 21). This seems consistent with the first detection of the variant.[10]

The origin of the variant is unknown but there are a number of hypotheses.

- **Co-infection** - Evolved from a co-infection with seasonal coronaviruses (eg HCoV-229E). A preprint study that analysed the mutations noted that there is an insert (ins214EPE), which has only been observed in the Omicron variant.[11]

- **Chronically infected patient** – This hypothesis is backed up by sequencing showing changes to the virus in chronically infected patients.[12]

  Selection analysis identified three clustered sets of mutations in the Spike protein, involving 13 amino acids that have previously been highly conserved across SARS-CoV-2 and other Sarbecoviruses (the viral subgenus containing SARS-CoV and SARS-CoV-2). Suggesting that the spike protein structure has accommodated significant sequence change, likely in response to selective pressures favouring increased transmission, immune evasion, or viral replication. It is hypothesised that this could have evolved either at the population level or in a single or group of chronically infected individuals.[5]

- **Natural selection** – Selective pressures play a role in the mechanism of SARS-CoV-2 evolution, which favours mutations that strengthen viral infectivity. Vaccine-breakthrough or antibody-resistant mutations, like those in Omicron, could become a dominating mechanism of SARS-CoV-2 evolution when most of the world's population is either vaccinated or infected.[13]

- **Animal reservoir** - There is a hypothesis that Omicron could have evolved in a nonhuman species, from which it recently spilled back into people. There is evidence of large reservoirs of the virus in nonhumans (eg more than 80% percent of the white-tailed deer sampled in different parts of Iowa between December 2020 and January 2021 tested positive for SARS-CoV-2).[14]

- **Limited surveillance** – Omicron may have been circulating and evolving in a population with little surveillance and sequencing.

The first sequence of the variant was uploaded by Hong Kong Special Administrative Region to GISAID EpiCoV on 22 November 2021, with 10 further sequences from Botswana and South Africa uploaded on 23 November 2021.[15] On 26 November 2021, WHO designated variant B.1.1.529 a variant of concern, named Omicron.[16]

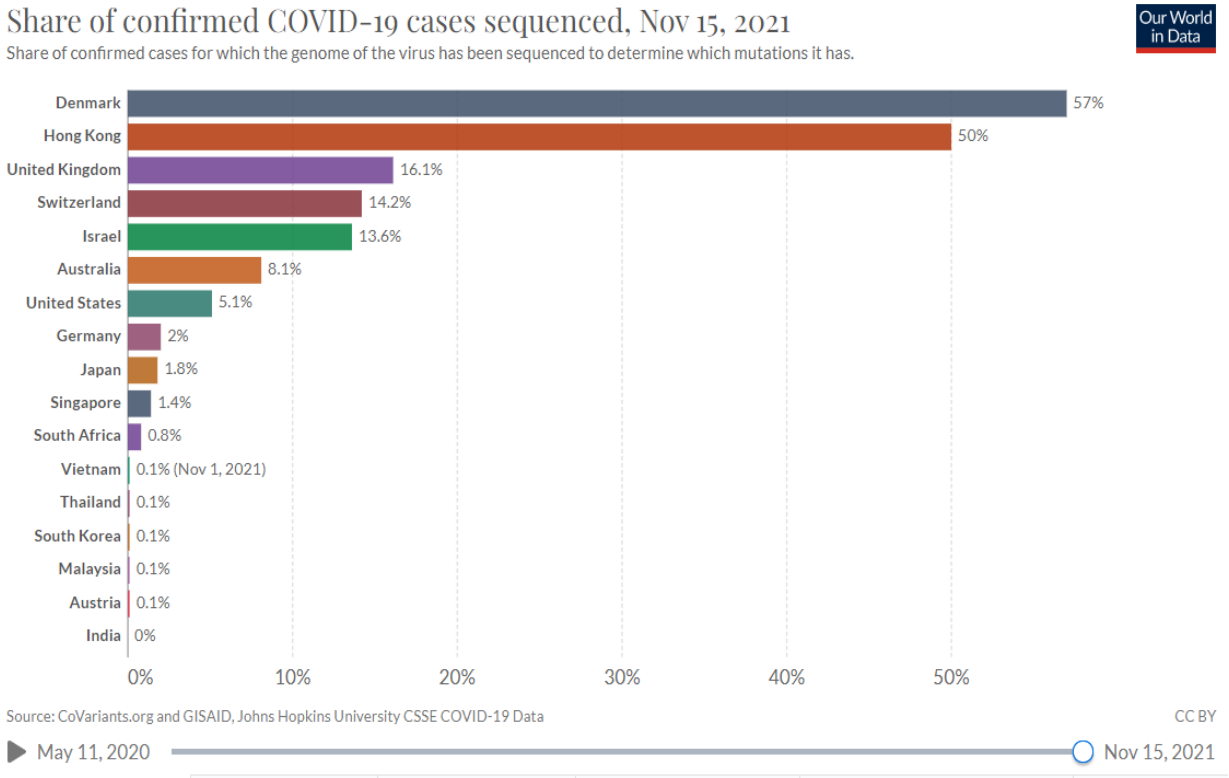
The earliest identification of widespread community transmission of Omicron was in Gauteng, South Africa, on 8 November 2021. By November sequencing in Gauteng found that the variant represented 74% of cases sequenced (n=183/249).[10]

Omicron has been identified in many countries across the globe. Many of the countries reporting Omicron have regular sequencing of positive cases.[17]

As of 8 Dec 2021, cases have been reported in 57 countries. In the first week of December most confirmed cases had an epidemiological link to cases with a history of travel to African countries, with some of those having taken connecting flights at other locations between Africa and Europe. However, many countries are now reporting significant levels of community transmission.[18,19]

It is highly likely that the variant is present, with community transmission, in many more countries but has not yet been identified due to low levels of sequencing.

A major issue is that many countries are still struggling with testing capacity for COVID-19, including genomic sequencing capacity. Testing rates in some countries, including African countries (but also many others), remain low−only 22.9% of tests administered worldwide have been used in low- and middle-income countries, despite these countries making up half of the global population.[20]

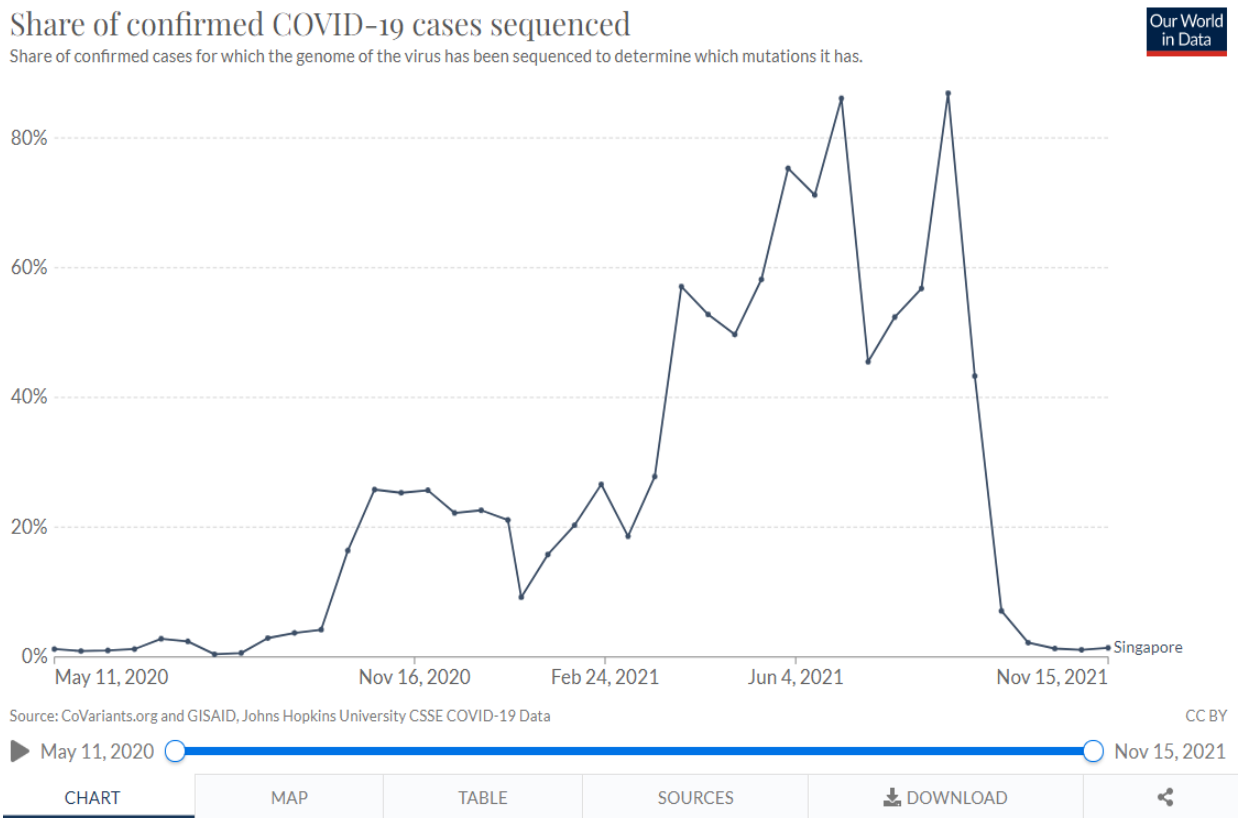


Our World in Data.[21]

Sequencing is also variable over time in some countries. With inconsistent and low levels of sequencing, there is less confidence in which variants are circulating in the community.

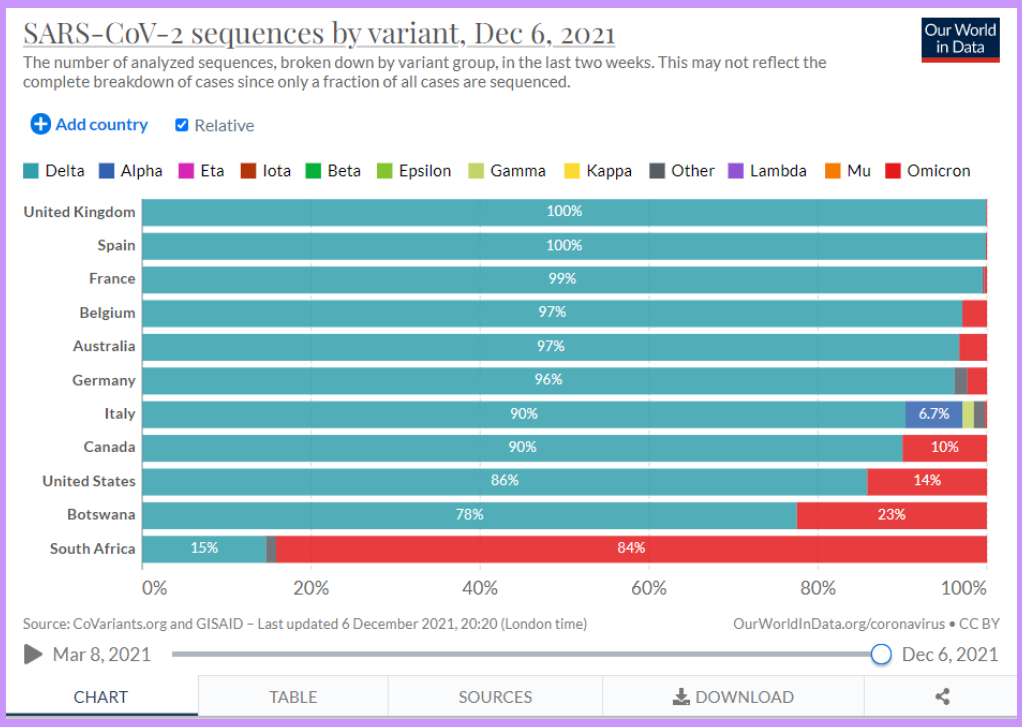
Our World in Data reports that 1.4% of positive cases in Singapore are sequenced, the UK sequences 18.6% (as at 15, November 2021 - updated data is unavailable).

Singapore reported six cases of Omicron to GISAID on 2 Dec, 2021 (believed to represent 0.9% of sequenced positive cases in the last four weeks).[22]



Our World in Data.[11]

Community transmission has occurred in many countries.



Our World in Data.[23]

The S gene target failure is being used as a proxy to track community spread of Omicron BA.1. Its cousin BA.2 does not have this drop out.

Data from the UK is showing an increase in S gene target failure in community testing data, which is likely linked to an increase in Omicron. Data of S gene target failure are located around in similar areas of the UK to the Omicron cases that have been confirmed so far.[24]

It is estimated that about 0.3% of the 50,000-odd positive daily cases in the UK – or 150 cases – have S-gene dropout, with up to two-thirds of these potentially Omicron.[25] This is higher in some areas: as at 7 Dec, Scotland reported 4% of cases sequenced had the S gene target failure.[26]

In Denmark, Omicron was 3.1% of all cases on the 5th of December.[27]

TRANSMISSION AND IMMUNE ESCAPE

The growth rate (in absolute terms and relative to Delta) will become clearer in the following days and weeks but the variant is potentially spreading rapidly.

Preliminary modelling from UK groups suggest a central projection for omicron growth rate of 0.1 to 0.4 per day with a rapid doubling time of between two and three days.[28]

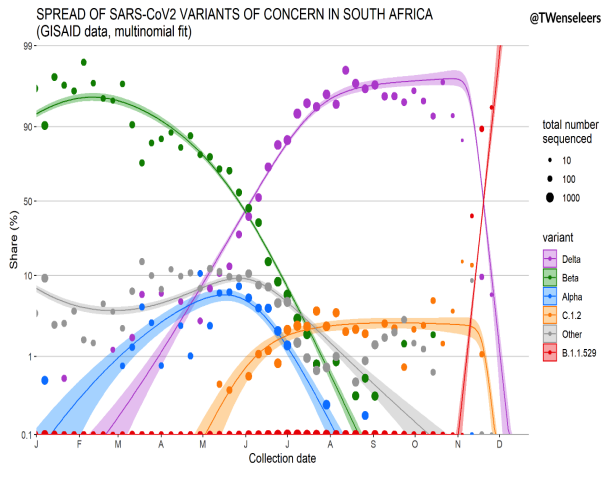
The Omicron variant likely will spread more easily than the original SARS-CoV-2 virus, and how easily Omicron spreads compared to Delta remains unknown. CDC expects that anyone with Omicron infection can spread the virus to others, even if they are vaccinated or don't have symptoms.[2]

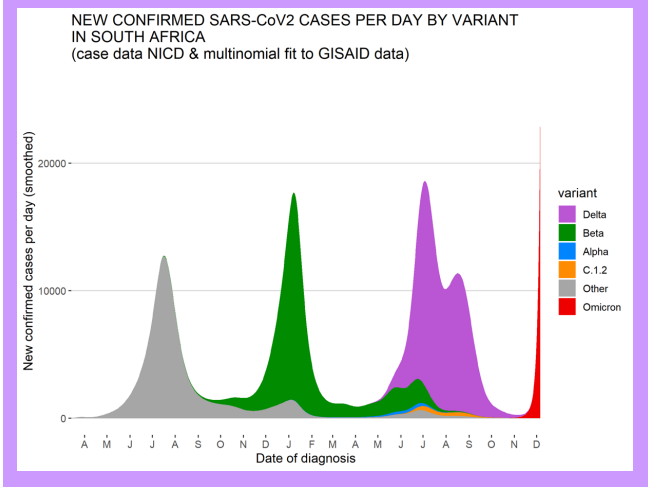
Based on the rise in COVID-19 cases and sequencing data, some estimates have suggested that Omicron can infect 3 to 6 times as many people as Delta over the same time period.[29] However, Dr Angelique Coetzee from South Africa reported that the R value is estimated to be around 6.[30]

Recent analysis from the UK Health Security Agency suggests that the window between infection and infectiousness may be shorter for the Omicron variant than the Delta variant.[31]

Key data points include the rapid displacement of existing Delta viruses by Omicron in Gauteng and South Africa. However, Omicron was detected when transmission of Delta was very low, so it had little competition; it will therefore be important to monitor carefully what happens around the world to understand whether Omicron can outcompete Delta.[19]

Estimates of logistic growth imply Omicron has ~5X the current transmission rate of Delta.[32] This estimate is expected to drop significantly as more data comes in.

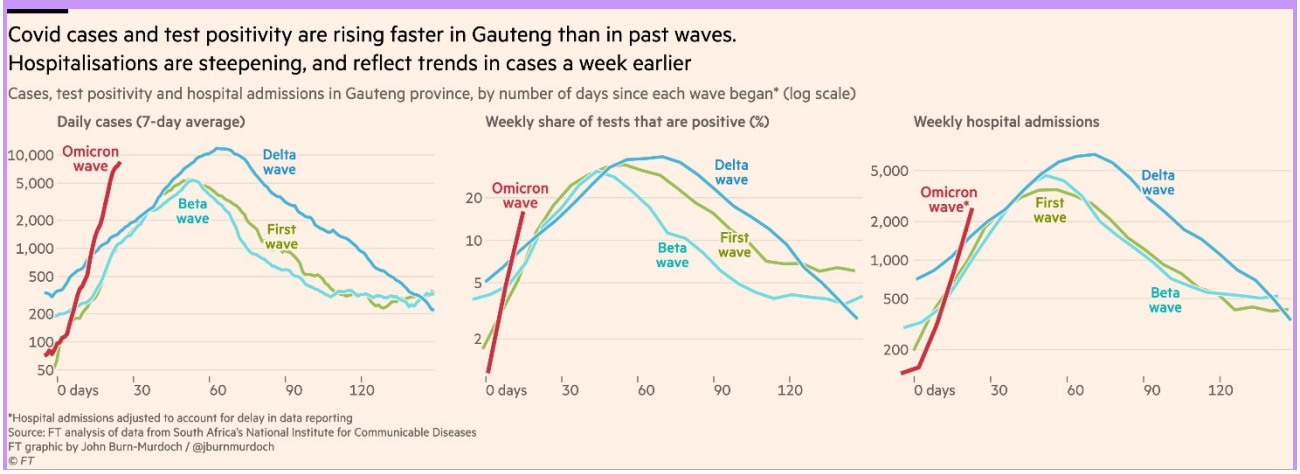




Tom Wenseleers (28 Nov 2021, 6 Dec 2021). [32]

South Africa data shows increasing test positivity.[33] Data suggests that the proportion of COVID-19 cases developing severe disease is lower than with Delta. This doesn't necessarily mean "Omicron is milder", it could be influenced by population characteristics of South Africa and previous waves of infection building up immune resistance, or of cases so far being predominantly younger people early on in the Omicron wave.[17]

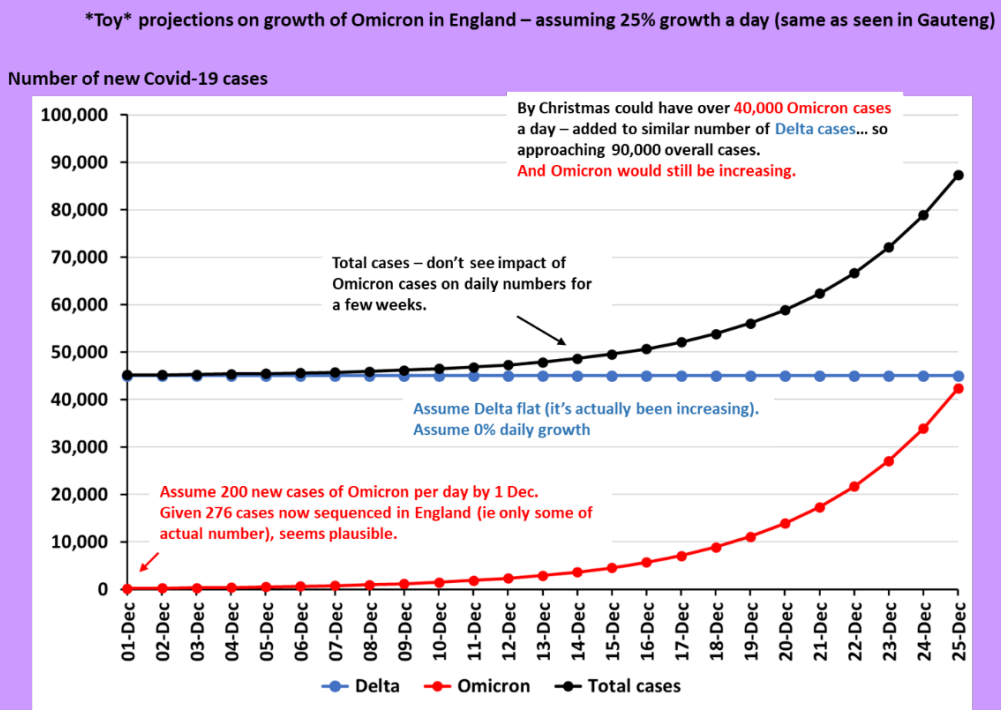
South Africa has recently seen an uptick in ICU utilisation, which may reflect cases spreading to older groups (see clinical characteristics section for further information).



John Burn-Murdoch FT (7 Dec 2021).[17]

The ECDC has stated that based on current knowledge, mathematical modelling indicates that the Omicron variant is expected to cause over half of all SARS-CoV-2 infections in Europe within the next few months.[15] The credibility of this modelling has been questioned and the assumptions put into the model, and the model itself is unavailable to review.[34]

In the UK, scientists have been increasingly expressing their concern about the new variant. Some speculate that as of 7 Dec there are likely over 1,000 cases in the UK and that it could become the dominant variant within weeks or a month.[35,36,37]



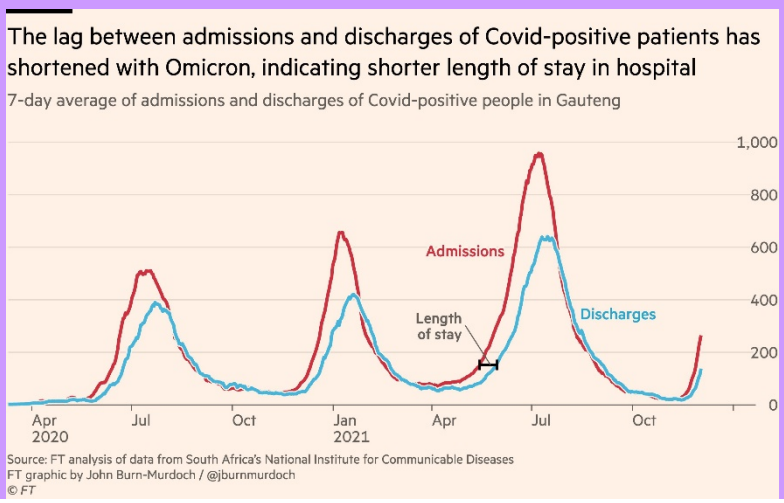
Christina Pagel (6 Dec, 2021).[36]

CLINICAL CHARACTERISTICS

There has been cautious optimism from South African medics that Omicron may be milder than previous variants. However, the number of confirmed cases is too low to understand if the disease differs from that of previously detected variants and there is a lag from confirmed cases to hospitalisation and death.[18]

On the 8 Dec 2021, the UK's Chief Medical Officer reported he had had calls with South African health officials and that hospitalisations for COVID had increased 300% in a week.[38]

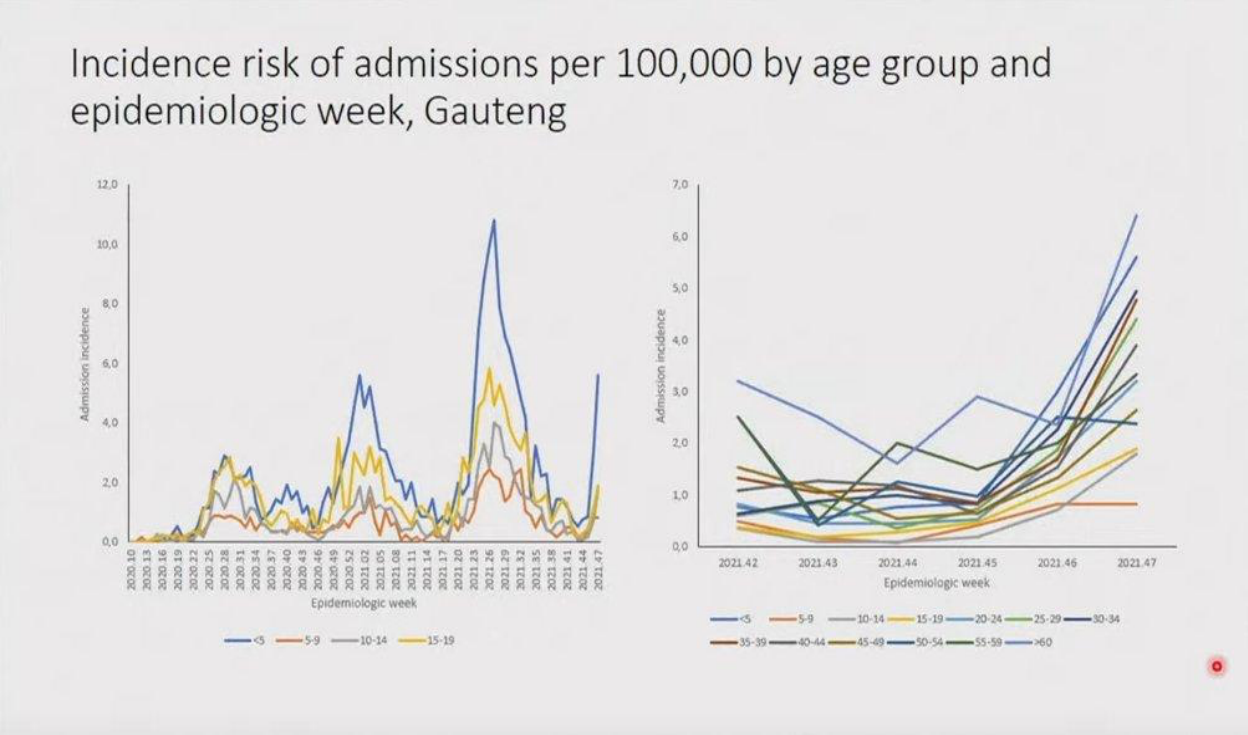
Tshwane Hospital in Gauteng Province, South Africa released two weeks of data on just 166 patients with presumed Omicron, covering the end of Nov and start of Dec. COVID infections were often identified after admission for another reason. 80% of admissions were below the age of 50 years. Most patients in the COVID wards were not oxygen dependent. There also appeared to be a shorter average length of stay of 2.8 days for SARS-CoV-2 positive patients admitted to the COVID wards over the last two weeks compared to an average length of stay of 8.5 days for the past 18 months. However, the report also found that of the 166 COVID patients, 9 died of COVID (5 died out of 33 admissions aged over 60 years).[39]



John Burns (7, Dec 2021).

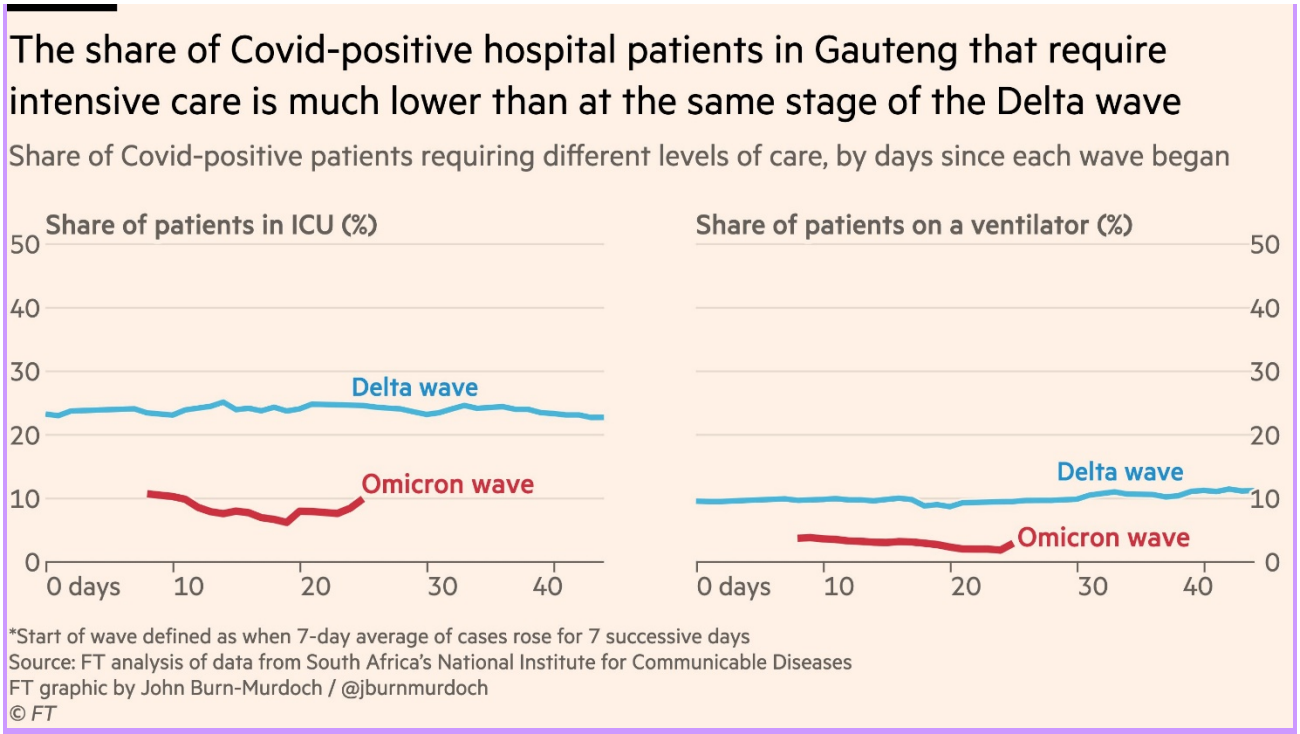
It is too early to determine if the Omicron variant is associated with a different cluster of symptoms. A primary care doctor in South Africa who treated Omicron patients says they are experiencing fatigue, body aches and mild headaches and had not experienced a loss of smell or taste.[40,41]

There is some early data that suggests increasing incidence of infections across all ages, particularly children under 5 years (although early in the wave and cases can rise early on in younger ages).[42]



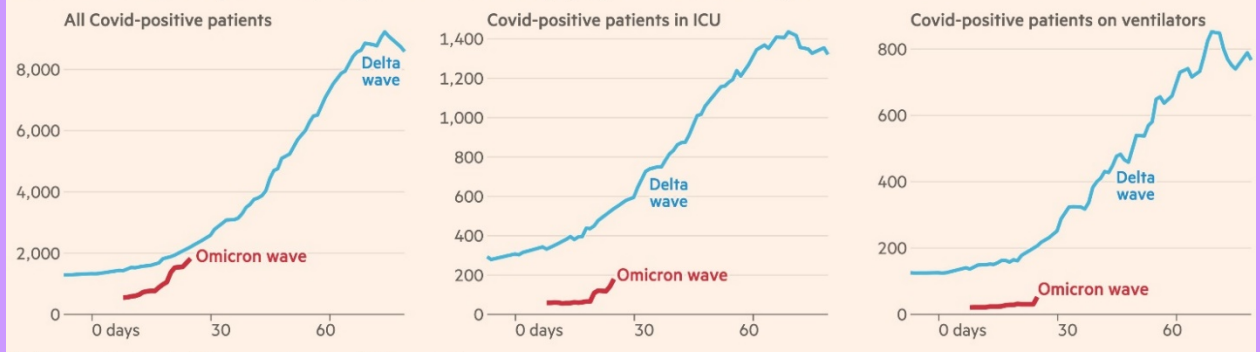
South Africa Ministry (3 Dec 2021).[42]

As at 4 Dec in Gauteng, South Africa, there is a much lower share of COVID-positive patients in this wave requiring oxygen or ICU than at same stage of Delta wave, but these indicators are increasing.[43] In Gauteng province, the share of COVID-positive patients in ICU or on ventilators is somewhere between 2-3x lower than it was at the same stage of the Delta wave.



Although the number of Covid-positive patients in Gauteng is approaching the level from the Delta wave, the number in ICU is much lower

Number of Covid-positive patients requiring different levels of care, by days since each wave began

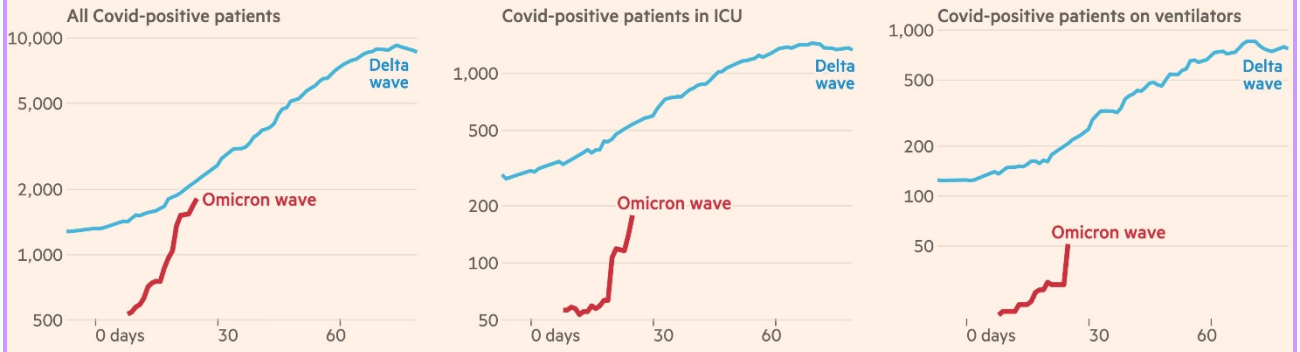


*Start of wave defined as when 7-day average of cases rose for 7 successive days
Source: FT analysis of data from South Africa's National Institute for Communicable Diseases
FT graphic by John Burn-Murdoch / @jburnmurdoch
© FT

On a log scale, the growth rates can be compared more clearly. On current trends, patients on oxygen (mostly due to COVID) will soon pass the Delta trajectory and numbers in ICU are also increasing. Again, there are the usual caveats of limited data and daily reporting anomalies.

But plotted on a log scale, the number of Omicron patients in ICU or on ventilators does seem to be rising faster than in the Delta wave

Number of Covid-positive patients requiring different levels of care, by days since each wave began



*Start of wave defined as when 7-day average of cases rose for 7 successive days
Source: FT analysis of data from South Africa's National Institute for Communicable Diseases
FT graphic by John Burn-Murdoch / @jburnmurdoch
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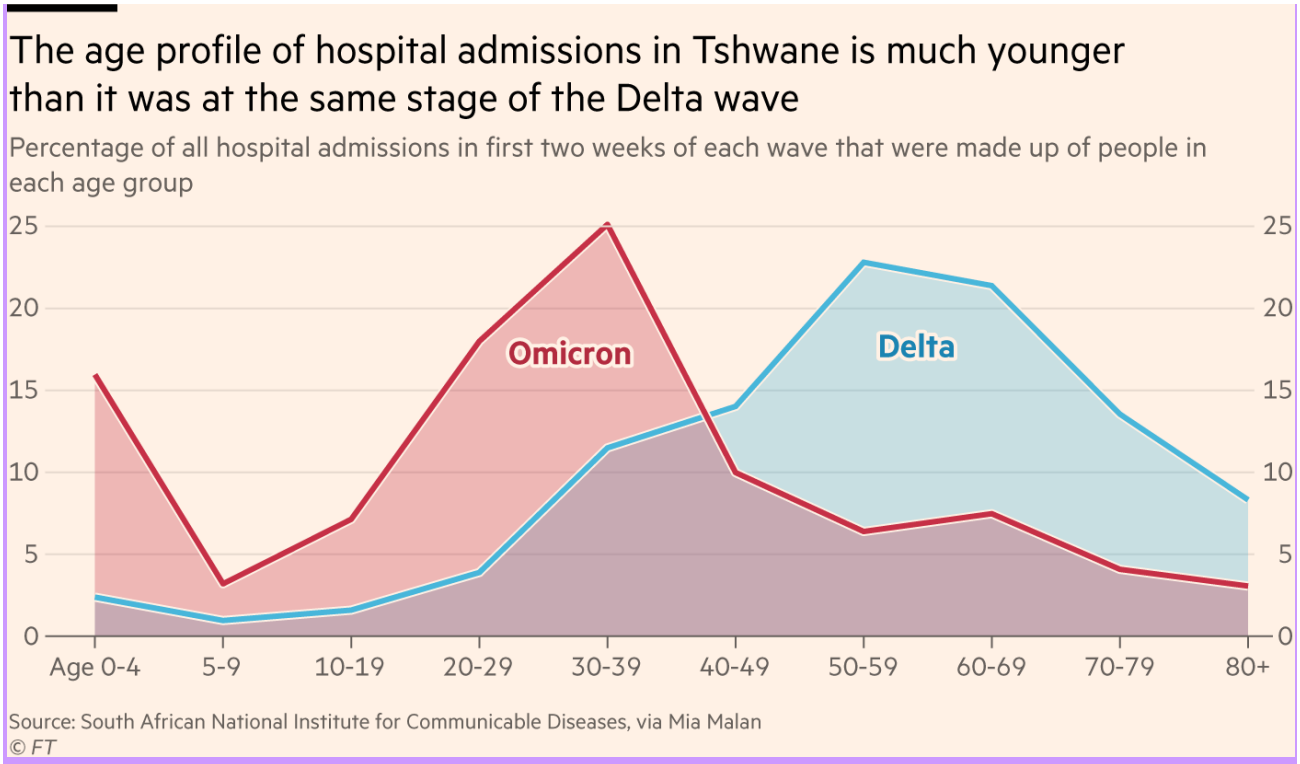
At this stage there are markedly different age profiles of the two waves. Over first two weeks of the Omicron wave cases and hospitalisations are younger – which would explain a lower level of ICU use compared to the Delta wave.



Cases in Gauteng are now spreading into older age-groups and that will likely feed into admissions/patients, shifting the risk profile.[44]

Little is known regarding the impact of Omicron infection on people aged over 50 and with comorbidities, as such cases have not been presented at the hospitals yet.[30]

Hospitalisations are likely to grow when cases are growing exponentially. The default is that they'll grow at more or less the same exponential rate. To determine whether it's milder, there needs to be confidence in what fraction of infections or cases leads to hospitalisation.[34]

In South Africa, where cases in early December were growing at something like 500% per week (30% per day has been reported in Dec) if the lag is mis-estimated by a couple of days in either direction, the estimate of "fraction hospitalised" might be out by 70% or more in either direction.[34]

On 2 Dec 2021, Prof Salim Abdool Karim of the Africa Task Force for Coronavirus stated that as with previous variants Beta and Delta, the full picture in South Africa will not become clear until "people get so sick that they need to go to the hospital" which is generally "three, four weeks later, but the feedback we're getting from the ground is that there's really no red flags - we're not seeing anything dramatically different, what we're seeing is what we are used to".[45]

Soweto Hospital reported that most admissions were unvaccinated and in the younger age groups, only 13% of admissions had been vaccinated.[46] However, the underlying health status and access to healthcare in parts of South Africa further compound the ability to understand disease severity at this early stage.[47] HIV prevalence among the general population is high at 20.4% and is the leading cause of death.[48] South Africa also has one of the highest Tuberculosis (and multi-drug Resistant Tuberculosis) in the world. In addition, South Africa is the most obese country in sub-Saharan Africa, with over 40% of adults overweight or obese.[49]

DIAGNOSTICS

Evidence indicates that PCR and rapid antigen tests can detect the new Omicron (B.1.1.529) variant of concern. .[20,50]

One of the omicron variant's mutations leads to "S gene target failure" (or "S gene dropout"), meaning that one of several areas of the gene that are targeted by PCR testing gives a false negative. This can be used as a "surrogate marker," allowing genome sequencing to be targeted, particularly where circulating strains are predominantly S gene-positive, as is the case with the Delta variant.[4]

Studies are ongoing to determine whether there is any impact on other types of tests, including rapid antigen detection tests.[16] Multiple companies have stated that they believe their test kits work in detecting Omicron.[51]

The Singapore Ministry of Health (MOH) has stated analysis so far has indicated that, in addition to the polymerase chain reaction (PCR) test, ARTs are also effective as a method of detecting COVID-19 infection, including Omicron cases.[52]

IMMUNE RESPONSE ESCAPE

"What we really need now is a coordinated research effort and not jumping to conclusions on you know, study by study. We are going to see a couple of weeks of every day, new information new studies. One study is not going to really prove anything." – Soumya Swaminathan, Chief Scientist, World Health Organization, WHO (8 Dec, 2021).[53]

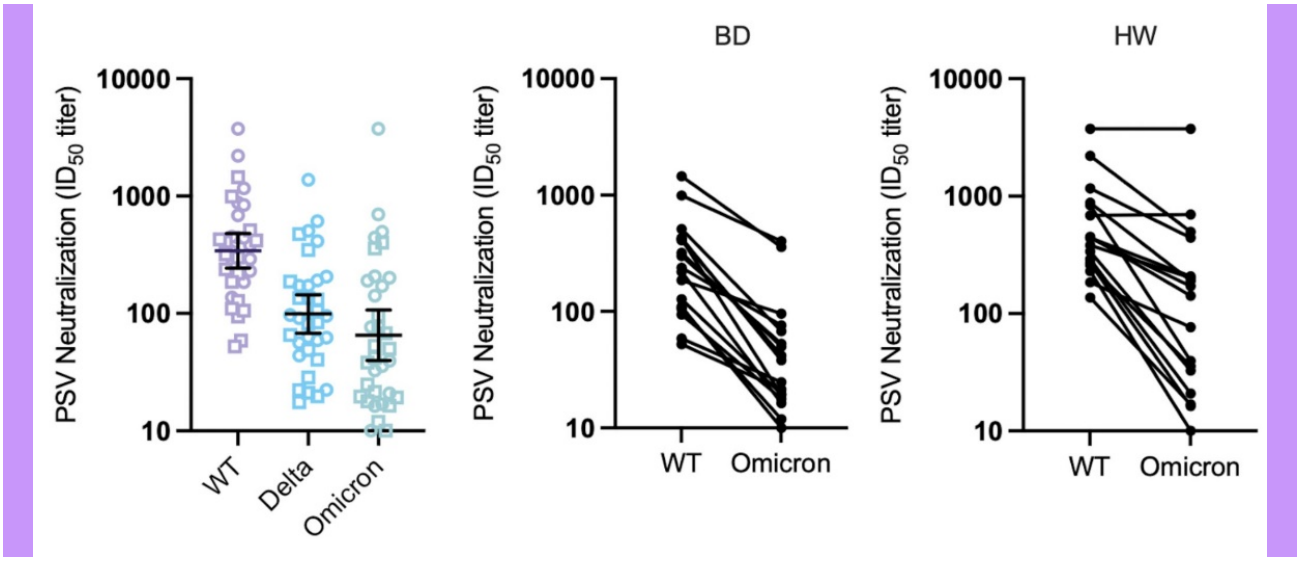
There have been anecdotal reports from South Africa of reinfection in people who have been previously infected with COVID-19.[54]

A preprint study on 2,796,982 individuals with positive laboratory-confirmed SARS-CoV-2 test results at least 90 days prior to 27 November 2021 in South Africa suggests that the Omicron variant is associated with an increased ability to evade immunity from prior infection compared to the Beta or Delta variants (albeit an increase from a low level of risk). However, there are significant limitations to the early study and more detailed work is ongoing.[55,56]

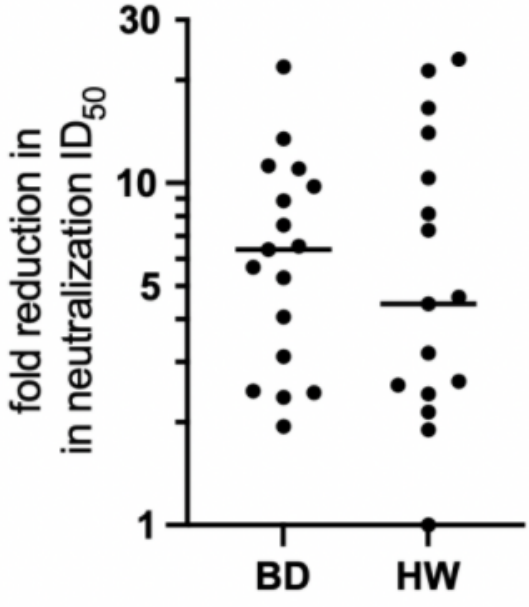
Neutralisation Experiments

Below is a summary of preliminary lab-based data, given the circumstances this has been rapidly released by researchers, but has caveats that it has not yet been peer reviewed and that studies are small. Real-world data will take time to establish.

One early lab study by researchers at Karolinska Institute found the loss of neutralisation against Omicron (relative to the original variant) was variable across blood sera from donors (n=17) and health workers (n=17) in Stockholm (presumably mostly vaccinated and uninfected – this is unknown). Some samples showed almost no loss and others up to ±25-fold loss relative to the original variant. The mean fold-reduction was around 7.[57,58]



Pseudovirus neutralisation titers for Blood Donors (BD; N=17) and Hospital Workers (HW; N=17) against the pandemic founder variant (WT), the B.1.617.2 variant (Delta) and the B.1.1.529 variant (Omicron).[58]

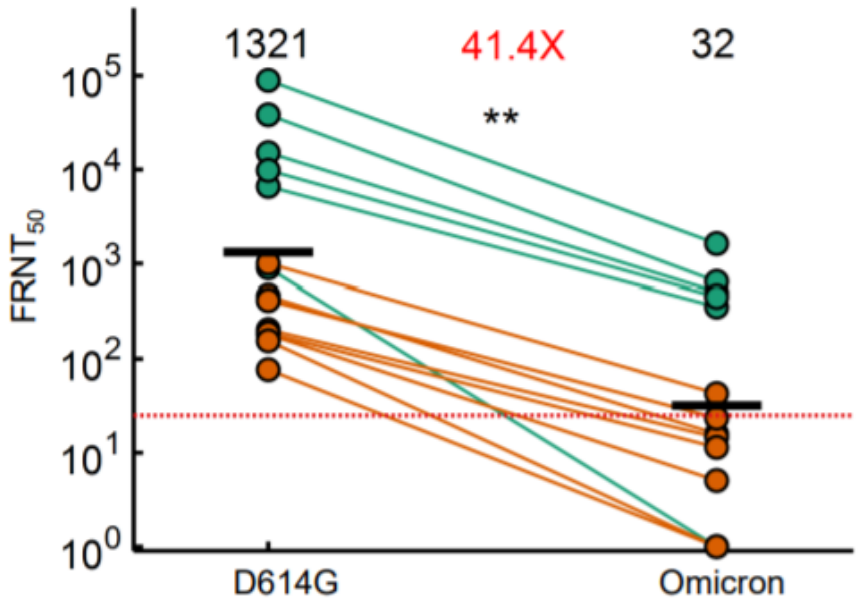


Fold reduction in neutralization of the Omicron variant compared to the pandemic founder variant for Blood Donors (BD, N=17) and Hospital Workers (HW, N=17) from Stockholm, Sweden.[58]

In parallel, researchers in South Africa have been working on live virus neutralisation assays and their results show a substantial average reduction - a 41x drop in vaccine neutralisation of Omicron.

Live virus neutralisation assays can show whether levels of antibodies in the blood (convalescent and vaccinated plasma) are high enough to prevent the virus from infecting cells in the lab.

This doesn't mean vaccines will be 41x less effective, those who received 2 doses of vaccine still retained some neutralisation. So called ‘hybrid immunity’ (infection and vaccination) demonstrated much better neutralisation. Analysis of infected and **not** vaccinated was not studied, so it is unclear the impact of the vaccine in neutralisation over and above natural infection.[59]



Neutralisation of the Omicron virus compared to D614G ancestral virus participants vaccinated with BNT162b2 and infected by ancestral SARSCoV-2 (green) or vaccinated only (orange).[59]

Researchers from the Karolinska Institute hypothesise that the differences between their results and the results out of South Africa may be due to blood samples from different continents with different exposure histories. There are also multiple technical differences attributable to the assays themselves.[57]

Researchers in Germany have also undertaken neutralisation experiments with a virus isolate (infectious virus), not with pseudoviruses. This study also included 'boosted individuals' (3x doses of vaccine in various combinations). There was a significant drop in neutralising antibody titres compared to the Delta variant (see graphic below).[60] Neutralisation against Omicron is reduced throughout, including for individuals with infection and 2 doses of BioNTech/Pfizer. A significant proportion of individuals show no neutralisation activity. The results do not suggest that neutralising antibody activity can be restored by a third dose.

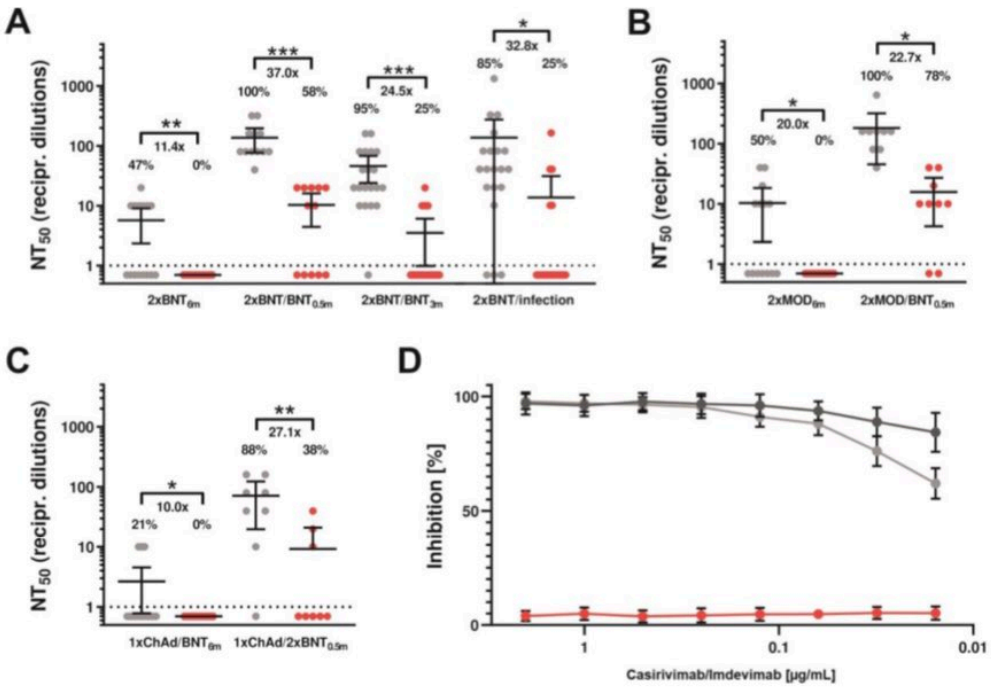


Figure 1 - Antibody-mediated neutralization efficacy against authentic SARS-CoV-2 variants Delta and Omicron. Values represent reciprocal dilutions of SARS-CoV-2 variants Delta (grey) and Omicron (red) micro-neutralization titers resulting in 50% virus neutralization (NT_{50}). **A)** Neutralization assays were performed using serum samples obtained from individuals double BNT162b2 vaccinated (2xBNT). Sera from additionally BNT162b2 boosted individuals were sampled 0.5 month (2xBNT/$BNT_{0.5m}$) or 3 month (2xBNT/BNT_{3m}) as well as sera from double BNT162b2 vaccinated and SARS-CoV-2 infected individuals (2xBNT/infection). **B)** Neutralization assays with sera from double mRNA-1273 vaccinated (2xMOD) and additionally BNT162b2 boosted (2xMOD/$MOD_{0.5m}$). **C)** Neutralization titers for sera from heterologous ChAdOx1 and BNT162b2 vaccinated (1xChAd/1x$BNT_{0.5m}$) and BNT162b2 boosted (1xChAd/2x$BNT_{0.5m}$) individuals. The x-fold reduction was determined using the difference between NT_{50} values for Delta and Omicron. Only Delta neutralizing samples were considered for the calculation. Negative titers were handled as 1. The percentages indicate the relative number of sera that achieved a measurable titer. Information regarding the sera donors (sex, age, antibody titers test and sampling dates) are summarized in in the Supplementary Appendix. **D)** Neutralization efficacy of monoclonal antibodies imdevimab and casirivimab against SARS-CoV-2 Omicron (red), B (dark grey), and Delta (grey). The indicated concentrations of mAbs casirivimab and imdevimab were applied in a 1:1 ratio. Mean values of two technical replicates per sample are depicted with 95% confidence intervals and SD. All experiments were verified using a second SARS-CoV-2 strain (**Supplementary Table 4**). Statistical significance compared to Delta was calculated by two-tailed, paired student's t-tests. Asterisks indicate p-values as * ($p < 0.05$), ** ($p < 0.01$), and *** ($p < 0.001$).

Early Data Release, Germany, 8 Dec 2021.[60]

Based on the early neutralisation experiments there maybe a 7 - 41 fold difference in reductions in neutralisation, with most reporting towards the upper end (20-40-fold reduction). The University of California has outlined a very rough extrapolation of what this would mean for vaccine effectiveness with analysis grounded in methods of previous analysis of vaccine effectiveness based on neutralisation studies.

Omicron's 30-40-fold reduction in neutralising antibody titers might lead to estimated:[61]

~40-60% reduction in symptomatic infection

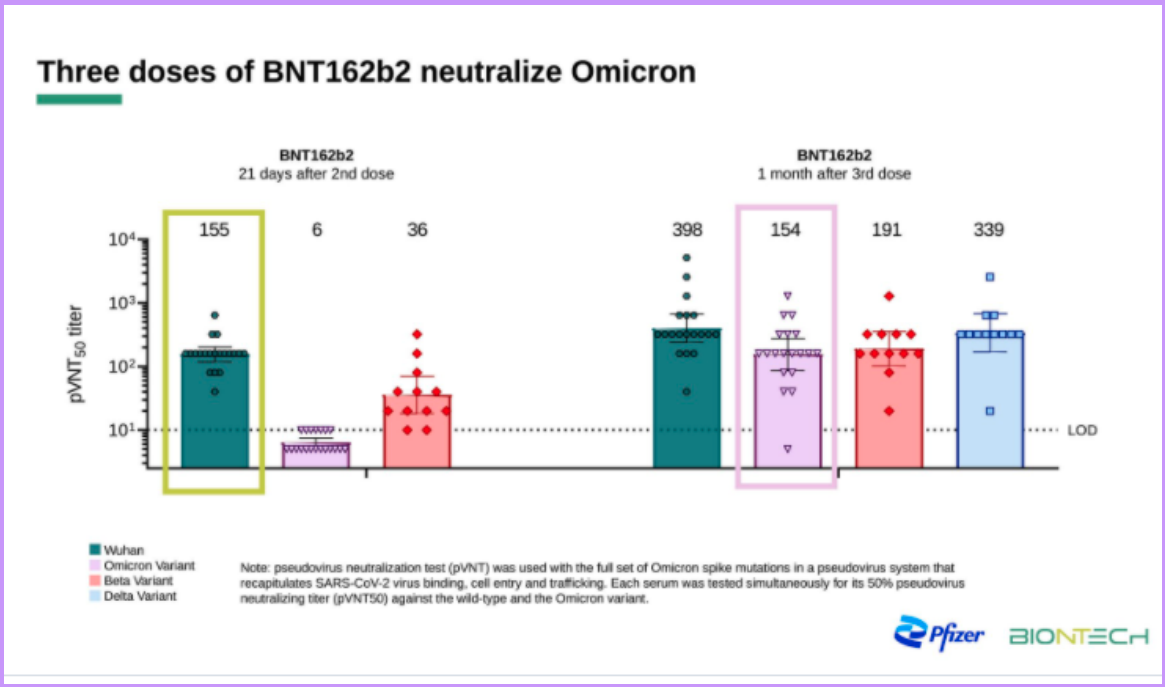
~10-14% reduction in vaccine effectiveness against hospitalisation

These figures are incredibly rough and reliable estimates of levels of protection from vaccines and previous infections will emerge in the coming weeks as the number of people with Omicron grows large enough to carry out proper analysis that adjusts for confounders.

These very early, small-scale, preliminary data on the neutralisation sensitivity of the Omicron variant require replication and confirmation with larger studies.

The impact of natural and vaccine-induced immune responses against severe disease from Omicron needs urgent investigation. In addition, studies on T-cell studies have yet to report, which may show more positive results in resistance from Omicron from vaccination alone.

A Pfizer press release on 8 Dec stated that their own laboratory studies on a small sample of sera found that having three doses of Pfizer may result in increased neutralising antibody titers against Omicron one month after vaccination compared to two doses (they state a 25-fold increase).[62] Replication of the experiment is needed on a wider sample and in independent laboratories to confirm this result. The outcome of monitoring of how fast antibody levels drop on average after boosting is also needed, which will indicate duration of protection from infection post-booster dose.

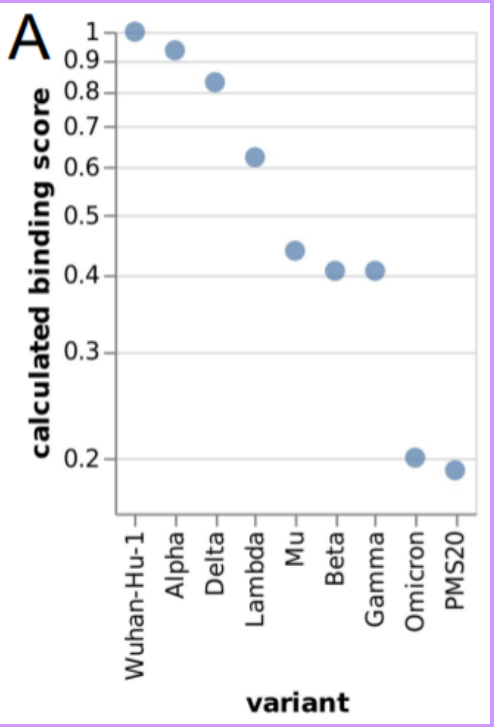


Pfizer Data.[62]

Computer Modelling

Analysis has also been undertaken of aggregating deep mutational scanning data into an “escape calculator” that estimates the antigenic effects of arbitrary combinations of mutations to the virus’s spike receptor-binding domain (RBD).

The calculator was used to intuitively visualise how mutations impact polyclonal antibody recognition and score the expected antigenic effect of combinations of mutations. These scores correlate with neutralisation assays performed on SARS-CoV-2 variants, and emphasise the ominous antigenic properties of the recently described Omicron variant.[63]



Escape calculations for the Omicron variant. The calculated binding scores for SARS-CoV-2 variants and the artificial polymutant spike (PMS20).

PMS20 was artificially engineered in a pseudovirus by Schmidt et al. (2021) to maximize escape from polyclonal serum antibodies.[64]

There has been a more favourable computational biology prediction for Omicron that suggests that although some structural changes in the receptor-binding domain may reduce antibody interaction, there are no drastic changes that would completely evade existing neutralising antibodies (and therefore current vaccines).[65]

VACCINES

There has been infection and transmission between people who have been vaccinated (and boostered), but it's not clear to what extent this means that individuals are going to get a severe case of Omicron.[66]

Reports from South Africa suggest higher proportions of unvaccinated patients among those admitted to hospitals with moderate to severe disease, suggesting that vaccines could still be effective in protection against severe disease. However, data is too limited at this stage to draw conclusions.[39] South Africa has a low vaccination rate at about 36% of the adult population, but the rate is particularly low in young people, especially men.[56]

Any wave of significant infection, almost irrespective of immune escape, will spill over into hospitalisations, and ultimately deaths. If initial estimates of transmission advantage and immune escape from South Africa are fairly accurate then there is the potential for a very substantial peak of infections. Even if severity of omicron were half that of delta, the sheer number of infections could lead to significantly more pressures on health settings. The UK Government reports that if omicron's immune escape reduces vaccine effectiveness against hospitalisation from, say, 96 per cent to 92 per cent, that would effectively double the number of vaccinated individuals who are not protected from hospitalisation.[28]

In response to Omicron, several countries have altered vaccination advice – hoping that booster will provide protection from severe disease. Anecdotally, there have been news reports of individuals who had been boostered becoming infected with Omicron and infecting others.[67,68]

The UK will offer boosters 3 months after the primary course, in order of descending age groups, with priority given to the vaccination of older adults and those in a COVID-19 at-risk group.[69] The CDC recommends booster for over 18's, 6 months after their initial Pfizer or Moderna series or 2 months after their initial J&J vaccine.[70]

There is a hypothesis that booster doses may increase the level of neutralising antibodies effective against Omicron, this is backed up by a lab-based study of a different 'polymutant spike' that suggested repeated exposure to the spike protein, be it through infection or a booster dose, may have a protective effect against Omicron.[29] Early analysis from Israel suggests that the rate of decline in efficacy from infection in most age groups is similar to that of the second dose of the Pfizer vaccine.[71] Preliminary small-scale neutralisation studies outlined in above also suggest limited effect of boosters.

Vaccine manufacturers are also looking to develop Omicron specific vaccines or boosters.

- **Pfizer** is developing an Omicron vaccine that could be ready in March 2022.[72] The company has already started working on a DNA template tailored to match Omicron.[73]

- **Moderna** is developing a vaccine specifically for Omicron that would be available in March 2022 and a multi-valent vaccine that would include up to four different coronavirus variants including Omicron.[74] It is also undertaking a small 306-person study to see if a higher dose booster of mRNA-1273 (100 µg) in healthy adults provides protection from Omicron.[75]

- **Johnson & Johnson** has been evaluating the effectiveness of its vaccine across variants, including Omicron, and testing blood serum from participants in completed and ongoing booster studies to look for neutralizing activity against the Omicron variant. It is also pursuing an Omicron-specific variant vaccine and will progress it as needed.[76]

- **AstraZeneca** is ready to rapidly develop an updated version of its vaccine if necessary.[77]

- **Sinovac** has stated it can rapidly mass produce a version against the Omicron variant if needed. [78]

- **Sinopharm** information could not be located.

- **Sputnik V** is developing a booster for Omicron.[79]

THERAPEUTIC OPTIONS

Neutralisation results are expected in mid-Dec, real-world data will take longer to come in.

The WHO stated that corticosteroids and IL6 Receptor Blockers will still be effective for managing patients with severe COVID-19. Other treatments will be assessed to see if they are still as effective given the changes to parts of the virus in the Omicron variant.[16]

Many antibody treatments focus entirely on the receptor-binding domain, where the virus binds to cells it is attacking. The Omicron strain has 15 mutations in this area. However, the current opinion is that some of the most promising drugs will still be effective against the new variant.

- **Pfizer's PAXLOVID** includes the new compound (PF-07321332) taken in combination with the repurposed HIV/AIDS drug ritonavir. PF-07321332 is a protease inhibitor targeting the 3CLpro SARS-CoV-2 protease (gene NSP5) reducing the ability of the virus to replicate in host cells. The NSP5 gene sequence remains essentially unchanged in the Omicron variant, and no particular loss of efficacy should a priori be anticipated for the Pfizer treatment.[80] A recent preprint presented in vitro data suggesting that the efficacy of specific Mpro inhibitors such as PF-07321332 is not compromised in current COVID-19 variants.[81]

- **Merck's Molnupiravir LAGEVRIO** is a nucleoside analogue, which means it mimics some of the building blocks of RNA and leads to the introduction of copying errors during viral RNA replication. If anything, the Omicron variant might be more susceptible than previous SARS-CoV-2 lineages to Molnupiravir given a large number of mutations it already carries in its spike protein. As such, Omicron may be more easily sent into "mutational meltdown".[80]

- **GlaxoSmithKline's Sotrovimab** is likely to be able to tackle the Omicron variant, according to early data. Lab testing had been undertaken against a variety of variants that shared mutations in Omicron. Also, one of the target areas of the spike is thought to be unchanged in Omicron.[82] A preprint has reported that Monoclonal Sotrovimab retains activity against Omicron, so it should still be an effective COVID therapeutic drug in high risk patients.[83]

- **Regeneron's Ronapreve** could be less effective against Omicron to the mutations.[82]

- **Eli Lilly's antibody treatment** has already shown signs of being less effective against other variants. The company advises against using one of its antibodies, bamlanivimab, on its own to tackle the Delta strain but says a combination can still treat the variant. It expects results on Omicron in the coming weeks.[82]

- **Gilead's Remdesivir** directly inhibits the SARS-CoV-2 replication inside infected cells by targeting the viral RNA polymerase. Studies by Gilead suggest that it will continue to be active against the new omicron variant.[84]

- **Monoclonal Imdevimab and Casirivimab** are reported to be ineffective with Omicron (small scale preliminary study from a German lab).[85]

LIMITATIONS

As of 2 Dec 2021, the ECDC summarised the current limitations and knowledge gaps:[15]

- There is a lack of clear understanding of the epidemiological situation in many countries that are likely to be affected given the lack of sequencing or screening using S-gene target failure.
- Current estimates of transmissibility remain uncertain and further studies, including contact tracing data on secondary attack rates, growth rates, Rt and R0 are needed to provide reliable estimates of the transmissibility of the variant overall and relative to measures in place in different community settings.
- Current estimates of severity (hospitalisation and deaths) remain highly uncertain and further studies, including longer-term follow up by age group, previous infection, and vaccination status of cases identified, are needed to provide more reliable estimates.
- Current estimates of immune escape are highly uncertain and further studies on virological characterisation, including in-vitro infectivity studies and neutralisation studies evaluating both vaccinee and convalescent sera, are needed.
- There is currently no information on vaccine escape and analyses of the vaccine effectiveness for different vaccines against Omicron (direct and indirect effects) for disease, transmission and severe disease by age group are needed.
- Information around cross-protection of natural immunity from other SARS-CoV-2 variants, in particular data on reinfection risk and reinfection severity in populations exposed to different SARS-CoV-2 variants during previous pandemic waves.

CONTRIBUTORS

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