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 (most of the studies cited have yet to be peer reviewed). It should be noted that robust evidence has yet to be established. Many international studies are underway to characterise Omicron.¹,²

Updates from last version are highlighted in Blue. The cut-off date for new information included in the rapid review was 23 Dec, 2021.

Where data and information from previous reports has become out of date it has been removed.

EVIDENCE SUMMARY

The evidence summary should be read alongside the full rapid-review report and takes key findings from the UK risk assessment.³ The characterisation of Omicron is still uncertain and so the following summary is likely to be subject to significant change over coming weeks and months.

<table>
<thead>
<tr>
<th>Evidence Confidence</th>
<th>Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transmissibility</td>
<td>Low</td>
</tr>
<tr>
<td>Growth Advantage</td>
<td>High</td>
</tr>
<tr>
<td>Infection severity</td>
<td>Low to Moderate</td>
</tr>
<tr>
<td>Naturally acquired immunity</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

**Evidence Confidence**

**Assessment**

- **Transmissibility**: Low At least as transmissible as currently circulating variants; gathering evidence of increased transmissibility
- **Growth Advantage**: High Growth advantage is visible in several countries
- **Infection severity**: Low to Moderate Preliminary data from some countries
- **Naturally acquired immunity**: Moderate Reduction in immune response against infection

Growing preliminary research indicating increased reinfection risk at the population level. Preliminary analyses indicate approximately three- to eight-fold increased risk of reinfection with the Omicron variant (to 4.9%).
**Vaccine acquired immunity**

**High**

**Reduction in immune protection against infection**

Multiple lab neutralising studies have reported around a 30-40 fold reduction in neutralising antibodies. Lack of evidence on protection from hospitalisation at this time.

Multiple lab neutralising studies that suggest a third dose / booster can improve neutralisation against Omicron (data on how long this protection lasts is limited).

**Therapeutics**

**Moderate**

**Most therapeutics may remain effective**

Lab data suggests significant reduction in effectiveness of some monoclonal antibody treatments.

The WHO states that overall threat posed by Omicron largely depends on three key questions, including: (1) how transmissible the variant is, (2) how well vaccines and prior infection protect against infection, transmission, clinical disease and death, and (3) how virulent the variant is compared to other variants.⁴

---

**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.⁵,⁶

*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.\(^7\)

Science.Org.\(^8\)

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.

The Omicron has two clades, BA.1 and BA.2. BA.1 is the clade currently of focus and spreading rapidly. Both clades carry almost all the same mutations, but BA.2 does not carry the spike:69/70 deletion and will therefore not be detectable by S-gene target failure.\(^9\)

The closest sequences are over a year ago.\(^{10}\) 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.\(^{11}\)

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.\(^{12}\)

- **Chronically infected patient** – This hypothesis is backed up by sequencing showing changes to the virus in chronically infected patients.\(^{13}\) 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.\(^6\)

- **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.\textsuperscript{14}

- **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 (e.g., 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).\textsuperscript{15}

- **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.\textsuperscript{16} On 26 November 2021, WHO designated variant B.1.1.529 a variant of concern, named Omicron.\textsuperscript{17}

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).\textsuperscript{11}

Omicron has been identified in many countries across the globe. Many of the countries reporting Omicron have regular sequencing of positive cases.\textsuperscript{18}

\textbf{As of 14 Dec, Omicron had been detected in more than 95 nations, with many reporting significant levels of community transmission.}\textsuperscript{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.\textsuperscript{20} 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 has reported cases of Omicron to GISAID. On 2 Dec, 2021 Omicron made up 0.9\% of sequenced positive cases in the previous four weeks, by 14 Dec this had increased to 1.8\%.\textsuperscript{21} According to CDC data, Omicron is estimated to make up 26.6\% of sequenced cases in the US for the week ending 18 Dec.\textsuperscript{22}

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. For example, in Scotland there was a dramatic increase in S gene target failure in community testing data over a short period of time: on 1 Dec it comprised of 1\% of positives, by 9 Dec it was 13.3\%. Both Scotland, and the wider UK predict that Omicron will become dominant before the end of the year.\textsuperscript{23}

\section*{TRANSMISSION AND IMMUNE ESCAPE}

The WHO states that based on current limited evidence Omicron appears to have a growth advantage over Delta. It is spreading faster than the Delta variant in South Africa where Delta circulation was low, but also appears to spread more quickly than the Delta variant
in other countries where the incidence of Delta is high, such as in the United Kingdom. Whether Omicron’s observed rapid growth rate in countries with high levels of population immunity is related to immune evasion, intrinsic increased transmissibility, or a combination of both remains uncertain. However, given the current available data, it is likely that Omicron will outpace the Delta variant where community transmission occurs.4

Growth Rate

A UK study found a higher risk of transmission to contacts from an Omicron index case, when compared to Delta index cases. These studies have not adjusted for vaccination or prior infection status of the contacts, due to current data quality. This means that the findings are describing overall growth advantage, rather than pure transmissibility. The findings include:9

- The risk of household transmission using routine testing data (adjusted odds ratio of transmission from an Omicron index case compared to a Delta index case 3.2 (95% CI 2.0-5.0))
- The risk of a close contact becoming a secondary case (adjusted odds ratio 2.09 (95% CI: 1.54-2.79))
- The household secondary attack rate using routine contact tracing data (Omicron, 21.6% (95% CI: 16.7%-27.4%), Delta 10.7% (95% CI: 10.5%-10.8%))

The estimated growth rate of Omicron in the UK is around 0.35 per day.9,24

A descriptive analysis of the genomic profile and early transmission dynamics of Omicron in South Africa estimated a growth advantage of 0.24 per day over Delta in Gauteng, which corresponds to a 5.4-fold weekly increase in cases compared to Delta. The study argues that considering the high population level of protective immunity in South Africa, partial immune evasion is a major driver for the observed dynamics of Omicron in South Africa.25 Another study using laboratory and epidemiological data from South Africa estimated growth advantage at 0.32 for Omicron in Gauteng relative to background variants, and ranging from 0.31 to 0.72 across different provinces.26

A recent lab study using ex vivo cultures of respiratory tract has found that Omicron infects and multiplies ~70 times faster than the Delta variant and the wild type SARS-CoV-2 in the human bronchus.27

Analysis of an Omicron cluster at an indoor party event with 117 people in Norway revealed that 81 out of 110 interviewed people caught the virus, indicating an attack rate of 74%. The high attack rate was likely attributable to the context and setting of the outbreak (indoor location, long exposure time, crowding, and vocal interactions). Out of the interviewed people, 99 had received two shots of mRNA vaccine (with no-one boostered), indicating high Omicron transmissibility even among fully vaccinated people.28

Incubation period

Early 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.29 Study of the party event cluster in Norway observed a median incubation period...
of 3 days, assuming attendees were infected at the party. This is short compared with previous reports for Delta and other previously circulating non-Delta SARS-CoV-2 (4.3 and 5.0 days, respectively).\textsuperscript{28}

**Modelling Studies**

The European Centre for Disease Prevention and Control 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.\textsuperscript{16}

A preliminary analysis of the initial Omicron cases reported to The European Surveillance System found that imported or travel-related cases account for 22 (13\%) cases, while 121 (70\%) of the cases reported have been acquired locally, including 78 (45\%) cases sampled as part of local outbreak investigations.\textsuperscript{30}

There is a consistent view that Omicron will result in a significant rapid wave of infections. Modelling from the UK, Norway and Denmark has found that Omicron is likely to become the dominant variant over the coming days and weeks as cases are doubling every two days.\textsuperscript{24} The latest data from the UK Health Security Agency is reflecting less than 2 day doubling time in the UK (close to 1.5 days in certain areas), with a \textasciitilde 2 to 3-fold increased risk of household transmission.\textsuperscript{31} There is likely to be an overlap for some time of increasing Delta cases as well as the rising Omicron wave.\textsuperscript{32,33,34,35}

![Graph showing estimated growth of Delta (blue) and Omicron (red) in the capital of Denmark. The circles indicate the last observations including the model and the colored areas indicate the 95\% safety intervals](image_url)
The UK currently has both a Delta wave (a high baseline of ~40,000 Delta cases/day) and a rapidly rising Omicron wave. Omicron infections will not replace Delta right away – this may take a month or so. The graph below is of London and shows these two variants rising.
Under UK modelling of the most optimistic scenario (low immune escape of Omicron and high effectiveness of boosters), a wave of infection is projected which could lead to a peak of over 2,000 daily hospital admissions, with 175,000 (95% CI: 139,000–198,000) hospitalisations and 24,700 (19,500–28,700) deaths between 1st December 2021 and 30th April 2022, if no additional control measures are implemented over and above the current ‘Plan B’ policy in England. In comparison, the most pessimistic scenario (high immune escape and lower effectiveness of boosters) projects a wave of infection which is likely to lead to a peak in hospital admissions around twice as high as the peak seen in January 2021, if no additional control measures are taken, with 492,000 (418,000–537,000) hospitalisations and 74,800 (63,500–82,900) deaths.\(^{35}\)

In the UK, the R value of the Omicron spread is estimated at between 3 and 5, while the R value of the current Delta epidemic is estimated at between 1.1 and 1.2.\(^{38}\)

In terms of South Africa, there has been late reporting of cases and so there is uncertainty around data. There may be early signs that the growth rate is slowing in Gauteng, where the variant was first identified to be causing an outbreak, but that it is growing rapidly in other areas of South Africa.

Louis Rossouw, a research and analytics expert in Cape Town is tracking the latest data from the South African NICD and reports that the % positive test rate has increased from around 10% at the end of November to around 35% by the 11 Dec.\(^{39}\)

The R number is around 1.56 for South Africa, but varies significantly across provinces, the highest currently is the Northern Cape at 2.37 [95% CI 1.91 - 2.89], the lowest is Gauteng 1.30 [95% CI 1.26 - 1.36].\(^{39}\)
Another study using laboratory and epidemiological data from South Africa estimated $R_t$ during mid-Nov at 4-4.7 (medians), depending on what is assumed about the time between infections (generation time) of Omicron. A doubling time of about 2 days was observed for the variant in Gauteng Province.\(^\text{26}\)

A modelling study assessing the potential consequences of the upcoming Omicron waves suggested that significant waves can be expected even in regions where the Delta variant is currently controlled by a combination of non-pharmaceutical interventions (NPIs) and population immunity. The following scenarios were mapped out: high peaks (scenarios b and d) in countries with high population immunity where Delta is contained with very mild/no NPIs, especially if Omicron is highly immune evasive; more flattened waves (scenarios a and c) in countries where population immunity is moderate and strong NPIs are being employed to contain Delta. If Omicron infections of those with prior immunity turn out to be overwhelmingly mild, then the severity is reflected by the red curves without the pink part, with scenarios a and c being more severe.\(^\text{40}\)
Epidemic curves of the Omicron wave under various assumptions on pre-existing immunity and the variant’s immune evasion, without any additional measures.\textsuperscript{40}

**CLINICAL CHARACTERISTICS**

**Severity and Virulence**

The WHO states that there are still limited data on the clinical severity of Omicron and more data are needed to understand the severity profile.\textsuperscript{4}

Preliminary real-world data was released from South Africa on 14 Dec outlining findings from the first 3 weeks of the outbreak (so it is likely to change). Data suggests that the severity of disease might be 29% lower than in the country’s previous wave (ie adults infected with Omicron were 29% less likely to be hospitalised vs. infection with other variants).\textsuperscript{41} However, even if most infections are mild, a highly transmissible variant could result in enough cases to overwhelm health systems.\textsuperscript{42}
Age-controlled data on case fatality ratio across the different COVID-19 waves in City of Tshwane Metro indicated that deaths among hospitalised patients were two-thirds lower in the Omicron wave.

![Graph showing COVID-19 in-hospital case fatality ratio in first 25 days of second, third and fourth wave, amongst patients with outcome, by age group in years, City of Tshwane Metro, 15 November-9 December 2020, 29 November-9 January 2020, 9 May-10 July 2021 and 7 November-4 December 2021.]

To note, there is high seroprevalence in the South African population (antibodies from previous infections) - in Gauteng it may be as high as 70% + of people. The below sketch outlines how a new variant may appear milder even with no change in underlying virulence. This can occur when calculating the fraction of cases that are severe, the denominator now includes many re-infections that had previously been averted. The severity profile of Omicron cases must be interpreted along with an understanding of its capacity to re-infect (and infect the vaccinated and the impact on vaccines in protecting from severe infection).

![Sketch illustrating how a new variant may appear milder even with no change in underlying virulence.]

Natalie E. Dean.

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. HIV prevalence among the general population is high at 20.4% and is the leading cause of death. 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.\textsuperscript{47}

Data on hospitalisations from South Africa is uncertain as there is a high level of incidental admissions for both adults and children (people going to hospital for conditions other than COVID and then are found to have tested positive at admission).\textsuperscript{41}

Across South Africa, the number of inpatients in week 45 was at 543 and in week 48 at 3,556, so the hospitalisation rate has increased 6.5 times in three weeks. In Gauteng, where it is assume that the omicron variant is dominant, the number of inpatients in week 45 was 148 and in week 48 at 2,157 and has thus increased 14.6 times in 3 weeks.\textsuperscript{33}

Weekly excess deaths data is an indicator of the impact of the Omicron wave. Although a lagging indicator, there is an uptick being seen in the data. The updates come out at the end of each Wednesday.

Report on Weekly Deaths in South Africa.\textsuperscript{48}

The case fatality rate of COVID-19 has dropped in South Africa recently with the Omicron wave. The figure below charts the moving-average case fatality rate of COVID-19 since Sep 2020 for South Africa, the UK, Denmark and Singapore.
In the UK, analysis of data from all PCR-confirmed SARS-CoV-2 cases specimen dated 1-14 Dec by the Imperial College outbreak modelling team found a reduction in risk of hospitalisation for Omicron relative to Delta infections, in the range of 20-25% when using any attendance at hospital as criteria and 40-45% when using hospitalisation ≥ 1 day as criteria. Assessment of more severe outcomes (eg. ICU/deaths) is not feasible with the existing data at this point. These hazard ratios also apply specifically to England, given that they average over all vaccination states, and should be placed in the context of reinfection risk in a country where a large proportion of the population may have already been infected. A previous infection reduces risk of any hospitalisation by about 50% and hospitalisation ≥ 1 day by about 61%. Vaccination status also reduces the risk of hospitalisation, although this appears to vary across different vaccines (see page 19).  

Anecdotally, in closed and vulnerable settings (hospital wards, care homes) the UK has seen very high attack rates (50-80%) but mostly asymptomatic and mild infections.  

Despite preliminary indications of reduction in hospitalisation for Omicron, the Imperial College study cautioned that the reductions should be balanced against the much larger risk of infection with Omicron.  

A separate cohort analysis of Omicron cases in Scotland pointed to a two-thirds reduction in risk of hospitalisation when compared to Delta. Again, the study case numbers are small and mostly among people aged 20 to 39, indicating the study’s limitations in reflecting severity of disease in elderly/more vulnerable people.  

In Denmark, based on data from 22 Nov to 15 Dec, among the 18,946 confirmed Omicron cases, 47 were admitted to hospital (0.6%), compared to 1.6% of other variant cases hospitalised over the same period.
In a 117 party event cluster in Norway where 81 out of 110 interviewed people caught Omicron, 80 had symptoms, there were 0 hospitalisations so far, and 62 (78%) of the 80 symptomatic cases were still experiencing symptoms at the time of the interviews (about 1.5 weeks after the event).²⁸

A recent lab study in Hong Kong using ex vivo cultures of respiratory tract has found that Omicron infects and multiplies ~70 times faster than the Delta variant and the wild type SARS-CoV-2 in the human bronchus, but ~10 times less efficiently in the lung. While less efficient replication in the lungs may suggest lower severity, it was pointed out that disease severity in humans is not determined only by virus replication but also by the host immune response to the infection, which may lead to dysregulation of the innate immune system. As such, the study’s findings indicate that overall threat from Omicron can be very significant considering that a very infectious virus may cause more severe disease and death even though the virus itself may be less pathogenic.²⁷

Experts have also warned about the potential global disruption Omicron can cause. Dr J. Stephen Morrison, Director of the Global Health Policy Centre at the Centre for International and Strategic Studies, pointed out that the sheer scale of infection could "overwhelm health systems, simply because the denominator will be potentially so big.".⁵³

On 20 Dec 2021, WHO chief scientist Soumya Swaminathan cautioned that it would be "unwise" to conclude from early evidence that Omicron was a milder variant than previous ones.⁵⁴ The updated UK Health Security Agency risk assessment as at 17 Dec 2021 also stated that “There is no signal that supports a difference in the intrinsic virulence of the Omicron virus compare to Delta”.⁵⁵

All in all, there has not been a strong case that Omicron will be a lot less dangerous than earlier strains everywhere. Preliminary indications of less severe symptomatic presentation should be balanced against the much larger risk of infection and therefore, a huge ‘denominator’. The South African, UK and Scotland data are also preliminary, with other factors at play, such as the larger proportion of youth cases (youth typically infected first), vaccinated cases being recent (for South Africa), a fair number of re-infections, and genetic variation or prior health histories (esp. for South Africa). Things could look quite different in older populations elsewhere in the world which have seen fewer infections.⁵⁶

**Symptoms**

It is too early to determine if the Omicron variant is associated with a different cluster of symptoms.

A UK study of positive cases in London observed that the top five symptoms reported in an app for omicron infection were runny nose, headache, fatigue (either mild or severe), sneezing, and sore throat. The analysis also found no clear differences between Delta and Omicron in the early symptoms (three days after testing).⁵⁷

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.⁵⁸,⁵⁹

Sir John Bell a Professor of Medicine at Oxford University reported that myalgia, (muscle pain), was a “distinguishing feature” of Omicron, particularly the back, as well as sore throat, a stuffy nose, some stomach upset and loose stools (this information is from South
Africa and the UK Zoe Symptom Tracker App). However, it is too soon to confirm these symptoms as not enough reliable data across all age groups has come in.60

Children who get hospitalised in South Africa and diagnosed with COVID seem to be diagnosed with bronchiolitis and pneumonia, often with severe gastrointestinal symptoms and dehydration. Most paediatric cases are mild and not hospitalised (sore throat, nasal congestion, headache, fever, resolves in three days). Early data suggests more admissions in the under 5 age group compared to previous waves (although there is data uncertainty).41

**DIAGNOSTICS**

Evidence and international consensus indicates that PCR and rapid antigen tests can detect Omicron.61,62,63,64,65,66

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.5

Anthony Fauci, Director of the National Institute of Allergy and Infectious Diseases (NIAID) and Chief Medical Advisor to the President, shared on 17 Dec 2021 that some ARTs may not accurately detect the Omicron variant.67 The FDA has announced a list of molecular tests whose performance may be impacted by mutations in the omicron variant. They have warned that the tests will return false negative results. The tests in the list are:

- Revogene SARS-CoV-2, Meridian Bioscience, Inc.
- DTPM COVID-19 RT-PCR test, Tide Laboratories
- Linea COVID-19 Assay Kit, Applied DNA Science66

European commission’s joint research centre (JRC) has developed a new detection method specific for the Omicron variant. The JRC identified a target region with a unique and Omicron-specific cluster of nucleic acid sequence. Using this region, JRC scientists designed a variant-specific set of primers to be used as an Omicron PCR detection method.68

**IMMUNE RESPONSE ESCAPE**

**Vaccines**

The WHO states that preliminary evidence, and the considerably altered antigenic profile of the Omicron spike protein, suggests a reduction in vaccine efficacy against infection and transmission associated with Omicron.4
Lab Neutralisation Studies

Computer modelling and numerous lab neutralisation studies have now shown a substantial reduction in vaccine neutralisation of Omicron - around a 30-40 fold reduction for Pfizer and with some showing no neutralisation. \(^{69,70,71,72,73,74,75,76,77,78}\) Broadly this substantial drop in neutralisation is found across all current vaccines in lab based studies.\(^ {79,80}\)

Neutralization of Omicron pseudovirus by plasma from COVID-19 convalescent and vaccinated individuals. Plasma neutralising activity in COVID-19 convalescent or vaccinated individuals (mRNA-1273, BNT162b2, AZD1222, Ad26.COV2.S (single dose), Sputnik V and BBIBP-CorV).\(^ {79}\)

A similar substantial drop has been found in neutralisation experiments for Sinovac (CoronaVac).\(^ {80}\)

Neutralisation of Omicron variant by sera from BNT162b2 (Pfizer) or Coronavac vaccine recipients.\(^ {80}\)

Researchers hypothesise that the differences between results may be due to blood samples from different continents with different exposure histories. There may also be multiple technical differences attributable to the assays themselves.\(^ {71}\)
This 30-40 (or more) fold reduction doesn't mean vaccines will be 30-40x less effective, as these studies do not consider memory cell immune responses.

The University of California has outlined a very rough extrapolation of what a 30-40-fold reduction in neutralising antibody titers could mean for vaccine effectiveness with analysis grounded in methods of previous analysis of vaccine effectiveness based on neutralisation studies:53,81,82

~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.

**Analysis of Cases**

On 14 Dec, South Africa outlined findings from the first 3 weeks of the outbreak. It found that two doses of Pfizer, without a booster, provided 33% protection against Omicron infection, down from 80% with Delta, and 70% protection against severe illness, down from 93% protection against Delta. Protection from hospital admission was maintained across all ages (18-79 years), but lower for older age groups (again, this data may be influenced by previous infection waves):41

- 18-29: 92%
- 30-39: 75%
- 40-49: 82%
- 50-59: 74%
- 60-69: 67%
- 70-79: 59%

There has been infection and transmission between people who have been vaccinated (and boostered), but it is not clear to what extent this means that individuals are going to get a severe case of Omicron.83

In Denmark, three-quarters of the Omicron cases have been in people who have received two vaccine doses, which is about the same fraction of the entire country that’s fully vaccinated. That high percentage indicates that vaccines are providing little protection from infection. This is similar to the findings from the US.32
Denmark: Vaccination status for individuals ≥12 years infected with Omicron compared to other variants, from 22 November to 15 December 2021.\textsuperscript{52}

A study of a party event cluster found that of the 117 people who attended the party, 99 had had two shots of mRNA vaccine (no-one boostered) and 81 out of 110 who were interviewed got Omicron.\textsuperscript{28}

Professor Tim Spector, who leads work on the UK Covid Zoe symptom tracker app, has stated reports to the app show "we are getting lots of breakthrough infections in people have had two or three vaccinations and that's more than we saw before."\textsuperscript{84}

Third Doses

In response to Omicron, several countries have altered vaccination advice – hoping that a third dose of Pfizer, 3 months after the second dose (often called a “booster”), will provide protection from severe disease (boosters combinations for other vaccines have also been recommended).\textsuperscript{85,86,87}

There are increasing reports of individuals who had been boostered becoming infected with Omicron and infecting others, but no data on disease severity.\textsuperscript{88,89}

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.\textsuperscript{90}

Lab Neutralisation Studies

Lab studies from Pfizer, Israel, UK, Germany and Australia report that having three doses of Pfizer or mRNA vaccines may result in increased neutralising antibody titers against Omicron one month after vaccination compared to two doses.\textsuperscript{70,76,91–97} How long this increase in neutralisation lasts is a key area of research.

An Australian study projected vaccine efficacy of AstraZeneca, Pfizer and Moderna based on a predictive model and estimated fold-drop in neutralisation titre against Omicron from earlier studies. It estimated that six months after primary immunisation, vaccine efficacy against Omicron wanes to:

- 7.5\% (95\% CI: 1.8-20.2) protection against symptomatic infection and 36.7\% (95\% CI: 7.7-73) protection against severe symptoms for AstraZeneca
- 28.1\% (95\% CI: 12.8-46.9) protection against symptomatic infection and 70.9\% (95\% CI: 32.9-91.5) protection against severe symptoms for Pfizer
- 40.4\% (95\% CI: 16.9-66) protection against symptomatic infection and 81.1\% (95\% CI: 42.1-96) protection against severe symptoms for Moderna

A third booster dose with an existing mRNA vaccine has the potential to raise efficacy against Omicron to 86.2\% (95\% CI: 72.6-94) against symptomatic infection and 98.2\% (95\% CI: 90.2-99.7) against severe infection.\textsuperscript{98}
A study from China suggested that a booster shot produced by Sinopharm had significantly lower neutralising activity against the Omicron, when compared with Sinopharm’s booster against an older coronavirus strain from Wuhan. The study qualified that the vaccine’s efficacy against Omicron remained unclear as neutralisation is only part of the human immune response.\textsuperscript{97}

**Case Analysis**

The UK Health Security Agency report that vaccine effectiveness of 70 to 75\% was seen in the early period after a booster / third dose (95\%CI: 41.8 to 86.0\%).\textsuperscript{9} The report stated that these results should be interpreted with caution due to the low numbers and the possible biases related to the populations with highest exposure to Omicron. The study was based on a test-negative case-control design to estimate vaccine effectiveness (VE) against symptomatic disease caused by the Omicron and Delta variants in England. The study used data on 581 cases of Omicron and 56,439 cases of Delta, with 130,867 test-negative controls. Omicron was found to have reduced vaccine effectiveness.\textsuperscript{99}

**Against Omicron:**

- No VE against Omicron from 15 weeks after two AstraZeneca doses.
- Two Pfizer doses: 88\% VE 2-9 weeks after (95\%CI: 65.9 to 95.8\%); 34\% - 37\% VE 15 weeks after.
- Two Pfizer doses and a third Pfizer dose: 71.4\% VE 2 weeks after (95\%CI: 41.8 to 86.0\%).

Data is not yet available for VE after a third dose beyond the short period of time of 2 weeks.

**Vaccine effectiveness against symptomatic diseases by period after dose 2 and a booster dose for Delta (black squares) and Omicron (grey circles) for recipients of two doses of ChAdOx1-S (AstraZeneca) as the primary course and BNT162b2 (Pfizer) as a booster and for recipients of two doses of BNT162b2 as the primary course and BNT162b2 as a booster**

In terms of the booster dose, the Australian study found a 4-fold reduction in neutralising antibody titer for the Omicron variant compared to wild-type virus.\textsuperscript{77} Other studies found similar results.
Neutralising antibody titer of variants Delta (green) and Omicron (blue) compared to wild-type (red, SARS-CoV-2 lineage A.2.2) black lines indicate the median titre at each timepoint.

A UK study analysing data from PCR-confirmed SARS-CoV-2 cases in England found a significantly increased risk of developing a symptomatic Omicron case compared to Delta for those who were two or more weeks past their second vaccine dose, and two or more weeks past their booster dose (for AstraZeneca and Pfizer vaccines). Depending on the estimates used for vaccine effectiveness against symptomatic infection from the Delta variant, this translates into vaccine effectiveness estimates against symptomatic Omicron infection of:

- between 0% and 20% after two doses,
- and between 55% and 80% after a booster dose.

Similar estimates were obtained using genotype data, albeit with greater uncertainty.24

The recent analysis of Omicron case data by the Imperial College outbreak modelling team in the UK stratified hospitalisation by vaccination state (see Fig. below). It found that by hazard ratios for hospitalisation with Omicron for Pfizer/Moderna are similar to those seen for Delta in the respective vaccination categories, while Omicron hazard ratios are generally lower than for Delta for the AstraZeneca vaccination categories. The findings are compatible with previous findings that while protection afforded against mild infection from AstraZeneca was substantially reduced with the emergency of Delta, protection against more severe outcomes was sustained. It should be noted that sample sizes to date are limited, and that net vaccine effectiveness against hospital attendance may not vary between the vaccines, given that Pfizer/Moderna maintain higher effectiveness against symptomatic infection with Omicron than AstraZeneca.49
Estimates of the hazard ratio (HR) for hospital attendance for Omicron vs Delta cases and for reinfections vs primary infections, stratified by vaccination status. The percentage of cases and hospitalisations that were reinfections is also shown. Uncorrected estimates (not shown in above table) are generated via conditional Poisson regression. Corrected estimates (only the mean estimates for Omicron are shown) adjust for under ascertainment of reinfection, assuming 1/3 of all infections are detected through community surveillance. D1, D2 and D3 categories are post-dose 1, 2 and 3, respectively. D3 categories all received a mRNA booster and are distinguished by the dose 1/2 vaccine used. Numbers in category names (14, 21) refer to days since last dose.49

The cohort analysis of Omicron cases in Scotland also found that the third/booster dose of vaccination, while offering the greatest protection against Delta, also offers substantial additional protection against the risk of symptomatic COVID-19 for Omicron compared to ≥25 weeks post second vaccine dose. However, there are limitations in the study sample size and case age profile.50

In summary, the growing body of preliminary research suggests the COVID-19 vaccines used in most of the world offer a low degree of protection against becoming infected by Omicron. Preliminary lab studies suggest that having three doses of mRNA vaccines may result in increased neutralising antibody titers against Omicron, although it is unknown how long this increase in neutralisations lasts. There is less data and research understanding on vaccines’ protection against severe disease, but two recent studies have indicated some level of protection of vaccines against hospitalisation.

Infection

Data 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.100,101

UK Health Security Agency stated on 10 Dec that cases of reinfection (at any interval) were identified amongst confirmed, highly probable and probable Omicron positive cases. In its technical briefing dated 17 Dec, 7.6% of Omicron cases are reinfections vs 1.5% of others. This is a 3 to 4-fold increased risk of reinfection with omicron.9,62
Professor Tim Spector, who leads work on the UK Covid Zoe symptom tracker app, has stated there are some reports of reinfection, generally these had an original infection at least 6-12 months ago (no detail on severity). Imperial College COVID-19 response team’s recent report also indicated that 11% of Omicron cases were reinfections versus 1.2% of others, and that Omicron was associated a 5.41 fold higher risk of reinfection compared with Delta, suggesting relatively low remaining low levels of immunity from prior infection. The Scottish cohort analysis also found that the proportion of possible reinfections among Omicron cases was 10 times that for non-Omicron cases.

A recent in vitro study found that sera from COVID-19 convalescent patients collected 6 or 12 months post symptoms displayed low or no neutralizing activity against Omicron.

Analysis from John Hopkins and the NIH from a small sample of sera from previously infected individuals found existing CD8+T-cell responses from a previous SARS-CoV-2 infections will still recognise Omicron and should provide a significant level of protection against COVID-19.

Analysis of reinfections from previous variant waves has found that prior infection conferred substantial protection against reinfection. Reinfections also had 90% lower odds of resulting in hospitalisation or death than primary infections. Immunity conferred by prior infection was also considerably long-lasting. However, it is unclear what these would mean for those at higher risk of disease and for the Omicron variant.

The recent analysis of data by the Imperial College outbreak modelling team in the UK indicated that a previous infection reduces the risk of any hospitalisation by approximately 50% and the risk of a hospital stay ≥ 1 day by 61% (before adjustments for under ascertainment of reinfections).

So called ‘hybrid immunity’ (infection and vaccination) has demonstrated significantly better neutralisation to Omicron compared to vaccination alone. Some are labelling this “super immunity”. Careful consideration of wording is required and grounded in expectation management and behavioural psychology. To note, analysis of infected and not vaccinated is often not well studied, so it is unclear the impact of the vaccine in neutralisation over and above natural infection.

A journal article recently pointed out that people who have been naturally infected with SARS-CoV-2 can also be naturally reinfected, as has been shown with endemic coronaviruses, influenza viruses, respiratory syncytial virus (RSV), and many other respiratory viruses. “Hybrid immunity’ has also so far not prevented the emergence and rapid spread of viral variants such as Delta. It remains unknown whether and how permanent protective immunity can be achieved.

VACCINES

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. The company has already started working on a DNA template tailored to match Omicron. Pfizer has also said that fourth doses of the original vaccine may be required.
Modernana 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.\textsuperscript{112} 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.\textsuperscript{113}

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.\textsuperscript{114}

AstraZeneca is ready to rapidly develop an updated version of its vaccine if necessary.\textsuperscript{115}

Sinovac has stated it can rapidly mass produce a version against the Omicron variant if needed.\textsuperscript{116}

Sinopharm information could not be located.

Sputnik V is developing a booster for Omicron.\textsuperscript{117}

Considering the limitation of current SARS-CoV-2 vaccines (incomplete and transient protective immunity), experts have suggested that they will ultimately need to be replaced by second-generation vaccines that induce more broadly protective and more durable immunity. The development of broadly protective vaccines, such as universal influenza vaccines that are being developed and tested, should be prioritised.\textsuperscript{108}

THERAPEUTIC OPTIONS

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

The WHO states that therapeutic interventions for the management of patients with severe or critical COVID-19 associated with the Omicron variant that target host responses (such as corticosteroids, and interleukin 6 receptor blockers and prophylaxis with anticoagulation) are expected to remain effective. However, monoclonal antibodies will need to be tested individually, for their antigen binding and virus neutralization and these studies should be prioritised.\textsuperscript{4}

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. A recent in vitro study from Europe suggested that Omicron escapes most therapeutic monoclonal antibodies.\textsuperscript{70} 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.\textsuperscript{118} 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.\textsuperscript{119}
- **Merck’s Molnupivarir 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”.118
- **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.120
- **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.121 Several preprints reported that Monoclonal Sotrovimab retains activity against Omicron, so it should still be an effective COVID therapeutic drug in high risk patients.78,122

  GlaxoSmithKline plc and Vir Biotechnology, Inc. announced on 17 Dec 2021 that the European Commission (EC) has granted marketing authorisation to Sotrovimab for the early treatment of COVID-19. Sotrovimab is now approved in the EU for the treatment of adults and adolescents (aged 12 years and over and weighing at least 40kg) with COVID-19 who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19.123
- **Regeneron’s Ronapreve** has been confirmed to be less effective against the omicron variant, though being still active against delta. German researchers have found that it loses most of its effectiveness when exposed in laboratory tests to Omicron.124,125
- **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.121 A recent study pointing out that several highly neutralizing mAbs have significantly lost inhibitory activity against the omicron variant included Lilly’s bamlanivimab and etesevimab in its list.125
- **Brii Biosciences’ antibody cocktail.** On 7 December, China approved the cocktail. Lab tests have found the treatment retains its efficacy against the omicron variant, despite one of the antibodies having a substantial drop in activity.126–128
- **AstraZeneca’s Evushield** has been found to retain neutralising activity against Omicron. According to pre-clinical data, the combination of tixagevimab and cilgavimab was confirmed by investigators at the FDA to have an inhibitory concentration 50 (IC50) level that is within the range of neutralizing titres found in someone who has been previously infected with COVID-19.129,130 However, a recent study pointing out that several highly neutralizing mAbs have significantly lost inhibitory activity against the omicron variant included AstraZeneca’s Evushield in its list.125
- **Celltrion’s Regdanvimab.** A recent study pointing out that several highly neutralizing mAbs have significantly lost inhibitory activity against the omicron variant included Celltrion’s Regdanvimab in its list.125
- **Monoclonal Imdevimab and Casirivimab** has been reported to be ineffective against Omicron by several studies.131,78
LIMITATIONS

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

- 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, R\text{t} and R\text{0} 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

Ruth F Lewis, Jacinta IP Chen, Yi Mon, Bob XY Ng, Licia ML Tan, Yang Qian, Sharon HX Tan, Ian YH Ang, Jason CH Yap

Reviews by Alex R Cook, Hsu Li Yang

REFERENCES

1. SARS-CoV-2 variants of concern and variants under investigation. Briefing 30. UK Health Security Agency. Published online December 3, 2021:40.


5. Torjesen I. Covid-19: Omicron may be more transmissible than other variants and partly resistant to existing vaccines, scientists fear. *BMJ*. 2021;375:n2943. doi:10.1136/bmj.n2943


31. UK Health Security Agency. SARS-CoV-2 variants of concern and variants under investigation. Published online December 17, 2021:38.


42. CDC. SARS-CoV-2 B.1.1.529 (Omicron) Variant — United States, December 1–8, 2021. MMWR Morb Mortal Wkly Rep. 2021;70. doi:10.15585/mmwr.mm7050e1

43. Michael Lin, PhD-MD. Finally, what we’ve been waiting for: age-controlled data on Omicron severity, courtesy SA health ministry. Across all ages, deaths among hospitalized pts are 2/3 lower in Omicron wave. If more mild cases are admitted, this # goes down, but doesn’t seem likely that’s the reason https://t.co/BRDY8BQyCZ. @michaelzlin. Published December 17, 2021. Accessed December 22, 2021. https://twitter.com/michaelzlin/status/1471749391585214465


57. Iacobucci G. Covid-19: Runny nose, headache, and fatigue are commonest symptoms of omicron, early data show. BMJ. 2021;375:n3103. doi:10.1136/bmj.n3103


75. Peiris M, et al. HKUMed-CU Medicine joint study finds COVID-19 variant Omicron significantly reduces virus neutralisation ability of BioNTech vaccine. Published December


105. Cele S, Jackson L, Khan K, et al. SARS-CoV-2 Omicron has extensive but incomplete escape of Pfizer BNT162b2 elicited neutralization and requires ACE2 for infection. Published online December 7, 2021:9.


