Health Information and Quality Authority

An tÚdarás Um Fhaisnéis agus Cáilíocht Sláinte

Rolling summary of the evidence in relation to the Omicron (B.1.1.529) variant

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About the Health Information and Quality Authority

The Health Information and Quality Authority (HIQA) is an independent statutory authority established to promote safety and quality in the provision of health and social care services for the benefit of the health and welfare of the public.

HIQA's mandate to date extends across a wide range of public, private and voluntary sector services. Reporting to the Minister for Health and engaging with the Minister for Children, Equality, Disability, Integration and Youth, HIQA has responsibility for the following:

- **Setting standards for health and social care services** — Developing person-centred standards and guidance, based on evidence and international best practice, for health and social care services in Ireland.

- **Regulating social care services** — The Chief Inspector within HIQA is responsible for registering and inspecting residential services for older people and people with a disability, and children's special care units.

- **Regulating health services —** Regulating medical exposure to ionising radiation.

- **Monitoring services** — Monitoring the safety and quality of health services and children's social services, and investigating as necessary serious concerns about the health and welfare of people who use these services.

- **Health technology assessment** — Evaluating the clinical and cost-effectiveness of health programmes, policies, medicines, medical equipment, diagnostic and surgical techniques, health promotion and protection activities, and providing advice to enable the best use of resources and the best outcomes for people who use our health service.

- **Health information** — Advising on the efficient and secure collection and sharing of health information, setting standards, evaluating information resources and publishing information on the delivery and performance of Ireland's health and social care services.

- **National Care Experience Programme** — Carrying out national service-user experience surveys across a range of health services, in conjunction with the Department of Health and the HSE.

Version History

Version number	Date	Details
V1.0	9 December 2021	First version of report
V2.0	14 December 2021	Updated summary of evidence to 13 December
V3.0	15 December 2021	Updated summary of evidence to 14 December

Table of contents

Scientific Evidence Summary

Key points

- On 26 November 2021, the World Health Organization (WHO) designated the variant B.1.1.529 a variant of concern (VOC) named 'Omicron', following its discovery in South Africa. There are many unknowns relating to the Omicron variant, including its transmissibility, its virulence (severity of disease), and its capacity for immune escape. Studies are rapidly emerging to address these areas; information available as of 11.59pm, 14 December 2021 is summarised in this report. Studies and assessments emerging in the following days may present information that supersedes the contents of this report.

Transmissibility and Transmission:

- Based on mutational analysis, it is biologically plausible that Omicron is more transmissible than Delta. One (preprint) laboratory assay study examining infectivity found that Omicron had four times the infectivity of wild type SARS-CoV-2 and twice the infectivity of Delta; these findings require confirmation.
- In South Africa, there was an increase in the effective reproductive number (Re) in November, indicating potential higher transmissibility of Omicron. Omicron is now the dominant strain in South Africa. As of 14 December 2021, based on specimens collected on 11 and 12 December 2021, 51.8% of cases of SARS-CoV-2 in London represented SGTF cases (a proxy for Omicron), suggesting that Omicron was at this time the dominant strain in London.
- Omicron has been classified by the UK Health Security Agency (UKHSA) as at least as transmissible as Delta. It is currently displaying a growth advantage over Delta in the UK, with increased household transmission risk, increased secondary attack rates, and increased growth rates compared to Delta. There is high confidence that this growth advantage results from immune evasion, and it is plausible that an increase in transmissibility is also contributing.
- Several 'superspreading events' associated with the Omicron variant have been reported in settings such as restaurants, concerts, parties, schools, a cruise ship, a boat, a gym, a wedding, a convention and a detention centre. However, it is not possible to ascertain from the reports of these events whether the Omicron variant is associated with greater transmissibility compared with other strains of SARS-CoV-2.

- Little has been published regarding the potential for higher rates of aerosol transmission than observed previously. However, one study from Hong Kong indicated a high likelihood of airborne spread based on one transmission incident, which occurred in a quarantine hotel. Airborne transmission is suspected due to the lack of contact or shared space/items (as demonstrated by CCTV footage) between the two cases.

Virulence:

- The UKHSA risk assessment of Omicron, published 9 December 2021, stated that there were insufficient data available to inform an assessment of infection severity, as is expected in the early period of the emergence of a new variant. A similar statement was also made in the ECDC rapid risk assessment published 15 December 2021.

- Early experience from South Africa (largely a younger, less vaccinated cohort) does not indicate a more severe form of illness. To date, as with infections associated with other variants in South Africa, the majority of infections have been reported to be mild.

- On the 14 December 2021, the ECDC noted that all Omicron cases within the EU/EEA, for which there was information available on severity, were either asymptomatic or mild. The ECDC highlighted that these data should be assessed with caution, as the number of confirmed cases was too low to understand if the spectrum of disease in Omicron differs from previously detected variants of concern. While the ECDC report noted at this time no Omicron-related deaths in the EU/EEA, as of 14 December 2021 at least one death was reported within the UK from data available to 12 December 2021.

- Early data on Omicron hospitalisations in Denmark are being published on a daily basis. Based on data to 11 December 2021, 0.8% of Omicron cases (38 of 4,498) had been hospitalised, of which nine were classified as hospital-acquired infections. The number of cases currently hospitalised as of 14 December 2021 was 12, with fewer than five patients with Omicron in ICU.

- The proportion of Omicron cases currently observed to be mild should be considered in light of the extent to which Omicron demonstrates greater infectivity and greater capacity for immune escape, and the extent to which the population possesses immunity (from either prior infection or vaccination). The virulence of Omicron may not be fully understood by observing patterns of

severity in the overall population, as this includes those with natural or vaccine-derived immunity, who will have less severe infections if they occur.

- It is important to consider that if transmission were to increase substantially, any significant wave of infection, irrespective of changes in virulence or immune escape, would very likely result in increased hospitalisations and mortality.

Immune escape:

- Multiple mutations in the spike protein of the Omicron variant indicate a high likelihood of reduction of neutralising activity by antibodies induced by infection or vaccination.
- Early data from South Africa indicate a higher risk of reinfection than that experienced with previous variants. The UKHSA Technical Briefing, published 10 December 2021, noted that there was, as yet, no evidence of increased reinfection risk at the population level (all cases of reinfection), but preliminary analyses using data from those confirmed to be reinfected with SARS-CoV-2 indicated approximately three- to eight-fold increased risk of reinfection from the Omicron variant compared to other variants. The UKHSA analyses were based on case data in England collected prior to 8 December 2021.
- Several epidemiological reports have noted the occurrence of breakthrough infections including a case series from South Africa that reported the occurrence of breakthrough infection in seven individuals who had received COVID-19 booster doses.
- As of 14 December 2021, two vaccine effectiveness studies have been reported (Andrews et al., preprint, England, and Discovery Health, press release, South Africa).
    - Andrews et al. published a preprint reporting a test negative case control study in England, which is also described in the UKHSA Technical Briefing published 10 December 2021. The study suggested that vaccine effectiveness against symptomatic disease was significantly lower for Omicron than for Delta. However, a moderate to high vaccine effectiveness of 70% to 75% was seen in the early period after a booster dose.
    - The health insurer Discovery Health, South Africa, reported a study within a press release published on 14 December 2021. It included analysis of data from the first three weeks of Omicron in South Africa.

While little detail on methodology was provided, individuals who received two doses of the Pfizer-BioNTech vaccine were reported to have had 70% protection against hospital admission, compared with 93% protection observed during the Delta wave. These are the first data that represent vaccine effectiveness for the outcome of hospitalisation with Omicron (a proxy for severe disease).

- As of 14 December 2021, fourteen laboratory studies have been reported that examined the neutralisation activity of vaccines, and or prior infection against the Omicron variant. Currently, most of these data examine neutralisation following the Pfizer vaccine (BNT162b2). Overall, these studies found that:
    - Sera from those who had received two doses of any COVID-19 vaccine (Pfizer BioNTech BNT162b2, Moderna/Spikevax mRNA-1273, AstraZeneca ChAdOx1) or one dose of Janssen Ad26.COV2.S, produced limited, if any, neutralisation activity against Omicron, with up to 127-fold reductions reported in one study for Pfizer BNT162b2 compared with the ancestral strain.
    - Sera from those who had received three doses of vaccine had higher neutralisation activity against Omicron compared with those receiving two doses, but activity was still lower overall compared with previous strains. The reported increase in neutralising antibodies against Omicron ranged from 25-fold to greater than 130-fold between the second vaccine dose and the Pfizer BNT162b2 booster. However, the neutralisation activity of the booster dose against the Omicron variant was still reduced compared with previous strains, with estimates ranging from 2.5-fold to 37-fold reductions across studies.
    - Immunity resulting from a combination of prior infection plus full vaccination was associated with greater neutralisation activity against Omicron compared with prior infection alone (in two studies) or two-dose vaccination alone (in three studies).
    - Though based on limited data, lower neutralisation activity against Omicron was observed for sera from AstraZeneca (ChAdOx1) and Janssen (Ad26.COV2) versus sera from mRNA vaccinees. For a high proportion of the former, neutralising activity fell below the limit of quantification in the assay.
    - Caution is urged in the interpretation of these neutralisation assay studies as the results represent in vitro analysis (as opposed to clinical

or epidemiological studies), involve small sample sizes, and often have limited information to support their interpretation. Reductions in neutralisation activity do not directly equate to reductions in vaccine effectiveness in real-world settings, and these studies do not consider the impact of conserved non-neutralising antibodies or memory T cell responses which likely contribute to protection from severe disease.

- The UKHSA risk assessment of Omicron published 9 December 2021 concluded with high certainty that Omicron displays a reduction in immune protection against infection, relative to Delta. This risk was assigned 'red' status (i.e., high risk), and was based on neutralisation data from multiple laboratories and preliminary assessment of real-world vaccine effectiveness in the UK (Andrews et al. study).

Treatment efficacy:

- Current treatments for COVID-19, which are used in the hospital setting, include those which target the SARS-CoV-2 virus, and those which target the host immune response. Generally, treatments that target the SARS-CoV-2 virus itself, and specifically, regions of the virus in which the Omicron variant possesses mutations (for example, monoclonal antibodies which bind to certain virus sites), may experience altered efficacy against Omicron. Treatments that target the host immune response rather than the virus (for example, non-specific treatments such as corticosteroids) will not be affected.

- Several treatments are being evaluated to understand their likely efficacy against Omicron. The antiviral drug remdesivir, and some treatments which are not yet licensed for use in Ireland, for example, the antiviral drug molnupiravir, are not expected by their manufacturers to be impacted by Omicron. Recent neutralisation assay results have suggested the activity of the monoclonal antibody sotrovimab is preserved, or somewhat reduced.

- Several neutralisation assays have been published which suggest substantially reduced, or abolished, activity against Omicron for several neutralising antibody drugs developed to target SARS-CoV-2. These include the combination monoclonal antibody treatments casirivimab plus imdevimab, and etesevimab plus bamlanivimab. This reduction in activity is thought to be due to mutations at the virus site to which the antibodies bind.

Test accuracy:

- Current available tests are expected to be capable of identifying the Omicron variant as SARS-CoV-2. However, the designation of two genetically distinct sublineages of Omicron (BA.1 and BA.2), and the finding that BA.2 does not exhibit S-Gene Target Failure (SGTF), has implications for detection of the Omicron variant as distinct from the prevailing dominant strain. The absence of S-Gene Target Failure with BA.2 renders RT-PCR assays ineffective at early surveillance; genomic sequencing (requiring several days) is required to identify Omicron from such samples.

- Use of single-target PCR tests that target mutated regions in Omicron will result in false negatives. The FDA has identified two such tests, both of which fall under Emergency Use Authorization in the US.

Overall assessments of risk and impact:

- An updated risk assessment by the Norwegian Institute of Public Health (NIPH), published 13 December 2021, stated that the situation in Norway is becoming increasingly serious. The NIPH stated there is an urgent need to curb the COVID-19 epidemic with significant measures, with the aim of avoiding the Omicron variant causing an epidemic wave that results in a large disease burden and overloads the health service.

- A study that aimed to model the potential impact of Omicron in England, published as a preprint on 11 December 2021, projected a wave of COVID-19 transmission for all scenarios modelled. In the most optimistic scenario, the authors concluded that bringing in control measures early in 2022 which are equivalent in stringency to 'Step 2' of the UK roadmap (involving restrictions on indoor hospitality, closure of some entertainment venues, and restrictions on gathering sizes) would be sufficient to substantially control this wave.

- On 15 December 2021, the ECDC published a rapid risk assessment. The following overall risk assessment was made: 'Based on the currently available limited evidence, and considering the high level of uncertainty, the overall level of risk to public health associated with the further emergence and spread of the SARS-CoV-2 Omicron VOC in the EU/EEA is assessed as very high'. The assessment stated that non-pharmaceutical interventions (NPIs) should be strengthened without delay, and noted that, without increased booster vaccination and reduction of contact rates through the implementation of NPIs, levels of transmission could rapidly overwhelm EU/EEA healthcare systems.

Background

On 26 November 2021, the World Health Organization (WHO) designated the variant B.1.1.529 a variant of concern (VOC) named 'Omicron'.[1] Further information on the epidemiological events leading up this designation is detailed in a Science Brief published by the US CDC.[2]

Compared to the reference strain of SARS-CoV-2, the Omicron variant sequence possesses 51 mutations, comprising 33 on the Spike protein and 15 on the receptor binding protein (RBD). The Spike protein of the Omicron variant has at least twice the number of mutations found in other variants[3] and the Omicron variant forms a unique clade that is phylogenetically distant from previously recognised variants.[4]

There are many unknowns relating to the Omicron variant including its transmissibility, its virulence (severity of disease), and its capacity for immune escape.[5] Studies are rapidly emerging to address these areas; information available as of 11.59pm, 14 December 2021 is summarised in this report.

Approach to summarising the evidence

This rolling summary of the evidence in relation to the Omicron variant commenced on 6 December 2021.

HIQA identified emerging evidence published internationally in relation to Omicron by searching the following sources at regular intervals throughout each day from the 6 December onwards:

- Preprint databases including EuropePMC and MedRxiv and BioRxiv, using the specific COVID-19 search filter for these databases.
- Databases of published academic literature, including Pubmed, Embase, WHO COVID-19 Database, Google Scholar.
- Scientific briefs and assessment documents published by national and international agencies authorities such as UKHSA, ECDC, FDA, EMA, CDC and WHO.

Searches were limited by publication date to November 2021 onwards and the following search strategy was used in Pubmed and translated to other databases: 'omicron[Title/Abstract] OR b.1.1.529[Title/Abstract]'

Twitter and news media posts and articles (identified via date-limited Twitter and Google searching) were also monitored to identify early reports of Omicron-related

studies released through these channels ahead of reporting within the preprint and published literature databases.

Results representing primary research findings, or secondary assessments by authorities, which concerned Omicron, were extracted and briefly summarised on a rolling basis.

It is important to note that this report does not present a review of the conduct of the included research, nor the validity of the findings, and, as such, this report does not make conclusions regarding the evidence. This report aims instead to provide a comprehensive snapshot of the current findings relating to the Omicron variant, as reported by the study authors, as they emerge.

Transmissibility and Transmission

Virological markers of transmissibility

- Four mutations (K417N, Q493R, N501Y, and Y505H) found on the RBD may enhance the binding ability of the virus to the 'human angiotensin I-converting enzyme 2' (hACE2) receptor and consequently increase its infectivity.[3]

- The binding affinity of the Omicron variant to hACE2 was assessed using protein-protein docking in a study by Kumar et al.[6] This yielded a higher docking score for the Omicron variant, indicative of increased hACE2 binding affinity than that observed with the Delta variant, and therefore, a higher potential for transmission.[6]

- The Omicron lineage does not possess the 'RNA-dependent RNA polymerase' RdRp G671S change. This mutation has been associated with a decrease in cycle threshold (Ct) values (that is, a higher viral load) observed with the Delta variant.[7]

Laboratory research – infectivity

- On 14 December 2021 a preprint by Garcia-Beltran et al. was published which largely comprised laboratory assay analysis of neutralisation efficiency (see below section on 'immune escape') but which also investigated the infectivity of Omicron.[8]
    - The authors examined the ability of pseudoviruses bearing wild type, Delta, and Omicron spike proteins to infect cells with or without the ACE2 receptor and confirmed that **Omicron remains dependent on ACE2 for entry**

- To quantify the infectivity of Omicron, the authors compared the efficiency of a panel of pseudoviruses (with the spike of circulating variants) to infect cells over a range of viral concentrations. The Omicron pseudovirus was found to infect target cells to a greater extent, regardless of concentration, when compared with all other tested variants. Comparing the linear regressions of each pseudovirus to wild type over the entire range revealed that, relative to wild type virus:
  - Gamma exhibited similar infectivity
  - Beta was less infectious
  - Delta was nearly twice as infectious
  - **Omicron was four times more infectious as wild type and twice as infectious as Delta.**

Epidemiological data and parameters

UK data

- As of 14 December 2021, the UKHSA has reported a total of 5,346 confirmed cases of the Omicron variant in the UK.[9] The true number of cases is likely to be much higher.[10] Also, as of 14 December 2021, based on specimens collected on 11 and 12 December 2021, 51.8% of cases of SARS-CoV-2 in London represented SGTF cases (a proxy for Omicron), suggesting that Omicron was the dominant strain in London.[11]

- Wastewater samples collected from sites across England up to 28 November 2021 were analysed by the UKHSA in order to determine early incidences of Omicron, and results were reported in the UKHSA technical briefing (no. 31), published on 10 December 2021. There were 'confirmed' and 'possible' detections of Omicron in **five samples collected between 26 and 28 November** from four sewage treatment works amongst 477 sites.

- The UKHSA technical briefing on SARS-CoV-2 variants of concern, published 10 December 2021, reported on the results of UKHSA characterisation analyses of Omicron cases in **England**. These included characterisation of the **Omicron growth rate and advantage**, **household transmission risk**, and **secondary attack rates** (see below section on immune escape and vaccine effectiveness for these characterisations). At the time of the data cut off (6 December) used for the analyses, there were 260 confirmed cases of Omicron identified through sequencing or genotyping in England.
  - Growth rates were computed for SGTF cases relative to S gene positive cases (as a proxy for Omicron versus Delta, respectively).The effective

reproduction number (Re) was calculated as **R=3.7 (3.3-4.2)**, with a **growth rate of 0.35/day**. It was considered that if Omicron continued to grow at this rate, it would reach parity with Delta by **mid-December**.

- In order to understand household transmission risk, a preliminary cohort analysis was performed including 72,882 index cases (72,761 Delta, 121 Omicron):
  - **19% (n=23) of Omicron index cases were found to give rise to a secondary household case, compared to 8.3%** (6,058) of Delta index cases. A multivariable logistic regression model found the adjusted odds ratio (OR) for **household transmission from an Omicron index case was OR = 3.2 (95%CI 2.0-5.0, p <0.001)** compared to Delta index cases.
- Secondary attack rates were calculated based on data from 1 November to 27 November 2021. Data included positive tests amongst contacts named to NHS Test and Trace by an original case identified to have Omicron, with date of symptom onset or positive test of the secondary case occurring two to seven days after original exposure. The UKHSA noted that low numbers of Omicron cases so far contribute to high uncertainty about estimated secondary attack ratess, and that rates may be influenced by improved ascertainment around Omicron cases. These studies did not adjust for vaccination or prior infection status of the contacts, due to current data quality. This means that the findings described overall growth advantage, rather than transmissibility specifically.
  - **Secondary attack rates in households** were higher for **Omicron (21.6%, 95% CI: 16.7% to 27.4%)** compared to **Delta (10.7%, 95% CI: 10.5% to 10.8%),** but the observed secondary attack rates were similar for non-household contacts. **The overall odds ratio**, **adjusted for household versus non-household exposure**, of a close contact becoming a case for confirmed Omicron compared to Delta index cases was **OR = 2.09 (95% CI: 1.54 to 2.79)**.

- The **Scottish government** published on 10 December 2021 an evidence paper on Omicron in Scotland.[12] The data presented largely represented counts of SGTF among PCR tests, which would not capture the BA.2 sublineage of Omicron, if present. (Note: the UKHSA stated on 10 December 2021 that BA.2 had not yet been observed in the UK data set and at that time comprised only a small number of sequences globally).[10]

- As of 9 December, SGTF cases represented **13.3% of all PCR tests** from Pillar 2 Lighthouse Labs. This proportion was expected to increase in the coming days and weeks, and, as of 9 December, was **increasing exponentially**.

- Based on data to 6 December, the doubling time for Scotland was estimated to be between **2.18 - 2.66 days**, using SGTF as a proxy for Omicron cases. These data suggest that Omicron is likely to make up the majority of cases in Scotland by **between mid-December and early January 2022**.

South African data

The following graphs illustrate changes in the effective reproductive number (Re) in South Africa over time and show an increase since the appearance of Omicron (Figures 1 and 2).[5, 13] This number represents the average number of secondary cases per infectious case, in a population made up of both susceptible and non-susceptible hosts. This increase in the effective reproductive number indicates potential higher transmissibility of Omicron.

Figure 1: Effective reproductive number (Re) in South Africa, April 2020 - December 2021

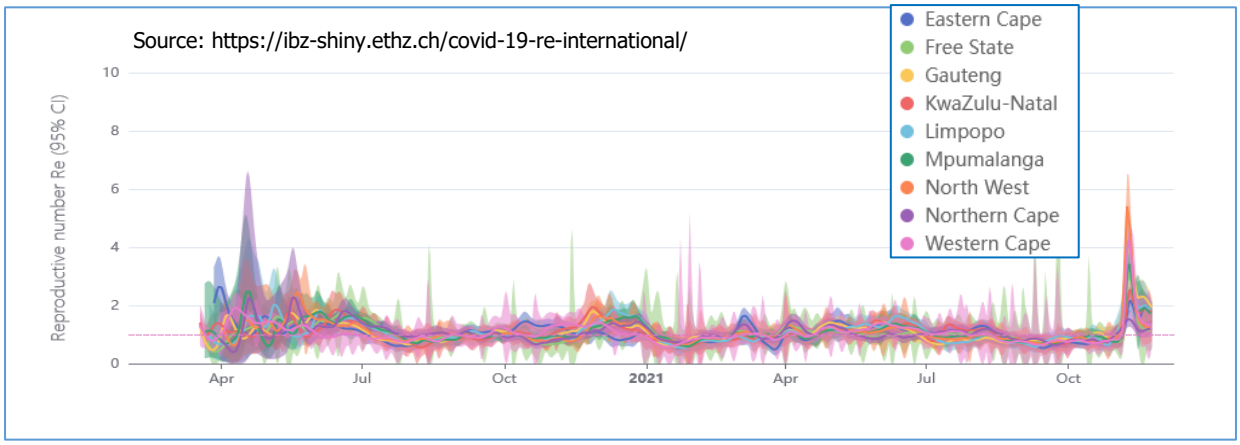
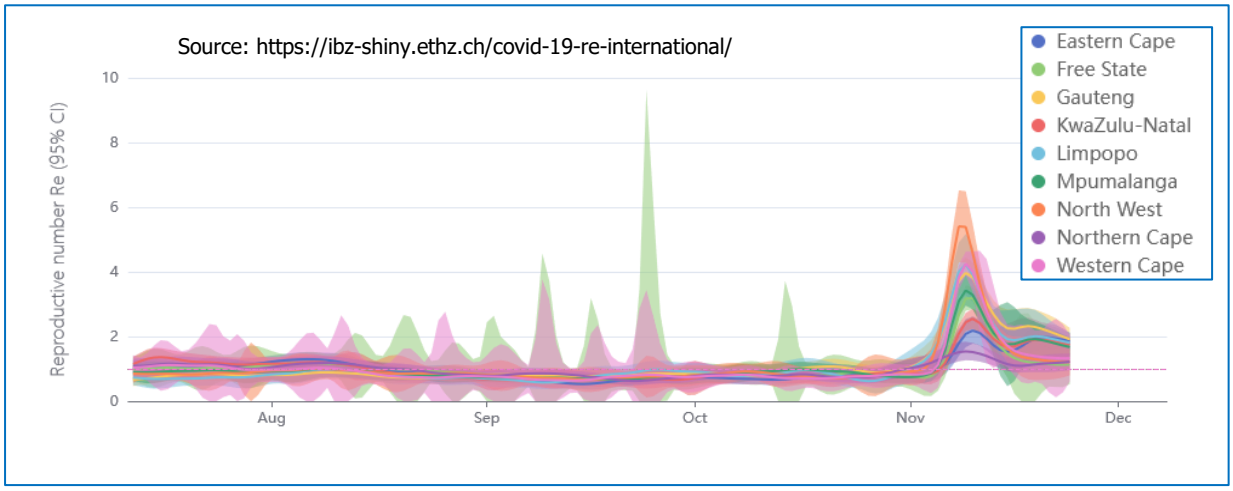


Figure 2: Effective reproductive number (Re) in South Africa, July 2021 – December 2021



- As of 8 December 2021, the Omicron variant represented 81% of all sequenced samples collected since the first identification of Omicron in South Africa.[14] Provisional data indicated that the test positivity rate in the Gauteng province of South Africa as of 8 December 2021 was 35%, with a 216% increase in the seven day rolling average of case numbers. The population vaccine coverage, as of 8 December 2021, was 28.7% in the province. It was considered at this time that doubling time for new cases may have lengthened from approximately every three days to every 7.5 days, though this observation should be interpreted with caution as it may reflect difficulties with testing capacity.[15] (Notably shorter doubling times have since been observed in the UK – see above). Hospitalisations in Guateng were doubling approximately every five days at the time of this report, though these figures are known to lag behind the case numbers by 1-3 weeks.[16]

Superspreading events

Superspreading events (SSEs), are considered to be events that result in the transmission of infection to a larger number of individuals than is usual.[17]

The following are some examples of superspreading events associated with the Omicron variant, which were identified as of 9 December 2021 (Table 1). As the information on these events is largely derived from news articles, it is important to consider the high likelihood of publication bias and the difficulty in verifying the findings. Beyond the examples tabulated, there have also been other reports of clusters and superspreading events where small numbers of cases of the Omicron variant have been observed. Note the list of superspreading events outlined in Table 1 is not exhaustive.

Due to the inability to control for the effects of the individual circumstances, it is not possible to ascertain from these reports if the Omicron variant is associated with greater transmissibility than the other SARS-CoV-2 strains. However, as several superspreading events have been identified since the designation of the Omicron variant, it is prudent to consider this risk. To-date, superspreading events associated with the Omicron variant have been reported in settings such as restaurants, concerts, parties, schools, a cruise ship, a boat, a wedding, a gym, a convention and a detention centre.

Table 1: Examples of superspreading events linked to the Omicron variant

Country, district	Setting	Date of event	Details of spread	Source of information
Denmark, Viborg	Christmas lunch among high school students, Viborg Cathedral School	27 Nov 2021	150 guests at lunch – as of 5 Dec 21, 53 confirmed infected with Omicron.	News article.[18, 19] Article notes that report was verified by Danish Agency for Patient Safety.
Denmark, Aalborg	Concert	27 Nov 2021	1,600 participants at concert. All 1,600 invited for testing on 1 Dec and 3 Dec. At least 10 cases infected with Omicron as of 5 Dec 21.	News article.[18] Article notes that report was verified by Danish Agency for Patient Safety.
Norway, Oslo	Restaurant – company Christmas party	26 Nov 2021	140 guests at Christmas party, all who reported a negative result (PCR test or rapid antigen test) 1-3 days previous to the event. Of those interviewed, 70% of just over 100 participants have been diagnosed with SARS-CoV-2, 17 of which are confirmed with the Omicron variant by sequencing as of 8 Dec 2021. All except 1 reported symptoms with most reporting symptom onset 3 days after the party. The preliminary results from the study show that there was widespread transmission at this event, even though the vast majority of participants were vaccinated with 2 doses of an mRNA vaccine. In addition, more than 60 people who visited the restaurant the same evening as the Christmas party have been confirmed as infected with SARS-CoV-2. Onward spread was observed in surrounding districts and municipalities.	News article. [20] Confirmed by Norwegian Institute of Public Health. [21]
Scotland, Nairn	Highland Singing at British Legion Club	27 Nov 2021	A "significant outbreak" of COVID-19 linked to a music event occurred with a small, unspecified, number confirmed as the Omicron variant.	News article.[22]
Scotland, Glasgow	Concert	22 Nov 2021	6 confirmed cases of Omicron so far among concert attendees.	News article.[23]
England, Somerset	Birthday party	Not reported	14 out of the 18 guests tested positive for Omicron. All guests were fully vaccinated and some had received a booster.	News article.[24]
Australia, Sydney	Indoor climbing gym, school	27 Nov 2021	13 cases initially among school students linked to the gym – of which 5 are confirmed due to the Omicron variant. The school closed for the rest of the year. A second school was linked to the cluster in the indoor climbing gym. Further spread in the schools possible as 20 Omicron cases now linked to the 2 schools.	News article.[25]

Australia, Sydney	Boat party	03 Dec 2021	5 attendees tested positive for SARS-CoV-2, 2 of those thought likely to have the new Omicron strain of the virus. 140 people attended the boat party in total.	News article.[26]
US, Wisconsin	Wedding	27 Nov 2021	5 of 12 cases confirmed as due to Omicron; genomic sequencing for the remaining 7 cases has not yet been completed. All 12 from Alameda County, California who attended a wedding in Wisconsin were vaccinated (with "most" having received boosters) and are "mildly symptomatic cases."	News article.[27]
US, New York	Anime convention	19-21 Nov 2021	Of a group of 30 who attended the conference, about 15 tested positive for SARS-CoV-2. At least 1 case was the Omicron variant. The status of the other 53,000 attendees is unknown.	News article.[28]
Toronto, Canada	Detention centre	26 Nov 2021	1 staff member tested positive for Omicron, and subsequently 4 inmates tested positive – however, variant is not yet confirmed among the inmates.	News article.[29]
US, New Orleans	Cruise ship	06 Dec 2021	The Louisiana state health department stated that a total of 17 people from a cruise ship, which boarded over 3,200 people, have tested positive. A single "probable" Omicron case was detected in a crew member. It is stated that all passengers and crew members were required to have been vaccinated against the coronavirus prior to departure.	News article.[30]

Modes of transmission

- One early release academic publication[31] published 3 December 2021, has indicated a high likelihood of airborne spread of the Omicron variant based on one transmission incident (two cases in total, including index case) occurring in a Hong Kong quarantine hotel; the two cases were isolating in separate rooms on either side of a corridor. Airborne transmission is suspected due to the lack of contact between the two cases, lack of shared space or items, and the similarity of the genetic profile of the viruses detected (indicating a transmission event occurred). Both cases had received two doses of mRNA vaccine. Further details are provided in Table 2.

Table 2: Evidence regarding potential airborne spread of the Omicron variant

Country, Setting	Details of cases	Details of transmission	Source of information
Hong Kong, China Quarantine hotel. 2 cases of Omicron detected. • Case A arrived in Hong Kong from South Africa on 11 Nov 2021. Case B arrived in Hong Kong from Canada on 10 Nov 2021. • Both had received 2 doses of Pfizer-BioNTech vaccine and had tested negative by RT-PCR within 72 hours of arrival. • On arrival in Hong Kong, both stayed in the same quarantine hotel with rooms across the corridor from each other.	2 Omicron cases identified 13 Nov 2021 – Case A (incoming from South Africa) tested positive and was hospitalised and isolated the next day. 17 Nov 2021 – Case B developed symptoms. Tested positive on 18 Nov 2021. As of 3 Dec 2021, none of the 12 persons staying in nearby rooms on the same floor during the study or related hotel staff have tested positive in repeated tests for SARS-CoV-2.	Viral genomes deduced from these 2 SARS-CoV-2–positive cases differed only by 1 nucleotide (high likelihood of transmission of virus from Case A to Case B). Retrospective investigation, including closed-circuit television camera footage, confirmed that neither case-patient left their room during the quarantine period. No items were shared between rooms, and other persons did not enter either room. The only time the 2 quarantined persons opened their respective doors was to collect food that was placed immediately outside each room door.	Early release research letter (short academic article),[31] 3 Dec 2021.

Assessments by authorities

- The **Network for Genomic Surveillance in South Africa** is monitoring the trajectory of the Omicron variant across South Africa and provides regular genomic surveillance updates.[7] The following update was provided as of 8 December 2021:
    - The earliest detection of Omicron in South Africa was on 8 November, in the Gauteng province.
    - Omicron dominated November sequencing data, with 70% of genomes sequenced in Gauteng (n=250/358) being identified as Omicron. Sequencing is ongoing to determine the prevalence of Omicron in other provinces.
    - As of 8 December 2021, Omicron had been detected in 42 countries worldwide.
- The **US CDC** Science Brief on the Omicron Variant, published on 2 December 2021,[2] noted that it is difficult to infer from analysis of the changes in the spike protein of the Omicron variant whether it is more transmissible than Delta. As stated by the CDC:
    - N501Y increases binding to the ACE2 receptor, which could increase transmission, and the combination of N501Y and Q498R may increase binding affinity even more; however, other substitutions in the Omicron spike protein are expected to decrease binding to ACE2. As such, receptor binding affinity needs to be assessed using the full spectrum of spike protein substitutions found in the Omicron variant.
    - H655Y is proximal to the furin cleavage site and may increase spike cleavage, which could aid transmission.
    - H679K is proximal to and adds to the polybasic nature of the furin cleavage site, which may also increase spike cleavage and could aid transmission.
    - P681H has been shown to enhance spike cleavage, which could aid transmission. This mutation is found in Alpha and an alternate mutation at this position (P681R) is found in Delta.

- The UK Health Security Agency (**UKHSA)** risk assessment for SARS-CoV-2 variants,[32] published 9 December 2021, made the following classifications regarding transmissibility and growth advantage of Omicron:
    - Omicron was classified as **at least as transmissible as Delta**. This risk was assigned 'amber' status (defined as established human to human transmission, which appears similar to wild type virus).[33] This risk assessment was assigned a low level of confidence (indicating little or poor-quality evidence, uncertainty or conflicting views amongst experts, or no experience with previous similar incidents). The assessment noted the following:
        - There is biological plausibility of increased transmissibility relative to Delta. This is due to the presence of furin cleavage site and nucleocapsid changes (associated in vitro with advantages for replication), as well as extensive changes to the RBD.
        - Structural modelling suggests that the mutations present may increase human ACE2 binding affinity to a much greater extent than that seen for any other variant.
        - However, there is as yet no demonstration of increased transmissibility as distinct from any other contributors (for example, immune escape) to growth advantage.
    - In the UK, Omicron is displaying a **growth advantage over Delta.** This risk was assigned **'red' status, with high confidence** (good quality evidence, multiple reliable sources, verified, expert opinion concurs, experience of previous similar incidents).
        - This assessment was based on analysis of **UK data showing increased household transmission risk, increased secondary attack rates,** and **increased growth rates compared to Delta** (see 'epidemiological data and parameters' in this section, below). Omicron was considered likely to outcompete Delta in the UK and to dominate by mid-December 2021.
        - The observed growth advantage **may be due to immune evasion or increased transmissibility**. As of 9 December 2021, it was considered that there is high confidence in the

component of immune evasion, but that, given the very high growth rate observed, it is plausible that an increase in transmissibility is also contributing.

- The **UK** Scientific Pandemic Influenza Group on Modelling, Operational sub-group (**SPI-M-O**)[34], released a consensus statement on 7 December 2021 which stated the following:
  - The burden of disease for any wave of Omicron infection will depend on the size of the pool of people who are susceptible to infection and the severity of those infections. If Omicron exhibits substantial immune escape, the pool of susceptible people in the UK could be large, and thus transmission could increase substantially. Any significant wave of infection, almost irrespective of immune escape, will spill over into hospitalisations. **If initial estimates of transmission advantage and immune escape from South Africa are applicable to the UK population, there is the potential for a peak of infections much larger than that experienced in January 2021**.
  - If Omicron combines increased transmissibility and immune escape, **irrespective of severity, it is highly likely that very stringent measures would be required to control growth and keep R below 1** in the UK. **Delaying any wave of infections in such a scenario would allow more time for vaccines and therapeutics to be modified to combat Omicron**.
  - Preliminary modelling from three SPI-M-O groups (updated as of 7 December 2021) suggested a central projection for Omicron growth rate of 0.1 to 0.4 per day – this is consistent with current S-gene target failure (SGTF) data suggesting a rapid doubling time of between two and three days. (Note: UKHSA analyses published on 10 December 2021 - see 'epidemiological data' below – calculated a growth rate of 0.35). As a result of this and currently increasing levels of Omicron cases, it was highly likely that, as of 7 December 2021, there were thousands of new Omicron infections per day in the UK. It was also considered highly likely that Omicron would account for the majority of new SARS-CoV-2 infections **within a few weeks**.
- As of 14 December 2021, the **ECDC** noted that cases had been reported by 25 countries in the EU/EEA, contributing to an **overall total of 2,127 confirmed cases**.[35]
  - The majority of confirmed cases have 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.

  - **Several EU/EEA countries** with high rates of sequencing have detected the Omicron VOC in samples from cases without history of travel to African countries, indicating **active secondary community transmission**.
  - Among confirmed Omicron cases reported by public sources as of **13 December 2021**, the highest numbers of cases have been recorded in the UK, Denmark, and South Africa.
- A rapid risk assessment update published by ECDC on 15 December 2021 stated that, depending on the growth advantage and level of immune escape associated with Omicron, this variant is likely to become the dominant variant in the EU/EEA within the first two months of 2022.[36] As of 15 December, community transmission of Omicron was ongoing in EU/EEA countries and a further rapid increase in Omicron cases was expected in the next two months.
- The Norwegian Institute for Public Health (NIPH) published an updated risk assessment on the Omicron variant on 13 December 2021 and warned that the number of detected cases of SARS-CoV-2 was increasing rapidly in Norway, followed by an increase in hospital admissions.[37]

Virulence

Virological markers

There is currently a lack of evidence on the virulence of the Omicron variant. However, the following early findings of mutations are suggestive of alterations in virulence:

- The Omicron mutation (T478K) also found in the Delta variant is associated with greater infectivity and less antibody neutralising activity.[3]

- Genome characterisation of Omicron highlighted that there has been insertion of PRRA amino acids into the S1/S2 subunit cleavage site. This cleavage site is associated with infectivity and pathogenicity. However, further investigation is required to determine the impact of this on virulence.[3]

Epidemiological data; early patient experience

Note on interpretation of data

The patterns of virulence currently being observed with Omicron should be considered in light of the extent to which Omicron demonstrates greater infectivity and greater capacity for immune escape, and the extent to which the population possesses immunity (from either prior infection or vaccination). If the population contains a large number of individuals who have previously been infected or possess

vaccine-derived immunity, and if there is a high capacity for reinfection or breakthrough infection observed with Omicron, a greater portion of the overall population may become infected. As reinfections and breakthrough infections tend to result in mild or asymptomatic cases, and given a greater number of the population being susceptible to infection if reinfection/breakthrough infection occurs more frequently with Omicron, the proportion of those who are infected who develop severe disease will appear lower than what would be observed in the absence of natural or vaccine-derived immunity. This could lead to the appearance of a milder presentation of disease overall within the population (and, therefore, the suggestion of lower virulence), relative to that observed with previous strains of SARS-CoV-2.

South African data

- Early information, published 4 December 2021, on the experience of patients infected with the Omicron variant is available from the Tshwane District, South Africa.[38] There has been an exponential rise in COVID-19 cases over the course of several weeks in this region, which has been largely attributed to the dominant Omicron variant. The early patient experience (first two weeks of the Omicron wave, between 14 and 29 November 2021) from the Steve Biko Academic and Tshwane District Hospitals (SBAH/TDH) Complex in Pretoria is discussed by the South African Medical Research Council (SAMRC):
    - A sharp rise in hospital admissions was observed with 166 new COVID-19 admissions between 14 and 29 November 2021. Given hospital policy to test everyone for SARS-CoV-2, COVID-19 was an incidental finding in the majority (approximately 66%) of the 166 admitted patients. Of 42 hospitalised patients (38 adults and 4 children) with COVID-19 on the 2 December 2021:
        - 69% (29 of 42 cases) were not oxygen dependent.
        - 31% (13 of 42 cases) were dependent on supplemental oxygen, of which nine had a diagnosis of COVID-19 pneumonia based on a combination of symptoms, clinical signs, chest x-ray and inflammatory markers. The remaining four patients were on oxygen for other medical reasons.
        - Four patients were in a high-dependency care unit and one in the ICU, which was noted by the authors to be much lower than in previous waves.

- Of the 38 adults, six were fully vaccinated, 24 were unvaccinated and 8 had unknown vaccination status.

- An analysis of the 166 patients admitted to the SBAH/TDH Complex during the period 14 -29 November 2021, found that the age profile differed markedly from the previous 18 months. During this period, approximately 80% of admissions were below the age of 50 years. This is in keeping with the age profile of admissions in all public and private hospitals in Tshwane and throughout the Gauteng Province during the same period as reported by the NICD (National Institute for Communicable Diseases) and the Gauteng Provincial Government. Nineteen percent were children aged 0-9 years with the highest number of admissions in the age group 30-39 years, comprising 28% of all total admissions. However, it is important to acknowledge that the age profile of South Africa,[39] is significantly younger than that of Ireland,[40] and vaccination coverage in South Africa is also significantly lower, particularly in younger age groups.[41]

- There were 10 deaths (6.6%) in the 166 patients admitted during the period 14 -29 November 2021 that tested positive for SARS-CoV-2. Four deaths were in adults aged 26 – 36 and five deaths were in adults aged over 60 years. One death was in a child in whom the cause of death was unrelated to COVID-19. The authors state that this in-hospital mortality rate compares favourably with previous waves (approximately 23% in-hospital mortality rate across all of South Africa during previous 18 months). However, due to the time lag between infection and mortality, it may be too soon to draw any conclusions regarding disease severity.

- A significant early finding in this analysis was the much 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. Caution is required given the preliminary nature of these data, as this average could be artificially lowered by the short time frame. The NICD reported a similar shorter length of stay for all hospitals in Tshwane in its weekly report. It was also less than the Gauteng or national average length of stay reported by the NICD in previous waves.

- On 9 December 2021, hospital surveillance data were reported for the period up to 4 December 2021 (week 48) from 665 facilities across all nine provinces in South Africa.[42]

- There has been an increase in weekly COVID-19 admissions in Gauteng in both private and public sectors since week 45. The current 14-day average admissions per day in Gauteng is 181 compared with 32.5 in the previous 14-day period, representing a 455% increase in COVID-19 hospital admissions. While the current 14-day average in-hospital COVID-19 deaths per day in Gauteng is 4.21 compared with 2.50 in the previous 14-day period, representing a 69% increase in COVID-19 deaths.

- In Gauteng, 9% of all COVID-19 admissions in the last three weeks were in children younger than five years old. However, this trend was changing and the proportion of admissions in children younger than 5 years old had decreased from 14% (week 46) to 11% (week 47) to 8% (week 48).

- In City of Tshwane Metro, from 14 November-8 December 2021, 1,633 admissions and 39 deaths due to COVID-19 were reported from the public and private health sectors. Among patients who already had a hospital outcome and were no longer still in hospital, during the early second wave, 66% of COVID-19 admissions were severe, during the early third wave, 67% were severe, and during the early fourth wave, 31% were severe.

- It must be noted that severity data has several limitations at the early phase of the wave when numbers are small, mild patients are more likely to be admitted as a precaution, patients are diagnosed with SARS-CoV-2 incidentally when admitted for other reasons, and because there has not been sufficient follow-up time for severity and outcomes to have accumulated.

- 'Discovery Health', South Africa's largest private health insurance administrator, published a press release on 14 December 2021, which included an analysis of 211,000 COVID-19 test results from the first three weeks of the Omicron wave in South Africa.[43] Details were not provided on the methodology of the analysis. The authors stated that Omicron was associated with a flatter trajectory of hospital admissions compared with that observed in previous waves of SARS-CoV-2. The authors also noted, however, that this apparent lesser severity could be confounded by the high seroprevalence levels of SARS CoV-2 antibodies in the general South African population, especially following an extensive Delta wave.

- Adults were found to experience a **29% lower admission risk** relative to South Africa's first wave of infection in early 2020. Furthermore, hospitalised adults were observed, at this time point, to have a lower propensity to be admitted to high-care and intensive-care units, relative to prior waves.

- Discovery Health's data indicated that **children** under the age of 18 had a **20% higher risk of admission** for complications of COVID-19 when infected with Omicron than with previous variants. However, children were **51% less likely to test positive for COVID-19 relative to adults** in the Omicron period. Where children required admission for complications of COVID-19, the primary diagnoses were bronchiolitis and pneumonia, often with severe gastrointestinal symptoms and dehydration. These were early and partial data and require careful follow-up, but the authors noted that this trend aligned with observations from the NICD (above) that an increase in paediatric admissions had been observed.

External analysis of South African data

- The **Norwegian Institute of Public Health (NIPH)** published an updated risk assessment on the Omicron variant on **13 December 2021**,[37] which included assessment of the severity of illness, and noted the following:

  - The South African Institute of Infection Control has a higher proportion of inpatients **under two years of age** than earlier in the course of the pandemic. However, in the context of all inpatients undergoing testing for infection with SARS-CoV-2 and a **low threshold for admission** for young children the high proportion of inpatients under two years of aged identified in the South Africa data likely reflect pre-admission screening rather than an increased incidence of serious illness in children infected with Omicron than with Delta.

  - The South African Institute of Infectious Disease Control reported that mortality has been lower recently than that observed with the Delta wave, across all age groups. However, the **lag time** for serious illness to occur, and the **younger age** of the South African cohort, must be taken into account. Furthermore, increased levels of screening may have occurred in the context of Omicron, which may have captured a greater number of milder or asymptomatic cases, thus diluting the observed severity within the population overall.

- The risk assessment concluded that it remains uncertain whether the Omicron variant results in more or less serious illness than that observed with Delta, but that a more serious presentation would likely have been observed by now. Also, the effects in different age groups were considered to remain unclear. Omicron was considered to probably result in "as serious" or "less serious" disease than that observed with Delta in those vaccinated, persons who have previously had COVID-19 and those unvaccinated.

- **John Burn-Murdoch** (Financial Times & London School of Economics) analysed data from South Africa's National Institute for Communicable Diseases and commented on the apparent severity of infection with the Omicron variant on Twitter on 4 December 2021,[44] and again on 10 December 2021.[45] It is important to note that these comments are highly speculative given the small number of patients and the cohort from which they are drawn (largely young population). The following are the main discussion points from this thread:

  - Based on data available as of 4 December 2021, the share of COVID-19 positive hospital patients in Gauteng that required ICU treatment was much lower than at the same stage of the Delta wave (approximately 8% vs. 25%), though the share of patients requiring oxygen appeared to be similar. However, the proportion of Omicron patients receiving oxygen or in ICU appeared to be rising faster than in the Delta wave.

  - The age group affected by the Omicron wave in South Africa has been substantially younger than that observed during the Delta wave.

  - The commentator stated that it is too early to determine whether Omicron is a less virulent strain or not. However, given the exponential rise in cases observed, the commentator suggests that even if lower numbers of patients require ICU during the Omicron wave compared with the Delta wave (for example 8% vs 25%), a small proportion of a rapidly increasing number of cases can still have a significant impact on health services.

  - Based on South African COVID-19 hospital surveillance data gathered to 4 December 2021, the share of COVID-19 patients requiring acute or intensive care continues to appear lower than that observed in previous waves of infection.[45] However, this may still represent a younger population at risk, in addition to the effects of natural

immunity within this population or the potential for increased infectivity, including increased rates of reinfection (inducing milder disease) with Omicron.

UK data (England)

- As of 13 December 2021, ten people were hospitalised in England with Omicron; these individuals were diagnosed on or before admission. Admissions were spread around the country, included a mix of ages between 18 to 85 years, with the majority having received two doses of vaccination. The first death of a patient in England diagnosed as having Omicron occurred on 13 December 2021. [(46)]

Denmark data

- The Statens Serum Institut publishes daily statistics on the cases of Omicron in Denmark.[(47)] On 14 December 2021, 12 patients were hospitalised in Denmark with Omicron, with fewer than five of these patients admitted to ICU. Overall, of 4,498 Omicron cases analysed, **38 (0.8%) were admitted to hospital**. Of these, **nine cases tested positive 48 hours or more after admission (and were therefore classified as hospital-acquired cases),** while 29 cases tested positive prior to or within 48 hours of admission. Across all other variants to date, 679 of 90,150 cases (0.8%) were hospitalised.

Assessments by authorities

- The **UKHSA** risk assessment for SARS-CoV-2 variants, published 9 December 2021, stated that there were insufficient data available to inform an assessment of infection severity, as is expected in the early period of emergence of a new variant.[(32)]

- The rapid risk assessment published by the **ECDC** on 15 December 2021 noted that data are currently too limited to assess the severity of disease caused by Omicron in the EU/EEA population with sufficient confidence.[(36)] The ECDC noted, however, that even if the severity of disease caused by Omicron is equal or lower than the severity of Delta, **the increased transmissibility and resulting exponential growth of cases would rapidly outweigh any benefits of a potentially reduced severity.** Omicron was therefore considered very likely to cause additional hospitalisations and fatalities, further to those already expected from previous forecasts that considered only the impact of Delta.

- At a media briefing on 8 December 2021, the **WHO** Director-General stated that "there is also some evidence that Omicron causes milder disease than Delta, but again, it's still too early to be definitive." The Director-General concluded that "new data are emerging every day, but scientists need time to complete studies and interpret the results." He urged against drawing firm conclusions at this time.[48] A technical brief by the WHO on enhancing readiness for Omicron, published 10 December 2021,[49] noted that there were still limited data on the clinical severity of Omicron at this point. The WHO stated that preliminary findings from South Africa have suggested that Omicron may be less severe than Delta, and that all cases reported in the EU/EEA to date have been mild or asymptomatic, but also that it remains unclear to what extent Omicron may be inherently less virulent. More data were considered needed to understand the severity profile.

- The **UKHSA** technical briefing on SARS-CoV-2 variants of concern, published 10 December 2021, stated that at this time it was not possible to compare the risk of hospitalisation or death with other variants. At that time (data accurate to 6 December 2021), none of the identified Omicron cases in the UK were known to have been hospitalised or to have died.[10] However, as of 14 December 2021, data analysed to 12 December 2021 showed that at least one patient in the UK had died with Omicron and 16 patients had been hospitalised with confirmed Omicron or SGTF cases of SARS-CoV-2 (proxy for Omicron).[11] The 10 December technical briefing noted that future updates will assess severe outcomes from Omicron against Delta cases from the same period.

Immune escape, and vaccine efficacy and effectiveness

Markers of immune escape

- A review of the mutations found on the Omicron spike protein found that the number of mutations associated with each SARS-CoV-2 variant was highest for Omicron compared to Beta, Gamma, and Delta.[50]

- A genomic analysis (3 December 2021) of Omicron sequences obtained from the GISAID database identified a unique mutation insertion (ins214EPE) that has not been identified in previous SARS-CoV-2 variants. This insertion is on the N-terminus domain (NTD), an area which is a known human T-cell epitope on SARS-CoV-2. The authors raise concerns that may impact on T-cell immunity.[51]

- Comparison with previously identified variants identified 12 mutations in the Omicron variant that were also present in Alpha, Beta, Gamma, and Delta. All 12 mutations have previously been linked with high transmissibility, increased viral binding affinity, and immune evasion.(52)

- An analysis (3 December 2021) of mutations on the RBD of Omicron confirmed the presence of the S477N mutation, which was previously observed in the B.1.620 variant (de-escalated variant as no longer circulating in the EU/EEA). Together with the N439K and N501Y mutations, the S477N mutation has been associated with increased viral affinity toward the hACE2 receptor and with immune escape.(3)

- Four mutations (K417N, K477N, T478K, and E484A) found in the RBD have previously been associated with immune escape.(3) There are 11 mutations associated with the "antigenic supersite" of the NTD, which are considered to be likely to contribute to the possibility for immune evasion.(52) Previous studies have found that variants with the E484 mutation have demonstrated resistance to neutralising antibodies generated by prior infection.(6)

- A study published as a preprint by Redd et al.(53) on 9 December 2021 examined if there were mutations in Omicron in the virus epitopes (the parts of SARS-CoV-2 which were targeted by the CD8+ T-cell response). Based on samples from 30 individuals who recovered from COVID-19 in 2020, only one of 52 epitopes identified contained an amino acid that was mutated in Omicron. These data suggest that the T-cell immune response in previously infected, and, most likely, vaccinated individuals, should still be effective against Omicron. However, the relative importance of cellular (T-cell) immunity, versus humoral immunity, to clinical outcomes in patients with COVID-19, has not been fully elucidated.

- Computational analysis of mutations indicates that there is concern over changes in epitopes that may increase the possibility of antibody escape with Omicron, resulting in increased risk of reinfection and a decrease in the effectiveness of vaccination. (54)

- All identified studies highlight that further evidence is required to determine the impact of the new mutations seen in Omicron on the immunity derived from vaccination or from previous infection.

Risk of reinfection – epidemiological research

- Research conducted (**Pulliam et al.**, published 2 December 2021) with South Africa's National Notifiable Medical Conditions Surveillance System indicated an increased risk of reinfection during the time period from 1 November 2021 to 27 November 2021.[55] The estimated hazard ratio for reinfection compared to primary infection during the first wave was 2.39 (95% confidence interval: 1.88–3.11).
    - Among those who had more than one reinfection, 14.2% experienced their third episode during November 2021. This was considered by the authors to be suggestive of transmission of the Omicron variant.[55]

- The **UKHSA technical briefing** on SARS-CoV-2 variants of concern, published 10 December 2021,[10] included an analysis of the risk of reinfection.
    - The briefing noted that reinfection rates are estimated based on the population of previous infections eligible to become a reinfection (that is, with a previous positive test result ≥90 days earlier). Using this as a measure of current reinfection rates in the population there is **currently no indication of an increase in overall reinfection rates**, though **this is being kept under ongoing review**.
    - A preliminary estimate of the relative risk of reinfection with the **Omicron variant** was estimated based on 361 Omicron cases and 85,460 non-Omicron cases which could be linked to whole genome sequence data between November 20 and December 5, 2021. Among these, there were 25 possible Omicron reinfections and 336 non-Omicron possible reinfections. Relative risks were estimated using Poisson regression and a binomial outcome representing at least one PCR-positive test more than 90 days prior to the specimen date. After adjusting for age group (0 to 18, 19 to 40, 40+), public health region, and type of testing, the relative risk (RR) of reinfection for Omicron was found to be **RR = 5.2 (95% CI 3.4 to 7.6).**

- 'Discovery Health', South Africa's largest private health insurance administrator, published a press release on 14 December 2021, which included an analysis of 211,000 COVID-19 test results from the first three weeks of the Omicron wave in South Africa.[43] For individuals who had previously had COVID-19, the relative risk of reinfection with Omicron was found to be significantly higher than with previous variants, though details were not provided on how this outcome was defined or calculated. The results, as reported by the authors found that, relative to those without prior

documented infection, those who were previously infected with COVID-19 during the:

- Delta wave faced a 40% relative risk of (re)infection with Omicron.
- Beta wave faced a 60% relative risk of (re)infection with Omicron.
- First wave faced a 73% risk of reinfection.

Risk of breakthrough infection (vaccine effectiveness in preventing infection) – epidemiological research

- The NIPH performed an investigation into the outcomes of the superspreading event at a Christmas dinner party in an Oslo restaurant on 26 November 2021.[21] Approximately **73% of 111 participants became infected with SARS-CoV-2, and over 70% of those infected reported COVID-19 symptoms**. As of 8 December 2021, 17 of those infected had been confirmed as being infected with Omicron. The vast majority of participants were vaccinated with two doses of mRNA. The NIPH, in their risk assessment published 13 December 2021, therefore cited this as an example of how young and middle-aged adults vaccinated with two doses of mRNA vaccine may still develop illness with Omicron.[37]

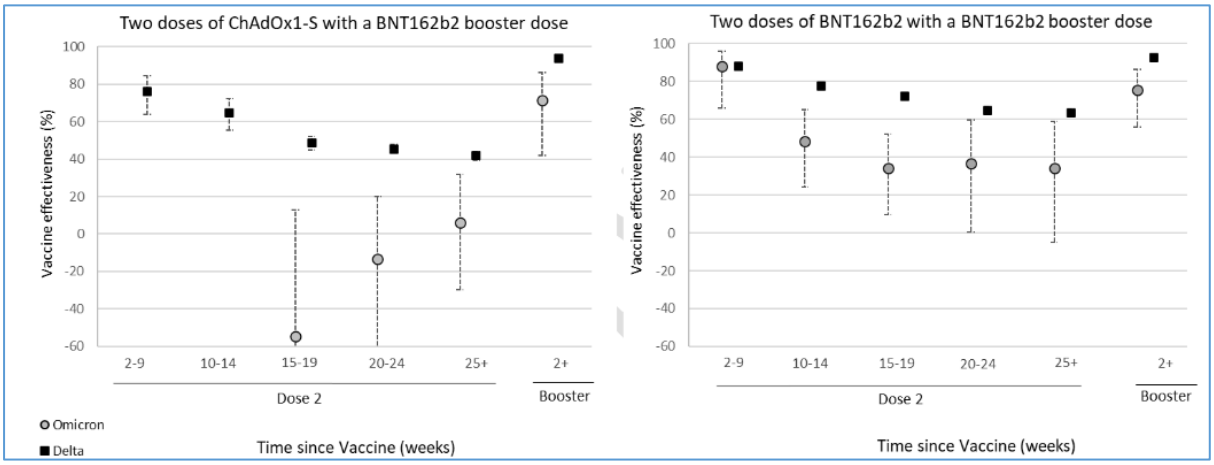
- A case series, published by Kuhlmann et al. as a preprint on 9 December 2021, **described breakthrough infections with the Omicron variant** in **seven** individuals in South Africa, who had **all received a booster dose** of an mRNA vaccine:[56]
  - Six of the seven cases had received two doses of Pfizer BioNTech BNT162b2; five of these had received a third BNT162b2 dose, while the sixth case had a Moderna/Spikevax mRNA-1273 booster. The remaining case had received a first dose of AstraZeneca ChAdOx1S followed by two doses of Pfizer BNT162b2. Booster doses were administered between five and 10 months after the second vaccine doses, and breakthrough infections occurred one to two months thereafter. None had a reported history of prior SARS-CoV-2 infection.
  - All seven people in the cluster (five women, two men; average age of 27.7 years) experienced symptomatic COVID-19, but clinical manifestations were mild to moderate. None required hospitalisation.
  - Viral loads ranged from 1.41×10^4 to 1.65×10^8 (mean 4.16×10^7) viral RNA copies per mL of swab eluate. The authors noted that the

average viral load observed among these seven cases appeared higher than that observed in a study of "wild-type" strain (mean 6.76 x 10^5). However, caution is required in comparing between these two small studies.

- All seven cases had high levels of viral spike protein binding antibodies (ranging from 15,011.2 to > 40,000 with a mean of approximately 23,000 arbitrary units / millilitre (AU/mL) of serum) as expected after receipt of booster vaccine doses.
- Given the case series design of this study, small sample size and no comparator group, the findings should be viewed with caution.

- The **UKHSA technical briefing** on SARS-CoV-2 variants of concern (no. 31), published 10 December 2021,[10] reported the findings of a **test negative case control study** performed by the UKHSA to estimate **vaccine effectiveness** against symptomatic COVID-19 with the Omicron variant relative to the Delta variant. This research was also published as a preprint by **Andrews et al. on 11 December 2021**.[57] Individuals who reported symptoms and were tested in community testing between 27 November and 6 December 2021 were included in the analysis, and comprised 56,439 Delta and 581 Omicron cases. The UKHSA noted 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 (including travellers and their close contacts) which cannot fully be accounted for.
    - In all periods, **effectiveness was lower for Omicron compared to Delta**, with the exception of those who had their second dose of Pfizer vaccine (BNT162b2) 2 to 9 weeks ago (which may reflect young adults who have recently received their second dose). **From 2 weeks after a Pfizer booster dose,** relative to unvaccinated individuals, **vaccine effectiveness against symptomatic disease increased to around 71% among those who received AstraZeneca as the primary course and to around 76% among those who received Pfizer as the primary course** (Figure 3).

Figure 3: UKHSA (Andrews et al.) figures – study of vaccine effectiveness against symptomatic diseases due to Omicron and Delta variants relative to unvaccinated individuals.[57]



Effectiveness by period after dose 1 and dose 2 for Delta (black squares) and Omicron (grey circles) for (A) recipients of 2 doses of AstraZeneca vaccine as the primary course and a Pfizer (BNT162b2) as a booster and (B) recipients of 2 doses of Pfizer vaccine as the primary course and Pfizer as a booster. Comparison is to unvaccinated individuals in order to estimate the absolute effectiveness of vaccination against Omicron and Delta variants.

- The authors note that the early observations for two doses of AstraZeneca (i.e. results Panel A) are particularly likely to be unreliable as they are based on relatively small numbers and are likely to reflect an older population and a population with more co-morbidities than those given the Pfizer vaccine. These caveats may explain the negative point estimates.
- These early estimates suggest that vaccine effectiveness against symptomatic disease with the Omicron variant is significantly lower than compared to the Delta variant. However, moderate to high vaccine effectiveness of 70 to 75% is seen in the early period after a booster dose.

- 'Discovery Health', South Africa's largest private health insurance administrator, published a press release on 14 December 2021, which included an analysis of 211,000 COVID-19 test results from the first three weeks of the Omicron wave in South Africa.[43] This analysis used a test-negative study design to establish the vaccine effectiveness of BNT162b2 against hospital admission from Omicron infection, though further details were not provided on the methodology of the analysis. The results, as reported by the authors, were that:

- Vaccinated individuals who received two doses of **Pfizer BioNTech** BNT162b2 had 33% protection against infection, relative to the unvaccinated, in the first weeks of the Omicron wave. This was considered a significant reduction relative to the 80% effectiveness observed in the earlier period.

- Vaccinated individuals who received two doses of Pfizer BioNTech BNT162b2 had 70% protection against hospital admission during this time period. This was a reduction from 93% protection observed during Delta.

- Protection against hospital admission appeared to be maintained across all ages in people aged 18 to 79, with slightly lower levels of protection for the elderly (67% in people aged 60 to 69, and 60% for people aged 70 to 79). Protection against admission was also found to be consistent across a range of individual chronic illnesses (diabetes, hypertension, hypercholesterolaeia, and heart disease).

Laboratory research – virus neutralisation studies

- Fourteen neutralisation assay studies have been published as preprints or posted online as a press release or raw data between 7 December 2021 and 14 December 2021. These studies involve determination of the extent to which Omicron is capable of infecting cells in cultures by examining the neutralisation activity of antibodies against the virus. The cultures contain sera from individuals who have received SARS-CoV-2 vaccines, and or have been previously infected. The findings of these studies are summarized in Table 3.
    - These studies are subject to various limitations, such as small sample sizes or the use of pseudovirus instead of live virus.
    - Importantly, reduction in neutralisation activity does not directly equate to reductions in vaccine effectiveness. These studies do not consider the impact of conserved non-neutralising antibodies or memory T cell responses which likely contribute to protection from severe disease. While it is likely that existing vaccines will provide at least some protection against severe disease,real-world evidence is required to determine vaccine effectiveness – see 'epidemiological research' section, above.

Table 3: Findings of 14 laboratory neutralisation assays published as of 14 December 2021

Author, Report type, date	Study type	Study size	Vaccine	Study Findings
Cele et al. Preprint [58] 7 Dec 2021	Live virus neutralisation assay Neutralisation activity of primary vaccination regimen, and prior infection plus vaccination, against Ancestral, Omicron.	14 samples (n=12 patients)	Pfizer BNT162b2	Omicron was associated with: ▪ a 41-fold reduction in neutralisation activity relative to the ancestral strain (with R346K mutation, which has been previously identified as an escape mutation) ▪ incomplete escape of two-dose Pfizer BNT162b2-elicited neutralisation ▪ a similar fold reduction in neutralisation activity, but from a higher starting point, in sera from those with prior infection plus two doses of Pfizer BNT162b2 vaccine. Using correlates between the loss in neutralisation and vaccine efficacy observed in previous clinical trials, neutralisation activity against Omicron in this study was estimated to correspond to a vaccine efficacy of 22.5% (95% CI: 8.5% to 40.7%) against symptomatic infection. Note: An important limitation of this study is that it involved only 14 samples from 12 participants, and did not include serum from any participants who had 3 doses of the vaccine.
Sheward et al. [59] Preprint 7 Dec 2021	Pseudovirus neutralisation assay Neutralisation assay versus Ancestral, Omicron	N=34 N=17 randomly selected blood donors N=17 previously infected HCW	Vaccination status not reported	Omicron was associated with: ▪ variable loss of neutralisation relative to the ancestral strain, with some samples showing almost no loss, and some showing up to 25-fold loss. ▪ lower neutralisation activity than against Delta, ranging from an approximately 7-fold-reduction among the 17 blood donors compared with a mean of a 4-fold reduction among the 17 previously-infected HCWs. However, when tested on a panel of standard WHO samples (which are used to neutralisation these assays), the reduction was found to be 40-fold, relative to the ancestral variant. Almost all serum samples evaluated retained some neutralisation activity against the Omicron variant. Note: this study involved a small sample size, and did not involve live virus strains.
Wilhelm et al. [60]	Live virus neutralisation assay	117 serum samples	▪ Pfizer BNT162b2	For each of the samples, the fold reduction in neutralising activity against Omicron, compared with Delta, was as follows:

Preprint 8 Dec 2021	Neutralisation activity of various combinations of primary vaccination regimens, booster doses, and prior infection, against Delta, Omicron.		▪ Moderna/Spikevax mRNA-1273 ▪ AstraZeneca ChAdOx1	▪ double-dose Pfizer BNT162b2 (>11-fold reduction, no neutralising activity observed) ▪ double-dose Pfizer BNT162b2 plus Pfizer BNT162b2 booster, sampled 0.5 months after the booster (37-fold reduction) ▪ double-dose Pfizer BNT162b2 plus Pfizer BNT162b2 booster, sampled 3 months after the booster (24-fold reduction) ▪ double-dose Pfizer BNT162b2 plus history of SARS-CoV-2 infection (32-fold reduction) ▪ double-dose Moderna/Spikevax mRNA-1273 (>20-fold reduction, no neutralising activity observed) ▪ double-dose Moderna/Spikevax mRNA-1273 plus booster with Pfizer BNT162b2 (22-fold reduction) ▪ heterologous AstraZeneca ChAdOx1 and Pfizer BNT162b2 (>10-fold reduction, no neutralising activity observed) ▪ heterologous AstraZeneca ChAdOx1 and Pfizer BNT162b2 plus booster with Pfizer BNT162b2 (27-fold reduction). Sera from individuals who received 2 doses of any of the vaccines or vaccine combinations did not show any neutralisation activity against Omicron (except where individuals had been previously infected). Sera from those who received a BNT162b2 booster dose (regardless of the primary vaccine schedule) still showed neutralisation against Omicron. Note: Timing information was unavailable for some of the samples, so it is uncertain if absence of neutralisation in those without booster doses is due to the Omicron variant, waning of immunity, or both.
Pfizer/BioNTech. [61] Press release 8 Dec 2021	Pseudovirus neutralisation assay Neutralisation activity versus Wild Type, Omicron,	Sample Size not reported	Pfizer BNT162b2	▪ Two doses showed significantly reduced neutralisation titres against Omicron compared with the ancestral strain (>25-fold reduction, no neutralising activity observed). ▪ Three doses showed a 2.5-fold reduction in neutralising activity against Omicron compared with the ancestral strain. However, the third dose was associated with a 25-fold increase in neutralising antibodies against Omicron, relative to two doses.

	Other variants (Type not reported)			Note: Given the limited availability of information within the press release, as well as the use of pseudovirus as opposed to live virus in the assay, caution is urged in the interpretation of these data.
Roessler et al.[62] Preprint 11 Dec 2021	Live virus neutralisation assay Neutralisation activity of various combinations of primary vaccination regimens, booster doses, prior infection, hybrid immunity, against Alpha, Beta, Delta, Omicron.	N=105 Alpha (n=10) Beta (n=8) Delta (n=7) mRNA-1273 (n=10) ChAdOx1 (n=20) BNT162b2 (n=20) ChAdOx1 prime/BNT162 b2 boost (n=20) Infected and then vaccinated (n=5) Vaccinated and then infected (n=5)	▪ Moderna mRNA-1273 ▪ AstraZeneca ChAdOx1 ▪ Pfizer BNT162b2	The proportion of samples that provided neutralising activity against the Omicron variant for each of the studied combinations, were as follows: ▪ Two dose mRNA-1273 – 1/10 (10%) ▪ Two dose ChAdOx1 – 0/20 (0%) ▪ Heterologous ChAdOx1/BNT162b2 – 13/20 (65%) ▪ Two dose BNT161b2 – 9/20 (45%) ▪ Convalescent Alpha – 0/10 (10%) ▪ Convalescent Beta – 1/8 (12.5%) ▪ Convalescent Delta – 1/7 (14.3%) ▪ Infection and then Vaccinated – 5/5 (100%), but activity lower than against Delta ▪ Vaccinated and then infected – 5/5 (100%), but activity lower than against Delta
Dejnirattisai et al.[63] Preprint 11 Dec 2021	Live virus neutralisation assay Neutralisation activity versus Victoria (an early pandemic strain), Beta, Delta,	N=43 ChAdOx1 (n=22) BNT162b2 (n=21)	▪ AstraZeneca ChAdOx1 ▪ Pfizer BNT162b2	▪ Neutralising titres on sera from participants who had received homologous ChAdOx1 dropped to below the detectable threshold in the sera of 21 of 22 participants. ▪ Median neutralising titres in sera from participants who had received homologous BNT162b2 dropped 29.8-fold, with serum from one participant dropping below the detection threshold. ▪ The median neutralising titres against Omicron in sera from participants who had received BNT162b2 was higher than that in those who received ChAdOx1.

	Omicron			
Zhang et al.[64] Published: Emerging Microbes & Infections. 10 Dec 2021	Pseudovirus neutralisation assay Neutralisation activity versus Ancestral, Alpha, Beta, Gamma, Delta, Pseudotyped Omicron.	N=28 samples from convalescent patients infected with ancestral strain	Vaccination status not reported (Sample timings would suggest unvaccinated)	▪ Neutralisation activity against Omicron decreased 8.4 fold compared with the ancestral strain. ▪ Compared with the ancestral strain, the neutralisation activity against Alpha, Beta, Gamma and Delta was reduced about 1.2, 2.8, 1.6 and 1.6-fold respectively. ▪ Greater fold reductions against Omicron from baseline were observed in serum samples collected 1 month compared with 3 months after infection (10.6-fold reduction vs. 5.1-fold reduction) but neutralising activity against Omicron was similar in both scenarios (ED50 = 68 and 65) as baseline activity against the ancestral strain was higher 1 month post infection. Note: This study involved a relatively small sample size and the use of pseudo- as opposed to live virus.
Nemet et al.[65] Preprint 14 Dec 2021	Neutralisation assay (not clear whether live or pseudovirus) Neutralisation activity versus Ancestral, Beta, Delta, Omicron.	N=20 2 groups of HCWs: - 5 to 6 months after second dose BNT162b2. - 1 month after third dose BNT162b2.	Pfizer BNT162b2	▪ Sera after two doses did not produce any neutralisation activity against Omicron (estimated 20-fold reduction compared to ancestral strain), but continued to produce activity against Delta and the ancestral strain. ▪ Booster doses was found to increase neutralisation activity. ○ Neutralisation activity against Omicron increased by >100-fold between the second and third dose, though overall, there was still lower activity against Omicron after three doses compared with the ancestral strain, with an approximate 10-fold reduction observed Note: These data should be considered preliminary and interpreted with caution as a full report is not yet available.

Schmidt et al[66]
Preprint
 	
13 Dec 2021
	Pseudovirus neutralisation assay
	
	Longitudinal neutralising activity was examined against pseudotyped
		N=169 samples from 47 individuals
		
		Convalescent = 20
		2 dose BNT162b = 18
			▪ Moderna mRNA-1273
			▪ Pfizer BNT162b2
			▪ Janssen Ad26.COV2.S
				Note: Plasma samples were collected approximately one, 5-6 and 12 months after initial vaccination or infection.
				▪ Compared with the ancestral strain, neutralising activity for Omicron in convalescent individuals was, on average, reduced:
				  ○ 58-fold at approximately 1.2 months post infection.
				  ○ 32-fold after six months.
				  ○ 43 fold after 12 months. Neutralising activity increased in samples of convalescent individuals who were vaccinated, but decreased substantially in those who were unvaccinated.

	Omicron, ancestral strain, and an artificially generated antibody resistant spike called PMS20.	3 dose BNT162b2 = 18 Ad26.COV2.S = 19 Convalescent and vaccinated (1 or two doses of Pfizer/Moderna) = 17		▪ The mean fold reduction in neutralising activity against Omicron in individuals who received mRNA vaccines, compared with the ancestral strain, was 127 for Omicron ~1.3 months prior to sampling, and 27 fold five months after vaccination. ▪ Neutralising titers in the Janssen vaccines could not be meaningfully calculated as many plasma samples did not contain detectable neutralising activity. ▪ Vaccination of convalescent individuals substantially increased neutralising activity against Omicron. Specifically, in individuals with prior infection who were later vaccinated 154-fold increase in neutralisation activity against Omicron was observed, compared to pre-vaccination. ▪ Sera for those for those vaccinated with two doses of mRNA vaccines ~six months previously and then boosted with a BNT161b2 dose one month prior to sampling, demonstrated a 38-fold increase in neutralisation activity against Omicron, compared to five months post-second dose.
Basile et al. (67) Preprint 13 Dec 2021	Live virus neutralisation assay Neutralisation activity versus Ancestral, Delta, Omicron.	N=14 sera samples from 12 individuals (Australian HCW)	Pfizer BNT162b2	• Sera collected one, three, and six months post two doses of Pfizer-BioNTech BNT162b2 were found to have a limited ability to neutralise SARS-CoV-2 (generally), though neutralising antibody titres were boosted four weeks after a third dose. • Considering Omicron, there was a 4-fold reduction in median neutralising antibody titres in contrast to the wild-type.
Garcia-Beltran et al. (8) Preprint 14 Dec 2021	Pseudovirus neutralisation assay Neutralisation activity versus Ancestral, Delta, Omicron.	▪ Recent Vaccination n=65 ▪ Distant vaccination n=62 ▪ Distant Vaccination plus infection n=41 ▪ Booster n=71	▪ mRNA-1273 (Moderna) ▪ BNT162b2 (Pfizer) ▪ Ad26.COV2.S Janssen	▪ Individuals who were recently vaccinated with mRNA-1273 or BNT162b2 (mRNA vaccines) achieved substantially higher wild type neutralisation titres than those who received Ad26.COV2.S vaccines. ▪ Compared to the wild type, Omicron neutralisation was decreased among all four groups. More than 50% of mRNA vaccine recipients demonstrated a complete loss of neutralisation with Omicron. There was a 43-fold decrease in geometric mean neutralisation titres (GMNT) for mRNA-1273 (Moderna) and 122-fold for BNT162b2 (Pfizer). ▪ Recently boosted vaccinees exhibited potent neutralisation of Omicron variant pseudovirus that was only moderately decreased relative to wild type neutralisation (GMNT decrease of 6-fold for mRNA-1273, 4-fold for BNT162b2, and 13-fold for Ad26.COV2.S).

				▪ Immunity resulting from a combination of prior infection plus full distant vaccination was associated with greater neutralisation activity compared with distant vaccination alone
Lu et al. (68) Preprint 14 Dec 2021	Live virus neutralisation assay Neutralisation activity versus Ancestral, Beta, Delta, Omicron.	BNT162b2: N=25 Coronovac: N=25	▪ Pfizer (BNT162b2) ▪ Coronovac	▪ Only 20% and 24% of Pfizer-BioNTech BNT162b2 recipients had detectable neutralising antibody against two strains of the Omicron variant HKU691 and HKU344-R346K, respectively ▪ No Coronovac recipient had a detectable neutralising antibody titre against either Omicron isolate. ▪ For Pfizer-BioNTech BNT162b2 recipients, the geometric mean neutralisation antibody titres (GMT) of the Omicron variant isolates(5.43 and 6.42) were 35.7 to 39.9-fold lower than that of the ancestral virus (229.4).
Gruell et al. (69) Preprint 14 Dec 2021	Pseudovirus neutralisation assay Neutralisation activity versus Ancestral, Alpha, Delta, Beta, Omicron.	Vaccinated Infection naïve cohort: N=30 ▪ Early _full ▪ Late – Full ▪ Early - Booster Previously infected cohort N=30: ▪ Early ▪ One vaccine dose – hybrid immunity	BNT162b2 (Pfizer).	▪ All samples showed high levels of neutralising activity against the wild-type strain but decreased neutralising activity against other variants (Alpha, Delta and Beta). ▪ Only eight out of the 30 vaccinated individuals (27%) displayed detectable serum neutralising activity against Omicron with titres significantly lower than the Beta variant. ▪ Neutralising serum activity to the Omicron variant increased by more than 130-fold following the booster dose of BNT162b2, and was detectable in all 30 participants (100%). ▪ Serum neutralising activity against Omicron following booster immunisation was higher than neutralising titres against the wild type after two doses of BNT162b2. ▪ No, or weak, neutralising activity was identified against Omicron at the early time points after infection. At the late time point, in general there was a lack of neutralising activity against Omicron, although a slight increase was observed in some individuals. ▪ A single dose of BNT162b2 in previously infected individuals induced a large increase in neutralising activity one month after vaccination (hybrid time point).
Ikemura et al. (70) Preprint	Pseudovirus neutralisation assay	N=8 BNT162b2	BNT162b2 (Pfizer).	▪ Vaccine sera obtained from eight persons vaccinated with the Pfizer-BioNTech vaccine BNT162b2 showed ~27-fold lower neutralisation titers against Omicron than the D614G mutation (parent virus).

14 Dec 2021	Neutralisation activity versus Ancestral, Alpha, Delta, Omicron.	Previously infected with Alpha n=Not reported Previously infected with Delta n=11		▪ Vaccine sera from those previously infected with SARS-CoV-2 showed lower titres for Omicron versus the ancestral strain. (47.1 fold and 17.4 fold lower titres compared with previous Alpha and Delta infection, respectively).

Use of laboratory neutralisation studies to estimate vaccine effectiveness

As of 14 December 2021, several studies were published which aimed to estimate vaccine effectiveness against Omicron based on the results of neutralisation assays. An important limitation of these studies is that they involved modelling based primarily on the correlation between neutralising antibody titres and protection against symptomatic disease, which has not been clinically established. They also exclude the contribution of other components of the immune system (for example, cellular immunity), which are known to contribute to protection against severe disease.

- A preprint study by **Gardner and Kilpatrick** published on 12 December 2021,[71] estimated vaccine effectiveness against Omicron based on the reductions in neutralisation activity observed in three assay studies previously mentioned.[58-60] The authors considered neutralising antibody titres as surrogates for vaccine effectiveness against SARS-CoV-2 infection, symptomatic disease and hospitalisation, and used correlations observed for other variants of concern to model the relationship.
    - The researchers estimated that the 40-fold estimated reduction in neutralising antibody titres for Omicron (observed in laboratory studies) was associated with a **four to five-fold increased relative risk of hospitalisation** and a **seven to ten-fold increased relative risk of symptomatic disease** for mRNA vaccinees, compared with the ancestral strain.
- A preprint study by **Volkov** published on 11 December 2021,[72] similarly used changes in neutralisation activity against Omicron to estimate the impact of the variant on vaccine effectiveness, specifically for Pfizer BNT161b2. Assuming 25-, 80- and 120-fold reductions in neutralisation activity, the researcher estimated vaccine effectiveness against symptomatic Omicron infection to be approximately 66%, 48% and 42%, respectively after a second dose of vaccine, and 81%, 67% and 61%, respectively after a third dose of vaccine. (Table 4)

Table 4: Summary of Volkov (preprint) findings on Pfizer vaccine effectiveness, based on assumed reductions in neutralisation activity [72]

	Vaccine Effectiveness		
Outcome:	25-fold reduction	80-fold reduction	120-fold reduction
Effectiveness for up to five months, starting 2-4 weeks **after the second dose** of the initial vaccination schedule	66% (95% CI: 42 to 86)	48% (95% CI: 25 to 72)	42% (95% CI: 20 to 66)
Effectiveness for up to five months, starting 2-4 weeks **after the third dose** (booster dose)	81% (95% CI: 59 to 95)	67% (95% CI: 43 to 87)	61% (95% CI: 37 to 82)

- A preprint meta-analysis by Khoury et al., published on 14 December 2021, synthesised the results of the above studies by Wilhelm et al., Sheward et al., Cele et al. and Pfizer/BioNTech (press release) with the aim of predicting vaccine efficacy against Omicron.[73] The authors concluded the following:
    - Six months after primary immunisation with an mRNA vaccine, efficacy against Omicron was estimated to have waned to around 80% against severe disease and 40% against symptomatic disease.
    - A booster dose with an existing mRNA vaccine was concluded to have the potential to raise efficacy against Omicron to 86.2% (95% CI: 72.6 to 94) against symptomatic infection and 98.2% (95% CI: 90.2 to 99.7) against severe infection.
    - The authors stated that these estimates were in close agreement with recent vaccine efficacy estimates as published by the UKHSA (see epidemiological research section, above).

Assessments by authorities

- Advice from the UK Joint Committee on Vaccination and Immunisation (JCVI) was issued on 29 November 2021,[74] and noted that the extent of protection that existing COVID-19 vaccines would provide against the Omicron variant was, at this time, unknown, and that protection against infection and serious diseetase may differ for the Omicron variant. JCVI advised that protection be optimised, ahead of a wave of infection, by accelerating deployment of vaccines, and particularly, the expansion of access to booster vaccines for all adults
- The US Food and Drug Administration issued a statement on 30 November 2021, noting that they were evaluating the potential impact of the Omicron variant on current vaccine effectiveness. The FDA urged the public to ensure that they are adequately vaccinated and that they avail of booster doses as required.[75]
- On 15 December 2021, the ECDC published a rapid risk assessment with the following points [36]:
    - Early evidence from in vitro neutralisation studies, not yet peer-reviewed, showed a **reduced neutralisation capacity of sera** from vaccine recipients and convalescent sera against Omicron as compared to other SARS-CoV-2 variants, although large uncertainties persist at this time.
    - Sufficient real-world data on effectiveness of vaccines authorised in the EU against Omicron were not yet available. According to the evidence that was available at this time, booster doses would increase protection against severe outcomes caused by Delta, and **preliminary evaluations also suggested boosters could increase protection against Omicron**, with an expected higher population impact if the booster dose is given within a short interval of time to most of the adult population.
- The **UKHSA** risk assessment for SARS-CoV-2 variants, published 9 December 2021,[32] and the UKHSA Technical Briefing no. 31, published on 10 December 2021,[10] made the following classifications regarding the **risk of immune evasion by Omicron** (including evasion of natural and vaccine-derived immunity) and **risk of reinfection**, respectively:
    - **Omicron displays a reduction in immune protection against infection** (no data regarding severe disease)**.** This risk was

assigned **'red' status,** with **high certainty.** This assessment was based on neutralisation data from multiple laboratories and preliminary assessment of real-world vaccine effectiveness in the UK (see above subsections on laboratory and epidemiological research). It was considered, however, that there were insufficient data to make any assessment of protection against severe disease.
    - There was considered to be no evidence of increased reinfection risk at the population level at the time of the assessment, but preliminary analyses indicated approximately **three- to eight-fold increased risk of reinfection with the Omicron variant**. (Further information on these analyses is provided in the above subsection on epidemiological research)

- The technical brief by the WHO on enhancing readiness for Omicron, published 10 December 2021,[49] noted that preliminary evidence from epidemiological, modelling and laboratory studies, suggests that humoral immunity is less protective against infection by Omicron than against other variants. The study by Pulliam et al. was cited as showing that the likelihood of reinfection with Omicron was higher than what would have been expected with previous variants, and early findings from unpublished modelling studies (personal communication) also suggested some level of immune evasion against infection is likely. The WHO stated that there remained significant uncertainty around the extent to which immune evasion or intrinsic increased transmissibility could explain current trends.

Treatment efficacy and effectiveness

Background

As of 13 December 2021, four treatments which were developed specifically to treat COVID-19 have been authorised by the EMA. These include the antiviral drug remdesivir (Veklury®) and three monoclonal antibody (mAb) treatments. The three mAb treatments include the single agent products regdanvimab (Regkirona™) and tocilizumab (RoActemra®), and the combination antibody treatment imdevimab and casirivimab (Ronapreve™ or 'REGEN-COV'). Marketing authorisation has been submitted to the EMA for several additional treatments: anakinra (Kineret®); molnupiravir (Lagevrio®); baricitinib (Olumiant®); sotrovimab (Xevudy™).

Table 5 provides information as to the proposed or available treatments for COVID-19, and the degree to which their efficacy against Omicron is expected to differ. Generally, treatments which target the SARS-CoV-2 virus itself, and specifically, regions of the virus in which the Omicron variant possesses mutations, may

experience altered efficacy against Omicron. Efficacy of treatments which target the host immune response rather than the virus (for example, non-specific treatments such as corticosteroids) will not be affected.

Table 5: Summary of Omicron-related information for proposed or available treatments for COVID-19 which have been assessed or considered by the European Medicines Agency (EMA)

Agent (brand name)	EMA status	Indication	Targets SARS-CoV-2	Targets host immune response	Information available in context of Omicron
remdesivir (Veklury®)	Authorised	Treatment of severe COVID-19 pneumonia	Yes – inhibits RNA synthesis, thus inhibiting viral replication	-	Manufacturer (Gilead) statement – no adverse impact anticipated. [76]
imdevimab and casirivimab (Ronapreve™ / REGEN-COV™)	Authorised	Treatment of COVID-19 in those at increased risk of progressing to severe COVID-19 Prevention of COVID-19	**Yes** – **antibody binds** to RBD of virus spike protein	-	Manufacturer (Regeneron) statement expressing concern regarding reduced efficacy.[77] Wilhelm et al. study indicating reduced neutralisation activity against Omicron.[60] Cao et al. psuedovirus neutralisation assay demonstrated Omicron escape.[78] Sheward et al. study indicated reduced neutralisation activity against Omicron for both imdevimab and casirivimab.[59]

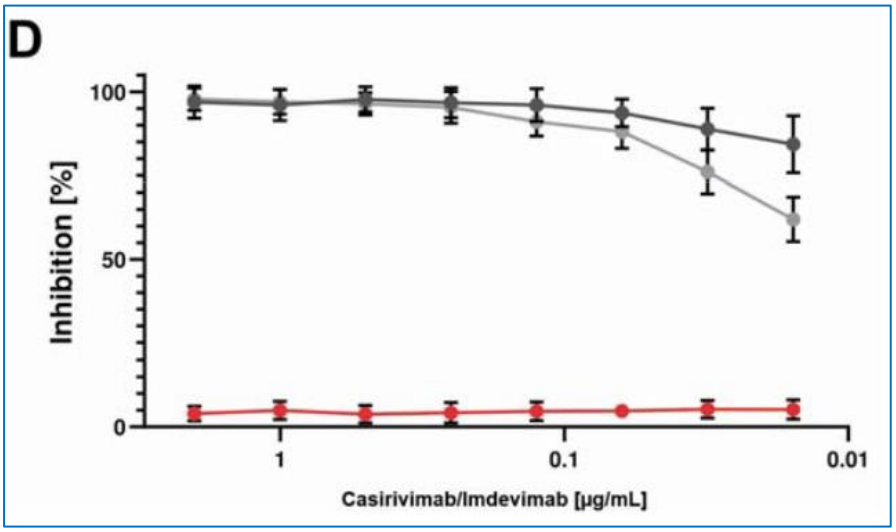
Agent (brand name)	**EMA status**	**Indication**	**Targets SARS-CoV-2**	**Targets host immune response**	**Information available in context of Omicron**
					Ikemura et al.[70] and Gruell et al.[69] studies indicate failure to neutralise Omicron.
regdanvimab (Regkirona™)	Authorised	Treatment of COVID-19 in those at increased risk of progressing to severe COVID-19	**Yes** – **antibody binds** to RBD of virus spike protein	-	No information identified from manufacturer.
anakinra (Kineret®)	Under evaluation	Treatment of COVID-19 in those at increased risk of progressing to severe COVID-19	-	Yes – immunosuppressant	Not expected to be affected, as does not target SARS-CoV-2. No information identified from manufacturer.
molnupiravir (Lagevrio®)	Under evaluation [79]	Treatment of COVID-19 in those at increased risk of progressing to severe COVID-19	Yes – oral antiviral which inhibits replication by inducing widespread mutations in RNA	-	Manufacturer (Merck) statement – no reduction in effectiveness anticipated based on currently available genomic information.[80]
baricitinib (Olumiant®)	Under evaluation	Treatment of COVID-19 in those at increased risk of progressing to severe COVID-19	-	Yes – anti-inflammatory	Not expected to be affected, as does not target SARS-CoV-2.
tocilizumab (RoActemra®)	Authorised	Treatment of severe COVID-19	-	Yes - immunomodulator	Not expected to be affected, as does not target

Agent (brand name)	EMA status	Indication	Targets SARS-CoV-2	Targets host immune response	Information available in context of Omicron
					SARS-CoV-2. (As stated by WHO).[1]
sotrovimab (Xevudy®)	Under evaluation– opinion expected by Jan[81] (Received emergency use authorisation in UK on 2 Dec 2021)	Treatment of mild-to-moderate COVID-19 in patients at increased risk for death or hospitalisation	**Yes** – **antibody binds** to RBD of virus spike protein	-	Manufacturer (GSK and Vir Biotechnology) statement that sotrovimab is effective against Omicron in pseudovirus tests.[82] Reduced neutralising activity observed by Cao et al.[78] Neutralising activity observed to be preserved (relative to other antibodies) in studies by Gruell et al.[69] and Ikemura et al.[70]
Bamlanivimab and etesevimab	Agent was previously under investigation by the CHMP as of March 2021, however the rolling review was ceased as the application was withdrawn. [83]	Treatment of mild-to-moderate COVID-19. Post-exposure prophylaxis for prevention of COVID-19 in persons who are neither fully vaccinated nor expected to build up enough of an immune response to the complete COVID-19 vaccination, where individuals have been exposed or are at high risk of exposure to those infected with SARS-COV-2.	Yes – binds to spike protein of SARS-CoV-2 at two different sites.	-	Two studies have indicated failure to neutralise Omicron.[69, 78] Sheward et al. found that higher concentrations were required to achieve neutralising activity for Omicron compared to the ancestral strain.[59]

Laboratory research on treatment efficacy

- **Wilhelm et al.** published (preprint) on 8 December 2021 the results of a **live virus neutralisation assay** which examined antibody-mediated neutralisation efficacy against live SARS-CoV-2 variants Delta and Omicron. [60] The currently used monoclonal antibody combination **imdevimab and casirivimab (Ronapreve™ or 'REGEN-COV')** efficiently prevented Delta infection, but **failed to neutralise Omicron**, which the authors speculated may be a consequence of amino acid substitutions. The authors suggested that **genotyping of SARS-CoV-2 may be needed before initiating treatment** with monoclonal antibodies such as imdevimab and casirivimab. Ronapreve™ (REGEN-COV) is indicated for the prevention of severe COVID-19 in those who are at increased risk of severe disease, and may also be used to prevent COVID-19.

Figure 4: Neutralisation efficacy of monoclonal antibodies imdevimab and casirivimab against SARS-CoV-2 Omicron (red), and Delta (light grey)- reproduced from Wilhelm et al.[60]



Wilhelm et al. Figure 1,D: **Neutralisation efficacy of monoclonal antibodies imdevimab and casirivimab** against SARS-CoV-2 Omicron (red), B, i.e, parent strain (dark grey), and Delta (grey). *Values represent reciprocal dilutions of SARS-CoV-2 variants Delta (grey), parent strain (dark grey), and Omicron (red) micro-neutralisation titers resulting in 50% virus neutralization (NT50). The indicated concentrations of 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.*

- Cao et al. published (preprint) on 9 December 2021 the findings of a psuedovirus neutralisation assay.[78] This study examined the neutralising

efficacy of nine (approved or experimental) SARS-CoV-2-targeted clinical antibody drugs, against Omicron, Delta, Beta, Gamma, Alpha and the ancestral strain. Of the nine examined neutralising antibody drugs (nAbs):

- Omicron escaped the following: etesevimab and bamlanivimab (LY-CoV016/LY-CoV555 cocktail), REGN-COV ('Ronapreve') cocktail (REGN-10933 and REGN-10987, that is, casirivimab and imdevimab), cilgavimab and tixagevimab (that is, 'Evusheld', AZD1061/AZD8895 cocktail) and amubarvimab (BRII-196).[84]
- Sotrovimab (that is, VIR7831) and DXP-604 were observed to provide neutralising activity against Omicron though at reduced efficacy.
- All demonstrated efficacy against the ancestral strain and all other VOCs, with the following exceptions: etesevimab and bamlanivimab (LY-CoV016 and LY-CoV555) were both escaped by Gamma and Beta variants; bamlanivimab (LY-CoV555) was escaped by Delta, and etesevimab (LY-CoV016) had reduced efficacy against the Alpha variant.

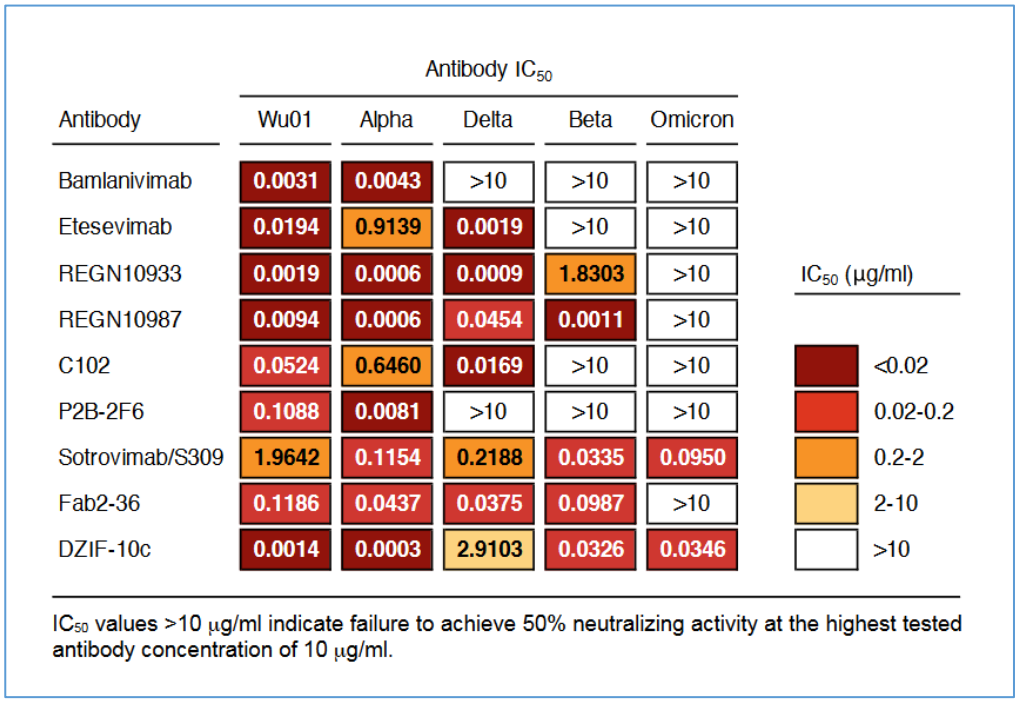
- On 12 December 2021, Sheward et al. released preliminary data from assays that assessed pseudovirus neutralisation by nine in-house monoclonal antibodies (S2H97, REGN-10933 (casirivimab), REGN-10987 (imdevimab),S2E12, G32A4, S309, LY-CoV016 (etesevimab), LY-CoV555 (bamlanivimab), and A23-58.1).[59] The Omicron variant was assessed in comparison with the ancestral strain (D614G). These preliminary data indicated that higher concentrations were required for all assessed monoclonal antibodies to achieve neutralising activity for Omicron compared to the ancestral strain. Antibody neutralising activity for Omicron ranged from having a two-fold (S2H97 and S309) to greater than a 1,400-fold (LY-CoV555) reduction, depending on the antibody. The preliminary data were found to be strongly concordant with previous research on five of the nine antibodies assessed in this study. However, the authors highlighted that independent corroboration is required for proper interpretation of the results.

- On 14 December 2021 Ikemura et al.[70] published a preprint which used pseudovirus neutralisation assays to examine the efficacy of neutralising antibodies. Omicron was found to escape the cocktail of imdevimab and casirivimab, whereas the efficacy of sotrovimab against Omicron was

found to be similar to that against wild-type. It was noted that sotrovimab targets a conserved region of Omicron and thereby avoids escape.

- On 14 December 2021 Gruell et al. published a preprint which used pseudovirus neutralisation assays to determine resistance among SARS-CoV-2 variants to different neutralising monoclonal antibodies in clinical use.[69] These included, amongs others, REGN10933 (casirivimab), REGN10987 (imdevimab), bamlanivimab, etesevimab and sotrovimab. Omicron escaped the majority of these antibodies, as depicted in Figure 5.

Figure 5: Figure from Gruell et al. - SARS-CoV-2-neutralising activity of monoclonal antibodies.[69]



Manufacturer assessments

- Remdesivir, is expected to continue to be active against the Omicron variant, based on preliminary analysis (statement posted 1 December 2021) of genetic information, as conducted by the manufacturer, Gilead.[76]

- The monoclonal antibody treatment casirivimab and imdevimab (REGEN-COV™, Ronapreve), is currently being evaluated by the manufacturer, Regeneron, regarding the potential impact of Omicron on the efficacy of this treatment.[77] A statement from Regeneron noted suspected reduced

efficacy: "*Prior in vitro analyses and structural modeling regarding the individual mutations present in the Omicron variant indicate that there may be reduced neutralisation activity of both vaccine-induced and monoclonal antibody conveyed immunity, including the current REGEN-COV antibodies. Further analyses are ongoing to confirm and quantify this potential impact using the actual Omicron variant.*"

- Preclinical (in vitro) findings were announced on 7 December 2021 for the potential efficacy of the monoclonal antibody treatment **sotrovimab** (GSK) against the Omicron variant.[85] Preclinical data were generated by the manufacturer through pseudo-virus testing of the combined known mutations of the Omicron variant. These data suggest that sotrovimab is expected to retain activity against all tested variants of concern, including Omicron.[82]

- Merck, the manufacturer of the antiviral drug molnupiravir, stated on 7 December 2021, that molnupiravir is expected to retain effectiveness against the Omicron variant.[80] This is based on the treatment's mechanism of action and the currently available genomic information.

- Brii Biosciences, the manufacturer of a neutralising antibody combination therapy recently (8 December 2021) approved in China,[86] (amubarvimab/romlusevimab), stated on 12 December 2021 that laboratory studies found this treatment retains activity against Omicron, though one of the antibodies showed a substantial drop in activity when tested alone (Note: Cao et al., above, found that amubarvimab was escaped by Omicron).[70]

- On 14 December 2021, Pfizer announced results of a phase 2/3 trial of PAXLOVID™ (nirmatrelvir and ritonavir tablets), which was investigated for its efficacy in reducing hospitalisation or death in non-hospitalised, high-risk adults with COVID-19.[61] As part of this announcement, Pfizer noted that recent in vitro data confirmed that nirmatrelvir is a potent inhibitor of an Omicron protease, which partly indicated that PAXLOVID™ would retain antiviral activity against omicron.

Advice and statements from authorities:

- As noted by the **WHO** on 28 November 2021, treatments such as corticosteroids and IL-6 Receptor blockers will still be effective for treating patients with severe COVID-19 regardless of variant status, as these treatments are not directed towards the SARS-CoV-2 virus.[1] The WHO

noted that targeted treatments (those directed towards SARS-CoV-2) will need to be assessed to determine their effectiveness against the Omicron variant. In the 'Enhancing Readiness for Omicron: Technical Brief and Priority Actions for Member States', published 10 December 2021, the WHO state that monoclonal antibodies will need to be tested individually, for their antigen binding and virus neutralisation.[49]

- The **UKHSA** risk assessment for SARS-CoV-2 variants, published 3 December 2021,[32] stated that Omicron mutations are suggestive of reduced effectiveness of a treatment in clinical use in the UK; the risk assessment noted that, based on structural modelling the mutations present in Omicron were likely to reduce the binding of most available therapeutic monoclonal antibodies (for example, 'Ronapreve'/REGEN-COV™, see above). The UKHSA noted that, on the same basis, the mutations are unlikely to affect current small molecule antivirals (for example, remdesivir). At the time of this assessment, there were no laboratory or clinical data to support these predictions. However, since this assessment, studies such as that by **Wilhelm et al.** (above) published as a preprint,[60] provided data which supported the concern regarding reduced efficacy of therapeutic monoclonal antibodies.

Test accuracy

- The large number of mutations identified in the spike gene of Omicron raises concerns for detection by some laboratory tests. As noted by Gu et al., these mutations may give rise to false-negative results in single target diagnostic RT-PCRs specific for the S gene.[87]
- The Foundation for Innovative New Diagnostics (FIND) is actively and independently monitoring and verifying information on the impact of Omicron on diagnostic test performance.[88]
    - FIND notes that, for the majority of molecular tests (RT-PCR), the overall sensitivity of detection is not expected to be impacted when the infection is due to Omicron, as these tests have multiple gene targets. For antigen tests, the potential impact on performance is less clear.
- The FDA issued a statement on 30 November 2021 stating that, on preliminary review, the FDA believes that high-volume polymerase chain reaction (PCR) and antigen (rapid) tests widely used in the US show low likelihood of being impacted by the Omicron variant. Since 9 December 2021,

the FDA has issued updates that two tests have reduced ability to detect Omicron:[89]

- The Meridian Bioscience, Inc. Revogene SARS-CoV-2 test: As this test is a single target test that targets a portion for the N-gene where deletions occur with Omicron, it is expected to fail to detect Omicron. Meridian Biosciences has not yet distributed this test and does not intend to distribute the test within or outside the US until this issue is resolved.[90]
- Tide Laboratories DTPM COVID-19 RT-PCR test (Emergency Use Authorisation under FDA): The single genetic target of this test covers the portion of the N-gene where deletions occur in Omicron. Since this is a single target test, the test is expected to fail to detect Omicron, resulting in false negative results.[90]

- Several manufacturers of COVID-19 tests have issued statements (Abbott, 27 November 2021, Hologic, 29 November 2021, Roche, 3 December 2021) to the effect that, following analysis of genetic sequences of Omicron, they expect that their SARS-CoV-2 tests correctly identify the Omicron variant as SARS-CoV-2.
- The UKHSA Technical Briefing no. 31 (published 10 December 2021) stated briefly that the UKHSA has performed an initial laboratory validation of the current lateral flow devices (RADTs) in use by the NHS Test and Trace programme and that preliminary data assessed these devices as being as effective at detecting Omicron as they were for Delta.[10]

Sublineage designation and impact on detection

- On 7 December 2021, the Pango Network (who are responsible for identifying and naming distinct sublineages of SARS-CoV-2),[91] designated two genetically distinct sublineages of Omicron (B.1.1.529) as BA.1 and BA.2. The prefix BA is now an alias for B.1.1.529. The proportion of Omicron cases that belong to the two sublineages is currently unknown. Preliminary analysis suggests that the:
  - BA.1 sublineage typically exhibits SGTF (S-Gene Target Failure) which can be detected using certain RT-PCR assays (for example, the TaqPath™ RT-PCR assay)
  - BA.2 sublineage does not exhibit SGTF, and so will not provide an S-gene drop out signal using certain RT-PCR assays.

- The implications of the BA.2 sublineage are that, where this sublineage is prevalent, reporting of SGTF using RT-PCR (with the intention of efficiently

triaging cases for full genomic sequencing) would result in an underestimate of the prevalence of Omicron. For example, the TaqPath™ RT-PCR assay is able to identify SGTF when one of the three targeted genes (the S gene) is not detected. This can therefore be used as an early marker (within several hours) for the prevalence of variants exhibiting this trait, pending genomic sequencing confirmation (generally several days to complete). However, as noted surveillance using SGTF will not capture the BA.2 sublineage.

Overall assessments of risk and impact

- As noted in relevant subsections of this report, the most recent **UKHSA risk assessment** for Omicron, published 9 December 2021,[32] provided the following risk classifications for four indicators of interest:

Indicator	Red, amber or green status (red = highest risk)	Confidence level	Assessment
Growth advantage	Red	**High**	Omicron is displaying a growth advantage over Delta
Transmissibility	Amber	Low	Omicron is at least as transmissible as Delta
Immune evasion (from natural and vaccine-derived immunity)	Red	**High**	Omicron displays a reduction in immune protection against infection (though NO data regarding severe disease)
Infection severity			Insufficient data

- The **WHO** published on 10 December 2021 a report entitled 'Enhancing Readiness for Omicron (B.1.1.529): Technical Brief and Priority Actions for Member States'.[49] This report provided a summary of the mutations associated with Omicron, the growth advantage associated with Omicron versus Delta, the current state of knowledge regarding clinical severity, the current data regarding vaccine effectiveness and risk of reinfection, the diagnostic accuracy of commonly used tests in the context of Omicron, and the efficacy of therapeutic interventions. The report stated that the 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. The report noted that public health advice is based on current information and will be tailored as more evidence emerges around those key questions.
    - The report stated that **the overall risk related to Omicron remains very high** as the global risk of COVID-19 remains very high overall and as preliminary evidence suggests potential humoral immune escape against infection and high transmission rates, which

could lead to further surges with severe consequences. This risk assessment will be updated as more information becomes available.

- Barnard et al. published on 11 December 2021,[92] as a preprint, a modelling study of the potential consequences of the Omicron variant on transmission and health outcomes in England, using modelling approaches from the **London School of Hygiene and Tropical Medicine** (previously used to inform UK policy). Scenarios varied the extent of immune escape, the effectiveness, uptake and speed of COVID-19 booster vaccinations, and the reintroduction of control measures. The results of the study suggested that Omicron has the potential to cause substantial surges in cases, hospital admissions and deaths in populations with high levels of immunity, including England, and that the reintroduction of additional non-pharmaceutical interventions might be required to prevent hospital admissions exceeding the levels seen in England during the previous peak in winter 2020–2021.
    - Under the most **optimistic** scenario (low immune escape of Omicron and high effectiveness of boosters), a wave of infection was 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 1 December 2021 and 30 April 2022, if no additional control measures were implemented over and above the 'Plan B' policy in England.
    - In this optimistic scenario, the authors concluded that the introduction of control measures early in 2022 which are equivalent in stringency to Step 2 of the UK roadmap (which involves restrictions on indoor hospitality, closure of some entertainment venues, and restrictions on gathering sizes) would be sufficient to substantially control this wave, reducing hospitalisations by 53,000 and deaths by 7,600.
    - The most **pessimistic** scenario (high immune escape and lower effectiveness of boosters) projected a wave of infection which was considered likely to lead to a peak in hospital admissions approximately twice as high as the peak seen in January 2021, if no additional control measures were taken, with 492,000 (418,000–537,000) hospitalisations and 74,800 (63,500–82,900) deaths.
    - In this pessimistic scenario, the authors estimated that stronger measures might be required to maintain the peak number of hospital admissions below the January 2021 peak.

- An update from the **Norwegian National Institute of Public Health (NIPH)** on 13 December 2021 indicated that there is concern over the greater transmissibility of the Omicron variant due to its ability to evade immunity following infection or vaccination.[37] The report summarised studies from Britain and South Africa showing reduced effectiveness of vaccination, though no episodes of severe disease were recorded. This reduced effectiveness was highlighted as a cause for concern as it may result in a large proportion of the population being at risk of infection and continuation of pressures on the health service.
    - The NIPH stated that there is an **urgent need to curb the COVID-19 epidemic with significant measures**. The stated aim was to avoid the Omicron variant causing an epidemic wave that results in a large disease burden and overloads the health service.
    - The report found: *"A lack of action now can result in a **major negative impact on society**, not just on the healthcare services in hospitals and the municipalities. High sickness absence will affect many sectors. The healthcare service and other sectors must review their continuity plans."*

- Le Rutte et al. published (preprint),[93] on 14 December 2021, an assessment of the impact of Omicron on SARS-CoV-2 dynamics and public health burden. The assessment included the use of the OpenCOVID individual-based model of SARS-CoV-2 transmission and COVID-19 illness. The authors concluded that:
    - Infectivity and immune evasion were identified as the main drivers behind Omicron's potential dominance, with negligible effect from increasing severity.
    - Expanded vaccination that includes a third-dose for adults, and child vaccination strategies, was projected to have the biggest public health benefit for a highly infective, highly severe variant with low immune evasion capacity.
    - **A highly immune-evading variant that becomes dominant would likely require alternative measures for control, such as strengthened physical distancing measures, novel treatments, and second-generation vaccines**, as they become available**.**
- On 15 December 2021, the ECDC published an updated rapid risk assessment: *'Assessment of the further emergence and potential impact of the SARS-CoV-2 Omicron VOC in the context of the ongoing Delta VOC transmission in the EU/EEA, 18th update'*.[36] Updated forecasts, informed by

the latest evidence on Omicron epidemiology, transmissibility, severity, and immune escape, were included. In summary:

- Delta was noted as remaining the most prevalent variant as of 15 December 2021, but given community-associated spread of Omicron occurring in the EU/EEA at this time, **Omicron was expected to become dominant in early 2022**, based on mathematical modelling predictions. The probability of further spread of the Omicron variant in the EU/EEA was therefore assessed as '**very high'**.
- Evidence to date raised concerns that vaccine effectiveness against transmission may be significantly reduced with Omicron. The ECDC considered that, **even in the case of lower severity** of Omicron disease, **a steep, exponential rise in cases caused by Omicron would result in an increasing number of cases with severe disease**. As EU/EEA countries are still being impacted by the Delta wave, **a further rise in hospitalisations could quickly overwhelm healthcare systems.** The risk associated with the impact of the spread of Omicron was therefore assessed as '**very high'**.
- The results of mathematical modelling performed by the ECDC suggested that **strong and immediate reductions in contact rates would be required** to avoid a high spike in cases caused by Omicron and to keep the COVID-19-related burden manageable in the short term, even with an immediate acceleration of vaccine roll-out.
- In response to high incidence of Delta, the ECDC considered that non-pharmaceutical interventions **(NPIs) should continue to be implemented by all countries** and, considering the likely upcoming dominance of Omicron, **these would need to be further strengthened without delay.** The immediate strengthening of NPIs would slow the spread of Omicron, to allow countries to gain time for further vaccination roll-out and to prevent a sudden high impact from the spread of this variant. **Without reduction of contact rates through the implementation of NPIs and increased booster vaccination, levels of transmission could rapidly overwhelm EU/EEA healthcare systems**.

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