



Date: 5 December 2022

# SARS-CoV-2 Variants of Concern Update

## Executive Summary

*Note: New information in this report is shown in red text.*

Section updated: 1 December 2022

In the second half of 2022, many new Omicron sub-variants have been reported. These variants demonstrate convergent evolution which is a process whereby variants from different lineages accumulate similar mutations. Mutations in the spike protein appear to be responsible for the enhanced characteristics of these variants, compared to previous Omicron variants.

Although many of these new sub-variants demonstrate a transmission advantage over earlier sub-variants (which can come from increases in innate transmissibility or from immune evasion), there is currently no evidence of an increase in severity of disease caused by these variants.

### New information in this report includes:

- A number of convergent subvariants (that is, different subvariants that have accumulated similar mutations) are displaying a growth advantage relative to BA.5.2 in the UK.(1) Estimated weekly growth rates for variants in the UK (relative to BA.5.2, at 9 November 2022) included 56.9% for XBB, 48.5% for BQ.1.1, 38.6% for BQ.1 (excluding BQ.1.1) and 44.7% for BN.1.
- Sequences submitted globally continue to show similar trends compared to recent weeks.(2) BA.5 descendent lineages remain dominant (72.1% of sequences) followed by BA.2 descendent lineages (9.2%). BA.4 descendent lineages continued to decline in prevalence (3%). There was a rise in BQ.1 sequences to 23.1% of sequences, and XBB sequences also increased, rising to 3.3%.
- A single study from the USA has estimated the vaccine effectiveness (VE) of BA.4/5 bivalent mRNA vaccines (as a third, fourth or fifth dose). Absolute VE against symptomatic infection (that is, compared to those who have received no doses of any COVID-19 vaccine) against symptomatic SARS-CoV-2 infection ranged from 22% (95% CI: 15-29) in those aged 65 and older, to 43% (95% CI: 39-46) in those aged 18-49 years (maximum of 2.5 months after the bivalent vaccine dose).(3) The study did not have a comparison group receiving the dose as an original formulation monovalent vaccine, so these data do not show whether the effect of the BA.4/5 dose is superior to the original formulation.
- Monoclonal antibody treatments: laboratory-based studies suggest that monoclonal antibody treatments (such as Evusheld and bebtelovimab) may be ineffective against some emerging variants. (4-7) The affected variants are not currently (at 1 December 2022) predominant in New Zealand (e.g. BQ.1.1 and XBB). Clinical effectiveness data for Evusheld (Aotearoa New Zealand's most used monoclonal antibody treatment) are available for a period of BA.1 predominance, (8) but not for later variants.



### New signals:

- XBF is a BA.5.2.3 and CJ.1 (a BA.2.75 sub-lineage) recombinant. Its spike is identical to CJ.1, and additional mutations (from BA.2.75) are S:486P, S:R346T, S:F490S. (9) XBF is growing in Australia and Denmark.(9) Appears to be growing less rapidly in South Asia than CH.1.1 (another BA.2.75 sub-lineage),(9) but epidemiology could be different in New Zealand. No data have yet emerged about the severity of XBF disease.



# Section 1 Key Omicron information

## Circulating variants across Aotearoa New Zealand

Section updated: 01 December 2022

The Institute of Environmental Science and Research (ESR) COVID-19 Genomics Insights (CGI) report was last produced on 01 December 2022, with data from the period of 12 - 25th November). (10) The percentage of sequenced cases (community, including hospital, and "border" cases combined) that were of each variant in this period are shown in figure 1 (noting that ~2.0% of all cases were sequenced in this fortnight, and only variants with a frequency 1% or higher are shown). Additionally, of the 933 cases sequenced, there were 20 XBC cases identified (non-hospitalised). (10)

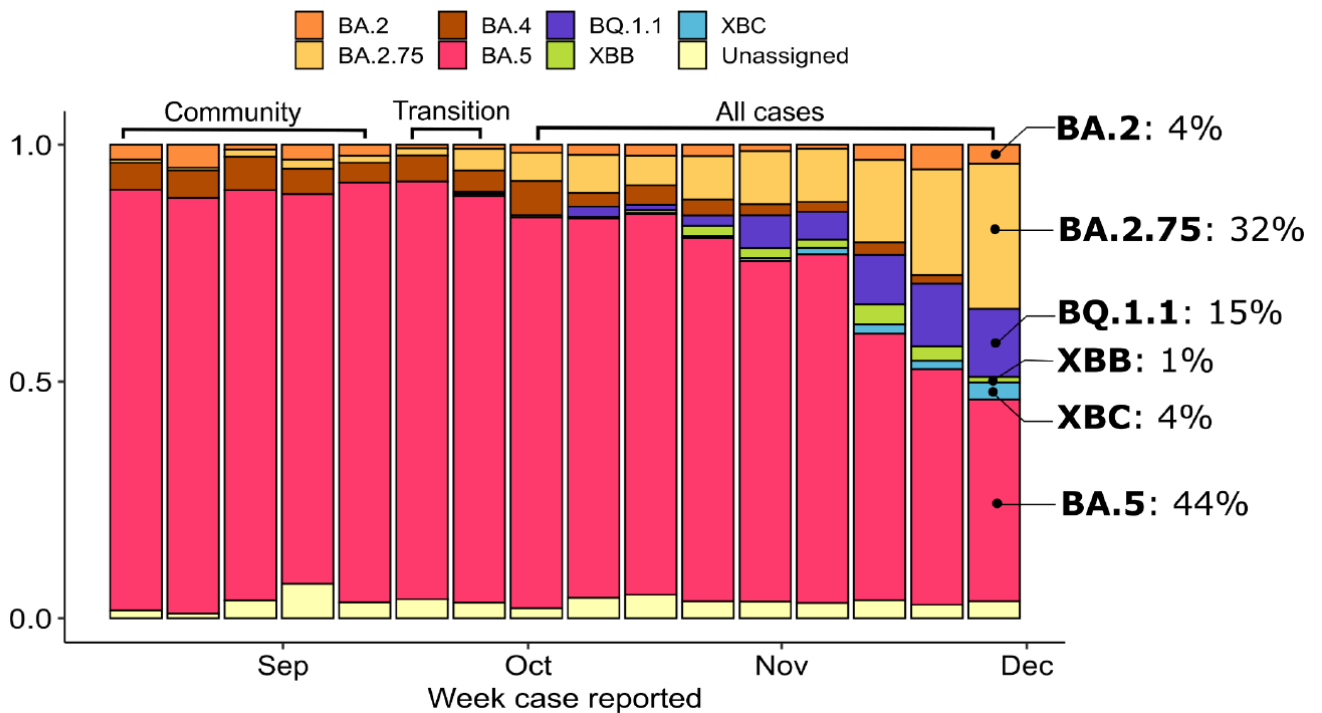


Figure 1: Frequency of SARS-CoV-2 variants in New Zealand each week. Only variants with a frequency above 1% are shown. Data is subject to change as samples may still be added to the most recent two-week period. Only data from community cases were used until September 2022, while in the "transition" period, cases known to be associated with the border are removed. Data from all cases (community, including hospital, and border) are used since October. Source: [ESR link](#)

BA.2.75 and BQ.1.1 have grown relative to BA.5 in recent weeks, and the growth of BA.2.75 is driven by several distinct descendants of the original BA.2.75 lineage (including CH.1.1, BA.2.75.8 and BM\* (BM sub-lineages). (10)

A publicly accessible version of the genomic report produced by ESR is available [here](#).



Wastewater sampling is less prone to selection bias than samples from cases (which, for example, overrepresents hospitalised cases and under-represent some regions in New Zealand). Wastewater surveillance (31 October – 13 November 2022) has seen similar patterns in variants to that seen in cases. BA.4/5 remains the dominant variant in wastewater (aggregate ~66%). However, detections of BA.2.75 and sub-lineages (~19%), BQ.1.1 (~10%) and XBB (~5%) are trending upward. (11) The publicly accessible ESR Wastewater surveillance dashboard can be accessed [here](#).

## Current overall variant risk status

*Section updated: 1 December 2022*

Subvariants detected in cases in New Zealand such as BQ.1.1, BA.2.75 sub-lineages (including CH.1.1), XBB and XBC. BQ.1.1 and XBB have demonstrated substantial immune evasion in laboratory testing compared to prior Omicron variants. Cases of these subvariants are likely to increase relative to BA.5 in the coming weeks. CH.1.1 may have driven growth in BA.2.75 and its sub-variants in New Zealand in November and is likely to further increase (relative to BA.5). However, it is unknown if one or more variants will cause a wave or produce overall higher baseline incidence.

There is no strong evidence of an increase in disease severity associated with these variants.

## Features of Omicron

*Section updated: 1 December 2022*

### Growth advantage/transmissibility

A number of convergent subvariants (that is, different subvariants that have accumulated similar mutations) are displaying a growth advantage relative to BA.5.2 in the UK.(1) The estimated the weekly growth rates for variants in the UK (relative to BA.5.2, at 9 November 2022) were:

- BQ.1.1 48.5% (95% credible interval (CrI): 43.3 to 54.1%)
- BQ.1 (excluding BQ.1.1) 38.6% (95% CrI: 33.9 to 44.0%)
- BN.1 44.7% (95% CrI: 37.8 to 52.3%)
- BA.2.75 (excluding BN.1) 22.5% (95% CrI: 19.1 to 26.0%)
- BA.4.6 4.4% (95% CrI: 3.1 to 5.7%)
- XBB 56.9% (95% CrI: 46.9 to 67.2%)

### Vaccine effectiveness, immune evasion

Formal estimates of vaccine effectiveness (VE) require cases to accumulate (usually requiring some time) before estimates can be calculated. VE estimates are therefore currently not available for most variants that emerged after BA.2 and BA.5. Where VE estimates are not available, laboratory testing can provide some information by, for example, measuring how well antibodies in the serum from vaccinated people neutralise each variant. However, results from such laboratory tests need to be confirmed by epidemiological data.



## Vaccine effectiveness

Vaccine effectiveness reported here is only for periods including BA.4/5 waves, as variants prior to BA.4/5 are now not often seen. VE for previous variants such as BA.1 are included in previous Variants of Concern Updates and so are not repeated here. VE is also only reported here for mRNA vaccines.

### VE against infection

#### Monovalent (Wild Type) original formulation vaccines

Three doses: Moderna vaccine shows VE (against BA.2, BA.2.12.1, BA.4 and BA.5) was 61.0% - 90.6% at 14 – 30 days post-third dose. (12) However, this diminished to levels below 20% against all subvariants after 5 months. (12)

Four doses: Moderna vaccine shows VE ranged between 64.3%-75.7% for BA.2, BA.2.12.1, and BA.4 and was 30.8%) against BA.5 at 14-30 days post-fourth dose. VE was low beyond 90 days for all subvariants. (12)

#### Bivalent (BA.4/5, Wild type) mRNA vaccines

A single study from the USA has estimated the VE against symptomatic infection of bivalent Omicron BA.4/5 mRNA vaccines (as a third, fourth or fifth dose). Absolute VE (that is, compared to those who have received no doses of any COVID-19 vaccine) against symptomatic SARS-CoV-2 infection ranged from 22% (95% CI: 15-29) in those aged 65 and older, to 43% (95% CI: 39-46) in those aged 18-49 years at a maximum of 2.5 months after the bivalent vaccine dose.(3) Relative VE (that is, compared to those who have received the same number of previous monovalent doses but not the bivalent booster) increased in all age group with the time since the most recent previous dose. It should be noted that this study was conducted in the USA from mid-September to mid-November 2022 so is in a setting with frequent prior infection (i.e., these estimates show additional protection provided by vaccination in a population that has experienced previous waves of infection), with numerous circulating Omicron sub-lineages.

### VE against severe disease

Two doses: mRNA vaccines during a BA.4/5 dominant period shows VE against hospitalisation or urgent care visit was 25% (95% CI: 17 - 32) at > 150 days post-vaccination. (13)

Three doses: Moderna vaccine shows VE against hospitalisation (time since vaccination unclear) was 97.5%, 82.0%, and 72.4% for BA.1, BA.2 and BA.4/5 respectively. (12) During a BA.4/5 dominant period, mRNA vaccines shows VE against hospitalisation or urgent care visit was 68% (95% CI: 50 - 80) at 7-119 days post-vaccination (13) and 36% (95% CI: 29 – 42 at > 120 days post-vaccination.(13)

Four doses: Moderna vaccine shows VE against hospitalization (time since vaccination unclear) for BA.4/BA.5 was 88.5%. (12)

### Protection from vaccination plus prior Omicron infection

Previous Omicron infection in triple-vaccinated individuals provides a high level of protection against BA.5 and BA.2 infections. The study assessed outcomes across the period of 10 April to 30 June 2022. (14)

- Protection against BA.5 infection was estimated to be 92.7% (95% CI: 91.6 – 93.7).
- Protection against BA.2 infection was estimated to be 97.1% (95% CI: 96.6 – 97.5).
- High levels of protection against hospitalisation were conferred by infection with BA.5 at 96.4% (95% CI: 74.2 - 99.5) and BA.2 at 91.2% (95% CI: 76.3 – 96.7).



## Immunological data

### **Monovalent (Wild Type) original formulation vaccines**

Evidence continues to accumulate that neutralising antibody levels against Omicron decline after a primary course of Pfizer vaccine (original monovalent, wild type vaccine), and are higher after a booster (third) dose, than after the primary course.(15-18) Similar results from a phase II clinical suggest that antibody titres increased following a booster (third or fourth) dose of Novavax (NVX-CoV2373) without increasing reactogenicity. (19)

Data show that the memory T cell response generated by monovalent (Wild Type (WT), original formulation) remains robust and is mostly unaffected by the mutations in Omicron (B.1.1.529).(20)

### **Bivalent (BA.4/5, Wild type) mRNA vaccines**

Immunogenicity data for BA.4/5 bivalent vaccines are mixed. **Early studies showed** little difference between bivalent vaccine and monovalent Wild Type (original formulation) vaccines. (21, 22)

**However, most subsequent studies (pre-prints) have suggested** BA.4/5 bivalent vaccines elicit greater neutralisation titres against Omicron variants than the WT monovalent vaccines (however, activity against Omicron variants were substantially lower than against WT virus):

- One study assessed neutralising activity against WT virus and Omicron variants including BA.1, BA.5, BA.2.75.2, and BQ.1.1. (23)
- Another assessed activity against WT virus and Omicron variants including BA.4/5, BA.4.6, BA.2.75.2, BQ.1.1 and XBB.1). (24)
- A small sub-study in Moderna's clinical trial showed similar positive results for the BA.4/5 bivalent vaccine (including robust neutralizing activity against BQ.1.1, despite an approximately 5-fold drop in titres for BQ.1.1 compared to BA.4/BA.5. (25)
- A small study of people aged 55 years and older suggest that a fourth dose of Pfizer's bivalent BA.4/5 vaccine is more immunogenic than the original BNT162b2 monovalent vaccine against circulating Omicron sub-lineages, including BQ.1.1, and XBB.1. (26)

Immunological data for bivalent vaccines will be superseded by clinical data (see section "Vaccine Effectiveness, above) as clinical data becomes available.

### Bivalent vaccines for children

There are no publicly available safety, immunogenicity or efficacy data (at 17 November 2022) for bivalent vaccines for 5-11 year olds. Emergency use authorisations (USA) or recommendation for marketing authorisation (EU) have been made on data including safety, immunogenicity, efficacy, and observational effectiveness data for the monovalent (original formulation, WT) vaccine, and immunogenicity data from other Pfizer bivalent vaccines.(27, 28)

### **Immunological response from vaccination plus prior Omicron infection**

There is some evidence to suggest that an individual's first exposure to a variant (either through infection or vaccination), shapes the immune response to future infections (how well the antibody produced neutralises a variant not previously encountered)." (29, 30)

## Safety of second booster

A pre-print of a study (including 250,000 people in Israel) about the safety of a second booster of Pfizer's BNT162b2 vaccine, found no significant differences in frequency of self-reported adverse events after the second booster compared with the first booster dose.(31)



## Disease course and clinical features (symptoms and severity)

Various studies continue to indicate a reduction in severity and lower mortality for the Omicron variant (and subvariants) as compared with the Delta variant. (32-34) However, Omicron infections still contribute to excess total mortality. A study from Italy found that excess total mortality persisted during the circulation of the Omicron variant in Italy (although data only available to 31 January 2022), contributing to a reversal in the long-term trend towards increasing life expectancy. (35)

Analysis from a large study in England from 1 May 2020 to 31 March 2022 showed some changes in symptom profiles associated with the different variants over that period, such as lower reporting of loss of sense of smell or taste for Omicron compared to previous variants. (36)

Laboratory studies have also been conducted to investigate pathogenicity of variants on cells. Such studies have supported Omicron severity being lower than previous variants (with one researcher suggesting that descendants of BA.5 and BA.2 (including BQ.1 and BQ.1.1) could cause slightly more severe disease than BA.1 or the original Omicron). However, these findings require validation from clinical data. (33, 37)

A study published in November 2022 reported an increased risk of death, hospitalisation, and sequelae with reinfection compared to no reinfection. (38) These results have been widely reported; however, the results should be interpreted very carefully as the follow-up time after symptom onset is not the same in the comparison groups, introducing bias.

## Therapeutics effectiveness

Monoclonal antibody treatments: laboratory-based studies suggest that monoclonal antibody treatments (such as Evusheld and bebtelovimab) may be ineffective against some emerging variants. (4-7) The affected variants are not currently (at 23 November 2022) predominant in New Zealand (e.g. BQ.1.1 and XBB). Clinical effectiveness data for Evusheld (Aotearoa New Zealand's most used monoclonal antibody treatment) are available for a period of BA.1 predominance, (8) but not for later variants.

Antivirals: There is currently no evidence to suggest any currently emerging variants have become resistant to Nirmatrelvir/ritonavir (Paxlovid).

## Detection/testing

There is some evidence to suggest changes in the performance of RATs to detect Omicron variants. However, data are limited and appears to be dependent on both the individual device and subvariant. Use of techniques such as serial testing may maximise sensitivity.

Growing international evidence suggests that clinically relevant changes in RAT performance for detection of Omicron variants differ on an individual device basis. (39-43) Comparability between studies is limited by difference in study design and objectives. The results are also dependent on which Omicron variant was assessed, making it difficult to determine whether evidence of reduced sensitivity is indicative of real-world device performance. Studies indicate that despite reports of reduced sensitivity, the data supports the continued use of RATs for self-testing. (39-43) Emerging evidence also highlights the need for techniques such as serial testing to maximise sensitivity against new Omicron variants of concern. (41, 43)



## Associated documentation

The following documents or ongoing work programmes draw upon the evidence in this document:

- New Variants of Concern Monitoring and preparedness
- Outlook Strategy Group
- New Variant Public Health Risk Assessments

## Key recent international documents

*Section updated: 1 December 2022*

In addition to selected recent pre-prints and published studies, key reports used in this update include:

1. World Health Organization (WHO) Weekly epidemiological update on COVID-19: [23 November 2022](#) (2)
2. UK Health Security Agency: SARS-CoV-2 Variants of Concern and Variants under Investigation in England, [Technical Briefing 48, 25 November 2022](#).(1)

### World Health Organization update

The WHO Weekly Epidemiology Update on 23 November reported the status of circulating variants compared to the previous week.(2) Sequences submitted globally continue to show similar trends to recent weeks with BA.5 descendent lineages remaining dominant (72.1% of sequences) followed by BA.2 descendent lineages (9.2%). BA.4 descendent lineages continued to decline in prevalence (3%). There was a rise in BQ.1 sequences to 23.1% of sequences, and XBB sequences also increased, rising to 3.3%.

### UK Health Security Agency update

The UK Health Security Agency update on 25 November 2022 reported the estimated the weekly growth rates for variants in the UK (relative to BA.5.2 at 9 November 2022).(1) Details are reported in section "Growth advantage/transmissibility"





# Section 2: Summary of Variants

## Public Health Risk Assessment BA.5

Updated: 1 December 2022

BA.5 has key spike mutations at positions: L452R, F486V, and R493Q. (44) Note: BA.4 and BA.5 have identical spike protein.

	Overall Risk Assessment*	Confidence level **	Assessment and rationale
Overall growth advantage	Increased risk	High	<p><b>Evidence of a growth advantage compared to BA.2.</b></p> <p>As at 25 November 2022, BA.5 remains the predominant variant in New Zealand, but makes up a declining proportion of sequenced cases (44% in fortnight ending 25 November. (10) BA.5 now makes up less than 50% of all cases sequenced.</p>
Transmissibility	Insufficient data	Insufficient data	<p>No direct data on intrinsic transmissibility. There is some laboratory evidence that ACE2 binding is increased for BA.5 compared to prior Omicron variants, and BA.5 may have increased infectivity. (45)</p>
Immune evasion	Increased risk	High	<p><b>There is evidence of increased immune evasion compared to BA.2, based on laboratory data; however, preliminary data suggest no substantial decrease in vaccine effectiveness. Growth advantage is likely mostly due to immune evasion properties, rather than changes to intrinsic transmissibility.</b></p> <p><i>Laboratory data:</i> BA.5 has moderate drop in neutralising antibodies compared to BA.1 and BA.2, and lower protection conferred from vaccination with 3 doses. Less of an impact was associated with 'hybrid' protection, e.g., by 'breakthrough' infections after vaccination.(46-48)</p> <p><i>Reinfection:</i> Limited evidence on the rates of reinfection in New Zealand or internationally, including after prior Omicron variant infection. Prior infection with BA.1 or BA.2 provides some protection against BA.5; prior infection with non-Omicron variants is lower.(49-51)</p>



<b>Vaccine Effectiveness</b>	<b>Low</b>	<b>Low/ Moderate</b>	<p><i>Vaccine effectiveness (VE) relative to BA.2:</i> Early data suggest there no indicators of a large change in VE against symptomatic infection from BA.2 to BA.5.(49, 52). Booster vaccination reported to be associated with a lower risk reduction against BA.5 for hospitalisation (77%) and death (88%) compared to the risk reduction for BA.2 of 92% and 94% respectively. (53)</p> <p><i>Vaccine effectiveness (VE):</i> Three doses of an mRNA vaccine confer a VE against infection for BA.5 that is initially high (~90%) but diminishes over time to levels unlikely to prevent infection &gt;150 days post-vaccination. (12) There is evidence of a decrease in VE against hospitalisation as time elapses since third dose of a mRNA vaccine, however a fourth dose may restore this. (12, 13) VE against severe disease at more than 120 days appears to be half that at less than 120 days. (13)</p>
<b>Severity</b>	<b>Possible increase in risk of hospitalisation</b>	<b>Low/ Moderate</b>	Evidence regarding the severity of BA.5/BA.4 compared to BA.2 has been mixed. (32) Some studies have found no clear indication of a change in severity whilst at least one study suggested an increased risk of hospitalisation with BA.5 infections compared with BA.2. (32)
<b>Therapeutics</b>	<b>Low</b>	<b>Moderate</b>	One <i>in vitro</i> study shows increased resistance to Evusheld compared to BA.2, (7) whilst another shows it retains activity. (54) Real-world evidence has indicated that Evusheld, when given to vaccinated people, provides an increased protection against symptomatic and severe COVID-19 compared to booster vaccination alone. (8)
<b>Testing</b>	<b>Insufficient Data</b>	<b>Insufficient data</b>	
<b>Overall Assessment</b>			<b>There is an increase in overall risk from the previous predominant variant, BA.2. BA.5 is more transmissible compared to BA.2. BA.5 produced a wave of cases in New Zealand but is now making up a declining proportion of sequenced cases.</b>

\*The 'Overall risk assessment' is presented in comparison to the prior or current predominant variant, in this case BA.2. 'Increased risk' indicates the assessed variant as worse than the previous predominant variant with regards to that characteristic; 'no change' means that the assessed variant poses equivalent risk; and 'decreased risk' means that the assessed variant is better than the previous predominant variant.

\*\*'Confidence level' indicates the overall quality of data that are available to make the risk assessment: 'High' (high quality, robust data); 'Moderate' (good data with limitations); 'Low' (very little data available). 'Insufficient data' indicates that there are no data of reasonable quality on which to base an assessment at this time.



# Public Health Risk assessment for BA.2.75

Updated: 1 December 2022

BA.2.75 has 8 key mutations from BA.2: 147E, 152R, 157L, 210V, 257S, 339H, 446S, 460K. (44)

	Overall risk assessment*	Confidence level **	Assessment and rationale
<b>Overall growth advantage</b>	<b>Increased Risk</b>	<b>Moderate</b>	<p><b>Evidence of a growth advantage compared to BA.5. Prevalence in New Zealand is increasing gradually.</b></p> <p>There is evidence that BA.2.75 has a growth advantage against BA.4/5 in some countries (India, Austria, Singapore). BA.2.75 and sub-lineages (excluding BN.1) have an estimated growth advantage of 22.5% per week (95% Credible Interval: 19.1 to 26.0%) compared to BA.5.2 in the UK (at 9 November 2022). (1)</p> <p>BA.2.75 (and its descendant sub-lineages) are making up an increasing proportion of sequenced cases in New Zealand.(11)In the fortnight ending 25 November 2022 it made up 32% of sequenced cases and 22% of isolates from hospital cases. (10)</p>
<b>Transmissibility</b>	<b>Insufficient data</b>	<b>Insufficient data</b>	There are no direct data on intrinsic transmissibility and there is no current ability to measure this directly from surveillance data.
<b>Immune evasion</b>	<b>No change in risk</b>	<b>Low</b>	<p><b>No evidence of increased immune evasion.</b></p> <p>Mutations suggest that BA.2.75 may have immune evasion potential. However, there is very limited data to evaluate immune evasion against vaccination, prior infection with BA.5, or a combination of the two (hybrid immunity). There are no estimates of vaccine effectiveness against BA.2.75.</p> <p>Laboratory data: Neutralisation studies found that BA.2.75 was similar or slightly less able to neutralise antibodies produced after vaccination and BA.2 infection, compared to BA.4 or BA.5. (55-59) Potentially higher</p>



			receptor binding compared to other Omicron lineages. There are no data on the ability of antibodies produced after BA.5 infection to neutralise BA.2.75.
<b>Severity</b>	<b>Insufficient data</b>	<b>Insufficient data</b>	<p><b>No evidence of a change in severity compared to BA.5</b></p> <p>Few formal evaluations of BA.2.75 severity are available. An early assessment of the severity of BA.2 sub-lineages in India indicates that BA.2.74, BA.2.75, and BA.2.76 are causing 'mild' disease with no evidence of an increased risk of hospital admission or severe disease. (60) Lab and animal studies suggest mixed results for binding compared to BA.5, (59) but overall pathogenicity similar to BA.5. (61) Some <i>in vitro</i> evidence to suggest an increases in cell-cell fusion and ability to infect lower airways compared to BA.2 which could alter pathogenicity. (62)</p>
<b>Therapeutics</b>	<b>Insufficient data</b>	<b>Insufficient data</b>	
<b>Testing</b>	<b>Insufficient data</b>	<b>Insufficient data</b>	
<b>Overall Assessment</b>	<p><b>There is an increase in overall risk from the previous predominant variant, BA.5. (Moderate confidence)</b></p> <p><b>BA.2.75 and associated sublineages are increasing in frequency in New Zealand and appear to be more transmissible and immune evasive.</b></p>		

\*The 'Overall risk assessment' is presented in comparison to the prior or current predominant variant, in this case BA.5 'Increased risk' indicates the assessed variant as worse than the previous predominant variant with regards to that characteristic; 'no change' means that the assessed variant poses equivalent risk; and 'decreased risk' means that the assessed variant is better than the previous predominant variant.

\*\*'Confidence level' indicates the overall quality of data that are available to make the risk assessment: 'High' (high quality, robust data); 'Moderate' (good data with limitations); 'Low' (very little data available). 'Insufficient data' indicates that there are no data of reasonable quality on which to base an assessment at this time.



# Public Health Risk assessment for BA.4.6

Updated: 1 December 2022

BA.4.6 has an identical spike to BA.5. However, BA.4.6 has an additional mutation at R346T. (44)

	Overall risk assessment*	Confidence level **	Assessment and rationale
<b>Overall growth advantage</b>	<b>Increased risk</b>	<b>Low</b>	<p><b>Evidence of a growth advantage compared to BA.4/5.</b></p> <p>BA.4.6 has an estimated growth advantage of 4.4% per week (95% Credible Interval: 3.1 to 5.7%) compared to BA.5.2 in the UK (at 9 November 2022).(1)</p> <p>BA4.6 has made up a relatively stable proportion of sequenced isolates (from wastewater and cases) in New Zealand since September 2022. (10) In the fortnight ending 25 November 2022 it made up less than 1% of all sequenced cases and less than 1% of isolates from hospital cases. (10)</p>
<b>Transmissibility</b>	<b>Insufficient data</b>	<b>Insufficient data</b>	
<b>Immune evasion</b>	<b>No change in risk</b>	<b>Low</b>	Early data shows that BA.4.6 has greater immune escape from vaccine serum than BA.5, showing on average 2.4 to 2.6-fold decrease in antibody neutralisation. (63)
<b>Severity</b>	<b>Insufficient data</b>	<b>Insufficient data</b>	
<b>Therapeutics</b>	<b>Increased risk</b>	<b>Low</b>	Some indication that Evusheld is less effective for this variant. (63)
<b>Testing</b>	<b>Insufficient Data</b>	<b>Insufficient Data</b>	



**Overall  
Assessment**

**No change in risk**

*\*The 'Overall risk assessment' is presented in comparison to the prior or current predominant variant, in this case BA.5. 'Increased risk' indicates the assessed variant as worse than the previous predominant variant with regards to that characteristic; 'no change' means that the assessed variant poses equivalent risk; and 'decreased risk' means that the assessed variant is better than the previous predominant variant.*

*\*\*'Confidence level' indicates the overall quality of data that are available to make the risk assessment: 'High' (high quality, robust data); 'Moderate' (good data with limitations); 'Low' (very little data available). 'Insufficient data' indicates that there are no data of reasonable quality on which to base an assessment at this time.*



# Public Health Risk assessment for BQ.1.1

Updated: 1 December 2022

BQ.1.1 is related to BA.5.3 but with Spike protein mutations 444T, 460K, 346T (44)

	Overall risk assessment*	Confidence level **	Assessment and rationale
Overall growth advantage	Increased risk	Moderate	<p><b>Evidence of a growth advantage compared to BA.5. (64-66)</b></p> <p>BQ.1.1 variant has an estimated growth advantage of 48.5% per week (95% Credible Interval: 43.3 to 54.1%) compared to BA.5.2 in the UK (at 9 November 2022).(1)</p> <p>Currently present in New Zealand and is growing relative to BA.5. (10) In the fortnight ending 25 November 2022, it made up 15% of sequenced cases and 11% of isolates from hospital cases. (10)</p>
Transmissibility	Insufficient data	Insufficient data	<p>No direct data on intrinsic transmissibility and there is no current ability to measure from surveillance data. There is some laboratory evidence that ACE2 binding is increased for BQ.1.1 compared to prior Omicron variants which may affect transmissibility/infectivity. (4)</p>
Immune evasion	Increased risk	Moderate	<p><b>Evidence of increased immune evasion.</b></p> <p>More resistant to neutralisation from sera of vaccinated and infected individuals. (4, 67) At least 2 small studies show that mRNA bivalent BA.4/5 vaccine produces robust neutralising activity against BQ.1.1 compared to monovalent wild type vaccine. (23, 25, 67)</p>
Severity	Insufficient data	Insufficient data	<p><b>No evidence of a change in severity compared to BA.5</b></p> <p>Evidence from a surge of cases of this variant in France suggests it is not causing increased rates of hospitalisations and deaths.(68)</p>



<b>Therapeutics</b>	<b>Increased risk</b>	<b>Low</b>	<i>In vitro</i> studies showed loss of efficacy of all currently approved clinical monoclonal antibody therapies including Evusheld and Bebtelovimab. (4, 67)
<b>Testing</b>	<b>Insufficient data</b>	<b>Insufficient data</b>	Evidence that suggests a clinically relevant decrease in the performance of RATs for detection of the Omicron variant (varies by device), (39-43) but it is uncertain how this will affect sensitivity specifically for BQ.1.1
<b>Overall Assessment</b>	<p>There is an increase in overall risk from the previous predominant variant, BA.5. (Moderate confidence)</p> <p>BQ.1.1 is increasing in frequency overseas and appears to be more transmissible and immune evasive.</p>		

\*The 'Overall risk assessment' is presented in comparison to the prior or current predominant variant, in this case BA.5. 'Increased risk' indicates the assessed variant as worse than the previous predominant variant with regards to that characteristic; 'no change' means that the assessed variant poses equivalent risk; and 'decreased risk' means that the assessed variant is better than the previous predominant variant.

\*\*'Confidence level' indicates the overall quality of data that are available to make the risk assessment: 'High' (high quality, robust data); 'Moderate' (good data with limitations); 'Low' (very little data available). 'Insufficient data' indicates that there are no data of reasonable quality on which to base an assessment at this time.





# Public Health Risk assessment for XBB

Updated: 1 December 2022

XBB is a recombinant virus ( related to BA.2 and BJ.1) with additional spike protein mutations 364T, 445P, 446S and 490V. (44)

	Overall risk assessment*	Confidence level **	Assessment and rationale
Overall growth advantage	Increased risk	Low	<p><b>Evidence of a growth advantage compared to BA.5</b></p> <p>XBB has an estimated growth advantage of 56.9% per week (95% Credible Interval: 46.9 to 67.2%) compared to BA.5.2 in the UK (at 9 November 2022).(1)</p> <p>Currently present in New Zealand and is fluctuating between 1-4% of sequenced cases. (10) In the fortnight ending 25 November 2022, it made up 1% of all sequenced cases and 1% of isolates from hospital cases. (10)</p>
Transmissibility	Insufficient data	Insufficient data	<p>No direct data on intrinsic transmissibility and there is no current ability to measure from surveillance data. There is some laboratory evidence that ACE2 binding is increased for XBB compared to prior Omicron variants which may affect transmissibility/infectivity. (4)</p>
Immune evasion	Increased risk	Moderate	<p><b>Evidence of increased immune evasion.</b></p> <p>More resistant to neutralisation from sera of vaccinated and breakthrough infected individuals. (4, 67)</p>
Severity	Insufficient data	Insufficient data	<p>In late October 2022 the World Health Organization Technical Advisory Group on SARS-CoV-2 Virus Evolution noted that current (limited) information does not indicate an increase in severity for XBB. (69)</p>
Therapeutics	Increased risk	Low	<p><i>In vitro</i> studies showed loss of efficacy of all currently approved clinical monoclonal antibody therapies including Evusheld and Bebtelovimab. (4, 67)</p>



<b>Testing</b>	<b>Insufficient data</b>	<b>Insufficient data</b>	Evidence that suggests a clinically relevant decrease in the performance of RATs for detection of the Omicron variant (varies by device), (39-43) but it is uncertain how this will affect sensitivity specifically for XBB.
<b>Overall Assessment</b>	<b>No change in risk</b>		

*\*The 'Overall risk assessment' is presented in comparison to the prior or current predominant variant, in this case BA.5. 'Increased risk' indicates the assessed variant as worse than the previous predominant variant with regards to that characteristic; 'no change' means that the assessed variant poses equivalent risk; and 'decreased risk' means that the assessed variant is better than the previous predominant variant.*

*\*\*Confidence level' indicates the overall quality of data that are available to make the risk assessment: 'High' (high quality, robust data); 'Moderate' (good data with limitations); 'Low' (very little data available). 'Insufficient data' indicates that there are no data of reasonable quality on which to base an assessment at this time.*



# New signals

Section updated: 1 December 2022

In the second half of 2022, many new Omicron sub-variants have been reported. These variants demonstrate convergent evolution which is a process whereby variants from different lineages accumulate similar mutations. For example, the ECDC has designated Omicron lineages with mutations at N460X and at either F490X or K444X (these include BQ.1, BQ.1.1, XBB, BN.1 and BN.2) as a variants under monitoring (VUM). The location of these mutations might produce a significant effect on neutralising activity. (70, 71)

For many BA.2.75 sub lineages, mutations on N-Terminal domain (NTD) can cause reduction in neutralisation titres. (4)

**In Australia and New Zealand, there is currently no single variant driving case numbers. (72)**

Details of BA.5, BA.2.75, BQ.1.1, BA.4.6, and XBB can be found above in the risk assessment section. Short summaries are provided here of newer variants which are not covered in the risk assessment section, but are of heightened concern because of their growth rate in New Zealand or internationally, or because there are other features of concern (e.g. if increased severity was suspected). Because these variants have only been recently detected, the growth advantage, immune escape potential, and characteristics of disease they cause (e.g. severity) is often not yet well understood.

## XBC

- XBC is a recombinant lineage that combines sequences from the Delta and Omicron variants.(11) **Some studies suggest that chronic infections may be contributing to the emergence of such recombinant variant lineages. (73)**
- **In the fortnight ending 25 November 2022, 20 cases caused by XBC have been detected in New Zealand. (10) As of 25 November 2022, XBC makes up just 2% of all sequenced hospitalised cases. (10)**
- **XBC appears to be most common in the Philippines and Brunei, circulating at a prevalence of around 5%. Sub-lineage XBC.1 (S:L452M) has been rising in Australia to most recently 1%. (9)**
- **The XBC lineage has been present in Australia and South East Asia for some time, with no indication of increased disease severity (albeit this is based on small case numbers). (11)**

## XBF

- **Sub-lineage from a BA.5.2.3 and CJ.1 (a BA.2.75 sub-lineage) recombinant. Spike identical to CJ.1, additional mutations (from BA.2.75) S:486P, S:R346T, S:F490S. (9)**
- **Growing in Australia and Denmark.(9) Appears to growing less rapidly in South Asia than CH.1.1 (another BA.2.75 sub-lineage),(9) but epidemiology could be different in New Zealand.**
- **No data have yet emerged about the severity of XBF disease.**

## BA.2.75.2

- **BA.2.75.2 is a BA.2.75 sub-lineage with mutations at 346T, 486S, and 1199.(44) These mutations may allow additional escape from neutralising antibodies (in one study, five-fold less effective at neutralising BA.2.75.2 compared to BA.5 (74))**



- BA.2.75.2 variant had an estimated growth advantage of 37% per week (95% Credible Interval: 33 – 42) compared to BA.5 in the UK (at 20 October 2022). (66)
- BA.2.75.2 may be resistant to neutralisation by Evusheld (tixagevimab and cilgavimab), (4, 74) but has remained sensitive to bebtelovimab. (74)

### CH.1.1

- CH.1.1 is derived from BM.4.1.1 (and consequently BA.2.75) and is defined by the S:L452R mutation.(75) CH.1.1 is derived from BM.4.1.1 (and consequently BA.2.75) and is defined by the S:L452R mutation.(75)
- In New Zealand, the BA.2.75 and sub-lineages accounted for 24% of sequenced for the fortnight ending 25 November 2022. (11) The growth in BA.2.75 October and November may be driven by an increase of CH.1.1 (40% of BA.2.75 cases in week ending 25 November). (10)
- The additional mutations are predicted to potentially render bebtelovimab ineffective (in addition to Evusheld) by authors of a preprint paper. (4)

### BR.2.1

- BA.2.75 with 3 extra spike mutations (L452R, F486I, R346T (sometimes reversed). (76)
- The majority of BR.2 sequences reported internationally to early November 2022 have originated from New South Wales (NSW) in Australia. (77) Also in other countries including Japan.(75)The majority of BR.2 sequences reported internationally to early November 2022 have originated from New South Wales (NSW) in Australia. (77) Also in other countries including Japan.(75)
- Marked increase in NSW of the proportion of community samples that are BA.2.75 (mostly BR.2 sub-lineage): week ending 15<sup>th</sup> October 7.7%, week ending 29<sup>th</sup> October 20.1% (77)
- In New Zealand, BR.2 makes up 12% of all BA.2.75 cases in the week ending 25 November 2022. The proportion of BR.2 cases is rising in recent weeks. (10)

### BN.1

- BN.1 is a descendant of BA.2.75.5 (and consequently BA.2.75), with S:R346T and S:490S mutations. (75)BN.1 is a descendant of BA.2.75.5 (and consequently BA.2.75), with S:R346T and S:490S mutations. (75)
- As of 11 November 2022, BN.1.X accounts for 4.3% of USA national cases.(78) The growth advantage and characteristics of disease it causes (e.g. severity) are not yet defined. As of 11 November 2022, BN.1.X accounts for 4.3% of USA national cases.(78)
- BN.1 has an estimated growth advantage of 44.7% per week (95% Credible Interval: 37.8 to 52.3%) compared to BA.5.2 in the UK (at 9 November 2022).(1)
- Appears to growing less rapidly in South Asia than CH.1.1 (another BA.2.75 sub-lineage),(9) but epidemiology could be different in New Zealand.
- BN.X sublineages made up 33% of BA.2.75 cases in week ending 25 November. (10)



# References

1. Public Health England (PHE). SARS-CoV-2 variants of concern and variants under investigation in England Technical briefing 48 [Available from: [https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment\\_data/file/1120304/technical-briefing-48-25-november-2022-final.pdf](https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1120304/technical-briefing-48-25-november-2022-final.pdf)].
2. World Health Organisation (WHO). Weekly epidemiological update on COVID-19 - 23 November 2022 [119:[Available from: <https://www.who.int/publications/m/item/weekly-epidemiological-update-on-covid-19---23-november-2022>].
3. Ruth Link-Gelles, Allison Avrich Ciesla, Katherine E. Fleming-Dutra, Zachary R. Smith, Amadea Britton, Ryan E. Wiegand, et al. Effectiveness of Bivalent mRNA Vaccines in Preventing Symptomatic SARS-CoV-2 Infection — Increasing Community Access to Testing Program, United States, September–November 2022: Morbidity and Mortality Weekly Report (MMWR); 2022 [Available from: <https://www.cdc.gov/mmwr/volumes/71/wr/mm7148e1.htm>].
4. Cao Y, Jian F, Wang J, Yu Y, Song W, Yisimayi A, et al. Imprinted SARS-CoV-2 humoral immunity induces converging Omicron RBD evolution 2022 [2022.09.15.507787]. Available from: <https://www.biorxiv.org/content/biorxiv/early/2022/09/23/2022.09.15.507787.full.pdf>.
5. Arora P, et al.,. Omicron sublineage BQ.1.1 resistance to monoclonal antibodies The lancet Infectious Disease 2022 [Available from: [https://www.thelancet.com/journals/laninf/article/PIIS1473-3099\(22\)00733-2/fulltext#:~:text=Vaccination%20represents%20the%20key%20strategy,risk%20of%20developing%20severe%20disease](https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(22)00733-2/fulltext#:~:text=Vaccination%20represents%20the%20key%20strategy,risk%20of%20developing%20severe%20disease)].
6. Chen J, Wang R, Gilby NB, Wei G-W. Omicron (B.1.1.529): Infectivity, vaccine breakthrough, and antibody resistance United States 2021 [Available from: <http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=pmnm&NEWS=N&AN=34873578>].
7. Yamasoba D, Kosugi Y, Kimura I, Fujita S, Uriu K, Ito J, et al. Neutralisation sensitivity of SARS-CoV-2 omicron subvariants to therapeutic monoclonal antibodies 2022 [updated 01 July 2022. 08 June 2022:[942-3]. Available from: [https://www.thelancet.com/journals/laninf/article/PIIS1473-3099\(22\)00365-6/fulltext](https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(22)00365-6/fulltext)].
8. Young-Xu Y, Epstein L, Marconi VC, Davey V, Zwain G, Smith J, et al. Tixagevimab/Cilgavimab for Prevention of COVID-19 during the Omicron Surge: Retrospective Analysis of National VA Electronic Data 2022 [2022.05.28.22275716]. Available from: <https://www.medrxiv.org/content/medrxiv/early/2022/05/29/2022.05.28.22275716.full.pdf>.
9. Roemer C, Neher R. Variant report 2022-11-23 2022 [Available from: [https://github.com/neherlab/SARS-CoV-2\\_variant-reports/blob/main/reports/variant\\_report\\_latest\\_draft.md](https://github.com/neherlab/SARS-CoV-2_variant-reports/blob/main/reports/variant_report_latest_draft.md)].
10. de Ligt J, Geoghegan J, Douglas J, Hadfield J, Winter D, Jefferies S, et al. COVID-19 Genomics Insight (CGI) Report. No.28 01 December 2022, Unpublished ESR report. 2022 [
11. de Ligt J, Douglas JGJ, Hadfield J, Winter D, Jefferies S, Welch D, et al. COVID-19 Genomics Insight (CGI) Report. No.27, 16 November 2022, Unpublished ESR report. 2022 [
12. Tseng HF, Ackerson BK, Bruxvoort KJ, Sy LS, Tubert JE, Lee GS, et al. Effectiveness of mRNA-1273 against infection and COVID-19 hospitalization with SARS-CoV-2 Omicron subvariants: BA.1, BA.2, BA.2.12.1, BA.4, and BA.5 2022 [2022.09.30.22280573]. Available from: <https://www.medrxiv.org/content/medrxiv/early/2022/10/01/2022.09.30.22280573.full.pdf>.
13. Link-Gelles R, Levy ME, Natarajan K, Reese SE, Naleway AL, Grannis SJ, et al. Association between COVID-19 mRNA vaccination and COVID-19 illness and severity during Omicron BA.4 and BA.5 sublineage periods 2022 [2022.10.04.22280459]. Available from: <https://www.medrxiv.org/content/medrxiv/early/2022/10/05/2022.10.04.22280459.full.pdf>.
14. Hansen CH, Friis NU, Bager P, Stegger M, Fonager J, Fomsgaard A, et al. Risk of reinfection, vaccine protection, and severity of infection with the BA.5 omicron subvariant: a nation-wide population-based study in Denmark: Elsevier; [Available from: [https://doi.org/10.1016/S1473-3099\(22\)00595-3](https://doi.org/10.1016/S1473-3099(22)00595-3)].



15. Gram MA, Emborg H-D, Schelde AB, Friis NU, Nielsen KF, Moustsen-Helms IR, et al. Vaccine effectiveness against SARS-CoV-2 infection and COVID-19-related hospitalization with the Alpha, Delta and Omicron SARS-CoV-2 variants: a nationwide Danish cohort study 2022 [2022.04.20.22274061]. Available from: <http://medrxiv.org/content/early/2022/04/20/2022.04.20.22274061.abstract>.
16. UK Health Security Agency. SARS-CoV-2 variants of concern and variants under investigation in England. Technical briefing 34 14 January 2022 [Available from: [https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment\\_data/file/1046853/technical-briefing-34-14-january-2022.pdf](https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1046853/technical-briefing-34-14-january-2022.pdf)].
17. Cheng HL, Lim SM, Jia H, Chen MW, Ng SY, Gao X, et al. Rapid Evaluation of Vaccine Booster Effectiveness against SARS-CoV-2 Variants [e02257-22]. Available from: <https://journals.asm.org/doi/abs/10.1128/spectrum.02257-22>.
18. Buchan SA, Chung H, Brown KA, Austin PC, Fell DB, Gubbay JB, et al. Effectiveness of COVID-19 vaccines against Omicron or Delta symptomatic infection and severe outcomes 2022 [2021.12.30.21268565]. Available from: <https://www.medrxiv.org/content/medrxiv/early/2022/01/28/2021.12.30.21268565.full.pdf>.
19. Alves K, Plested JS, Galbiati S, Chau G, Cloney-Clark S, Zhu M, et al. Immunogenicity and safety of a 4th homologous booster dose of a SARS-CoV-2 recombinant spike protein vaccine (NVX-CoV2373): a phase 2, randomized, placebo-controlled trial 2022 [2022.11.18.22282414]. Available from: <https://www.medrxiv.org/content/medrxiv/early/2022/11/20/2022.11.18.22282414.full.pdf>.
20. Dörnte C, Traska V, Jansen N, Kostyra J, Baurmann H, Lauer G, et al. Vaccines against the original strain of SARS-CoV-2 provide T cell memory to the B.1.1.529 variant. Communications Medicine. 2022;2(1):140. <https://doi.org/10.1038/s43856-022-00203-7>.
21. Wang Q, Bowen A, Valdez R, Gherasim C, Gordon A, Lihong L, et al. Antibody responses to Omicron BA.4/BA.5 bivalent mRNA vaccine booster shot 2022 [2022.10.22.513349]. Available from: <https://www.biorxiv.org/content/biorxiv/early/2022/10/24/2022.10.22.513349.full.pdf>.
22. Collier A-r, Miller J, Hachmann N, McMahan K, Liu J, Bondzie E, et al. Immunogenicity of the BA.5 Bivalent mRNA Vaccine Boosters 2022 [2022.10.24.513619]. Available from: <https://www.biorxiv.org/content/biorxiv/early/2022/10/25/2022.10.24.513619.full.pdf>.
23. Davis-Gardner ME, Lai L, Wali B, Samaha H, Solis D, Lee M, et al. mRNA bivalent booster enhances neutralization against BA.2.75.2 and BQ.1.1 2022 [2022.10.31.514636]. Available from: <http://biorxiv.org/content/early/2022/11/01/2022.10.31.514636.abstract>.
24. Kurhade C, Zou J, Xia H, Liu M, Chang HC, Ren P, et al. Low neutralization of SARS-CoV-2 Omicron BA.2.75.2, BQ.1.1, and XBB.1 by 4 doses of parental mRNA vaccine or a BA.5-bivalent booster 2022 [2022.10.31.514580]. Available from: <https://www.biorxiv.org/content/biorxiv/early/2022/11/02/2022.10.31.514580.full.pdf>.
25. Moderna. Moderna's BA.4/BA.5 targeting bivalent booster, mRNA-1273.222, meets primary endpoint of superiority against omicron variants compared to booster dose of mRNA-1273 in phase 2/3 clinical trial. 2022 [Available from: <https://investors.modernatx.com/news/news-details/2022/Modernas-BA.4BA.5-Targeting-Bivalent-Booster-mRNA-1273.222-Meets-Primary-Endpoint-of-Superiority-Against-Omicron-Variants-Compared-to-Booster-Dose-of-mRNA-1273-in-Phase-23-Clinical-Trial/default.aspx>].
26. Zou J, Kurhade C, Patel S, Kitchin N, Tompkins K, Cutler M, et al. Improved Neutralization of Omicron BA.4/5, BA.4.6, BA.2.75.2, BQ.1.1, and XBB.1 with Bivalent BA.4/5 Vaccine 2022 [2022.11.17.516898]. Available from: <https://www.biorxiv.org/content/biorxiv/early/2022/11/17/2022.11.17.516898.full.pdf>.
27. Food and Drug Administration (FDA). Emergency Use Authorization (EUA) for an Unapproved Product Review Memorandum (5 - 11 year olds) 2022 [updated 31 August 2022,]. Available from: <https://www.fda.gov/media/162410/download>.
28. Pfizer. Pfizer and BioNTech Receive Positive CHMP Opinion for Omicron BA.4/BA.5-Adapted Bivalent COVID-19 Vaccine Booster for Children 5 Through 11 Years of Age in European Union 2022 [Available from: <https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-receive-positive-chmp-opinion-omicron-1>].



29. Ju B, Fan Q, Wang M, Liao X, Guo H, Wang H, et al. Antigenic sin of wild-type SARS-CoV-2 vaccine shapes poor cross-neutralization of BA.4/5/2.75 subvariants in BA.2 breakthrough infections. *Nature Communications*. 2022;13(1):7120. <https://doi.org/10.1038/s41467-022-34400-8>.
30. Azuma H, Kawano Y, Shitaoka K, Kawahara T, Ito A, Higashiura A, et al. Vaccination with the Omicron spike RBD boosts broadly neutralizing antibody levels and confers sustained protection even after acquiring immunity to the original antigen 2022 [cited dxac055. Available from: <https://doi.org/10.1093/intimm/dxac055>.
31. Yechezkel M, Mofaz M, Painsky A, Patalon T, Gazit S, Shmueli E, et al. Safety of the fourth COVID-19 BNT162b2 mRNA (second booster) vaccine: a prospective and retrospective cohort study 2022 [updated 2022/11/18/. Available from: <https://www.sciencedirect.com/science/article/pii/S2213260022004076>.
32. Agency for Clinical Innovation. COVID-19 Critical Intelligence Unit: Living Evidence - SARS-CoV-2 variants: NSW Agency for Clinical Innovation; 2022 [updated 4 November 2022. Available from: <https://aci.health.nsw.gov.au/covid-19/critical-intelligence-unit/sars-cov-2-variants>.
33. Zambrano JL, Jaspe RC, Hidalgo M, Loureiro CL, Sulbarán Y, Moros ZC, et al. Sub-lineages of the Omicron variant of SARS-CoV-2: characteristic mutations and their relation to epidemiological behavior. *Investigacion Clinica*. 2022;63(3):262-74. <https://pesquisa.bvsalud.org/global-literature-on-novel-coronavirus-2019-ncov/resource/pt/covidwho-2030660>.
34. Wu Y, Long Y, Wang F, Liu W, Wang Y. Emergence of SARS-CoV-2 Omicron variant and strategies for tackling the infection [<https://doi.org/10.1002/iid3.733>]. John Wiley & Sons, Ltd; 2022 [updated 2022/12/01. e733]. Available from: <https://doi.org/10.1002/iid3.733>.
35. Alicandro G, Remuzzi G, Centanni S, Gerli A, La Vecchia C. Excess total mortality during the Covid-19 pandemic in Italy: updated estimates indicate persistent excess in recent months 2022 [updated Apr 26PMC9073760]. 20220426:[e2022021]. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9073760/>.
36. Whitaker M, Elliott J, Bodinier B, Barclay W, Ward H, Cooke G, et al. Variant-specific symptoms of COVID-19 in a study of 1,542,510 adults in England. *Nat Commun*. 2022;13(1):6856. <https://doi.org/10.1038/s41467-022-34244-2>.
37. Rodriguez A. BQ.1 and BQ.1.1 are now the dominant COVID variants. What does that mean? : *Medical Xpress*; 2022 [Available from: <https://medicalxpress.com/news/2022-11-bq1-bq11-dominant-covid-variants.html>].
38. Bowe B, Xie Y, Al-Aly Z. Acute and postacute sequelae associated with SARS-CoV-2 reinfection 2022 [Available from: <https://doi.org/10.1038/s41591-022-02051-3>].
39. Leuzinger K, Roloff T, Egli A, Hirsch HH. Impact of SARS-CoV-2 Omicron on Rapid Antigen Testing Developed for Early-Pandemic SARS-CoV-2 Variants 2022 [e02006-22]. Available from: <https://journals.asm.org/doi/abs/10.1128/spectrum.02006-22>.
40. Bekliz M, Adea K, Puhach O, Perez-Rodriguez F, Melancia SM, Baggio S, et al. Analytical Sensitivity of Eight Different SARS-CoV-2 Antigen-Detecting Rapid Tests for Omicron-BA.1 Variant 2022 [e00853-22]. Available from: <https://journals.asm.org/doi/abs/10.1128/spectrum.00853-22>.
41. Comparison of Rapid Antigen Tests' Performance Between Delta and Omicron Variants of SARS-CoV-2 [null]. Available from: <https://www.acpjournals.org/doi/abs/10.7326/M22-0760>.
42. Mak GCK, Lau SSY, Wong KKY, Lau C-S, Ng KHL, Lam ETK, et al. Analytical sensitivity of the Rapid Antigen Test kits for detection of SARS-CoV-2 Omicron variant BA.2 sublineage 2022 [5033-7]. Available from: <https://onlinelibrary.wiley.com/doi/abs/10.1002/jmv.27908>.
43. Soni A, Herbert C, Lin H, Pretz C, Stamegna P, Orwig T, et al. Performance of Screening for SARS-CoV-2 using Rapid Antigen Tests to Detect Incidence of Symptomatic and Asymptomatic SARS-CoV-2 Infection: findings from the Test Us at Home prospective cohort study 2022 [2022.08.05.22278466]. Available from: <https://www.medrxiv.org/content/medrxiv/early/2022/08/06/2022.08.05.22278466.full.pdf>.
44. de Ligt J, Douglas JGJ, Hadfield J, Winter D, Jefferies S, Welch D, et al. COVID-19 Genomics Insight (CGI) Report. No.26, 2 November 2022, Unpublished ESR report. 2022 [
45. Aggarwal A, Akerman A, Milogiannakis V, Silva MR, Walker G, Kidinger A, et al. SARS-CoV-2 Omicron BA.5: Evolving tropism and evasion of potent humoral responses and resistance to clinical



immunotherapeutics relative to viral variants of concern 2022 [Available from:

<http://medrxiv.org/content/early/2022/07/10/2022.07.07.22277128.abstract>.

46. Qu P, Faraone J, Evans JP, Zou X, Zheng YM, Carlin C, et al. Neutralization of the SARS-CoV-2 Omicron BA.4/5 and BA.2.12.1 Subvariants. *N Engl J Med*. 2022;386(26):2526-8.

<https://www.ncbi.nlm.nih.gov/pubmed/35704428>.

47. Hachmann NP, Miller J, Collier A-rY, Ventura JD, Yu J, Rowe M, et al. Neutralization Escape by the SARS-CoV-2 Omicron Variants BA.2.12.1 and BA.4/BA.5 2022 [Available from:

<https://www.medrxiv.org/content/medrxiv/early/2022/05/19/2022.05.16.22275151.full.pdf>.

48. Quandt J, Muik A, Salisch N, Lui BG, Lutz S, Kruger K, et al. Omicron BA.1 breakthrough infection drives cross-variant neutralization and memory B cell formation against conserved epitopes 2022 [updated Jun 2PMC9162083]. 20220602:[eabq2427]. Available from:

<https://www.ncbi.nlm.nih.gov/pubmed/35653438>.

49. Hansen CH, Friis NU, Bager P, Stegger M, Fonager J, Fomsgaard A, et al. Risk of Reinfection, Vaccine Protection, and Severity of Infection with the BA.5 Omicron Subvariant: A Danish Nation-Wide Population-Based Study 18 July 2022 [Available from: <https://ssrn.com/abstract=4165630>.

50. Altarawneh HN, Chemaitelly H, Ayoub HH, Hasan MR, Coyle P, Yassine HM, et al. Protection of SARS-CoV-2 natural infection against reinfection with the Omicron BA.4 or BA.5 subvariants 2022 [Available from:

<https://www.medrxiv.org/content/medrxiv/early/2022/07/12/2022.07.11.22277448.full.pdf>.

51. European Centre for Disease Prevention and Control. Communicable Disease Threats Report: Week 19, 8-14 May 2022 2022 [updated 13 May 2022. Available from:

<https://www.ecdc.europa.eu/sites/default/files/documents/Communicable-disease-threats-report-8-May-2022-public.pdf>.

52. UK Health Security Agency. SARS-CoV-2 variants of concern and variants under investigation in England Technical briefing 43 24 June 2022 [Available from:

[https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment\\_data/file/108649/4/Technical-Briefing-43-28.06.22.pdf](https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/108649/4/Technical-Briefing-43-28.06.22.pdf).

53. Kislaya I, Casaca P, Borges V, Sousa C, Ferreira BI, Fernandes E, et al. SARS-CoV-2 BA.5 vaccine breakthrough risk and severity compared with BA.2: a case-case and cohort study using Electronic Health Records in Portugal 2022 [2022.07.25.22277996]. Available from:

<https://www.medrxiv.org/content/medrxiv/early/2022/07/25/2022.07.25.22277996.full.pdf>.

54. Tuekprakhon A, Huo J, Nutalai R, Dijokaite-Guraliuc A, Zhou D, Ginn HM, et al. Further antibody escape by Omicron BA.4 and BA.5 from vaccine and BA.1 serum 2022 [2022.05.21.492554]. Available from:

<http://biorxiv.org/content/early/2022/05/23/2022.05.21.492554.abstract>.

55. Cao Y, Yu Y, Song W, Jian F, Yisimayi A, Yue C, et al. Neutralizing antibody evasion and receptor binding features of SARS-CoV-2 Omicron BA.2.75 2022 [2022.07.18.500332]. Available from:

<https://www.biorxiv.org/content/biorxiv/early/2022/07/19/2022.07.18.500332.full.pdf>.

56. Sheward DJ, Kim C, Fischbach J, Muschiol S, Ehling RA, Björkström NK, et al. Evasion of neutralizing antibodies by Omicron sublineage BA.2.75 2022 [2022.07.19.500716]. Available from:

<https://www.biorxiv.org/content/biorxiv/early/2022/07/20/2022.07.19.500716.full.pdf>.

57. Wang Q, Iketani S, Li Z, Guo Y, Yeh AY, Liu M, et al. Antigenic characterization of the SARS-CoV-2 Omicron subvariant BA.2.75 2022 [2022.07.31.502235]. Available from:

<https://www.biorxiv.org/content/biorxiv/early/2022/08/01/2022.07.31.502235.full.pdf>.

58. Gruell H, Vanshylla K, Tober-Lau P, Hillus D, Sander LE, Kurth F, et al. Neutralization sensitivity of the SARS-CoV-2 Omicron BA.2.75 sublineage 2022 [2022.08.04.502609]. Available from:

<https://www.biorxiv.org/content/biorxiv/early/2022/08/04/2022.08.04.502609.full.pdf>.

59. Qu P, Evans JP, Zheng Y-M, Carlin C, Saif LJ, Oltz EM, et al. Evasion of Neutralizing Antibody Response by the SARS-CoV-2 BA.2.75 Variant 2022 [2022.08.14.503921]. Available from:

<https://www.biorxiv.org/content/biorxiv/early/2022/08/15/2022.08.14.503921.full.pdf>.

60. Karyakarte RP, Das R, Taji N, et al. An Early and Preliminary Assessment of the Clinical Severity of the Emerging SARS-CoV-2 Omicron Variants in Maharashtra, India: Cureus; 2022 [Available from:

<https://www.cureus.com/articles/123067-an-early-and-preliminary-assessment-of-the-clinical-severity-of-the-emerging-sars-cov-2-omicron-variants-in-maharashtra-india>.





61. Saito A, Tamura T, Zahradnik J, Deguchi S, Tabata K, Kimura I, et al. Virological characteristics of the SARS-CoV-2 Omicron BA.2.75 2022 [2022.08.07.503115]. Available from: <https://www.biorxiv.org/content/biorxiv/early/2022/08/08/2022.08.07.503115.full.pdf>.
62. Arora P, Nehlmeier I, Kempf A, Cossmann A, Schulz SR, Dopfer-Jablonka A, et al. Lung cell entry, cell-cell fusion capacity, and neutralisation sensitivity of omicron sublineage BA.2.75. The Lancet Infectious Diseases. 2022;22(11):1537-8. [https://doi.org/10.1016/S1473-3099\(22\)00591-6](https://doi.org/10.1016/S1473-3099(22)00591-6).
63. Jian F, Yu Y, Song W, Yisimayi A, Yu L, Gao Y, et al. Further humoral immunity evasion of emerging SARS-CoV-2 BA.4 and BA.5 subvariants 2022 [2022.08.09.503384]. Available from: <https://www.biorxiv.org/content/biorxiv/early/2022/08/10/2022.08.09.503384.full.pdf>.
64. UK health Security Agency. SARS-CoV-2 variants of concern and variants under investigation in England: Technical briefing 46 2022 [Available from: [https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment\\_data/file/110982/0/Technical-Briefing-46.pdf](https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/110982/0/Technical-Briefing-46.pdf)].
65. Public Health Ontario. Evidence Brief: Risk Assessment for Omicron Sublineages BQ.1 and BQ.1.1 (as of Oct 5, 2022) 2022 [Available from: [https://www.publichealthontario.ca/-/media/Documents/nCoV/voc/2022/10/omicron-bq1-bq11-oct-5.pdf?sc\\_lang=en](https://www.publichealthontario.ca/-/media/Documents/nCoV/voc/2022/10/omicron-bq1-bq11-oct-5.pdf?sc_lang=en)].
66. UK health Security Agency. SARS-CoV-2 variants of concern and variants under investigation in England: Technical briefing 47 2022 [Available from: [https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment\\_data/file/111507/7/Technical-Briefing-47.pdf](https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/111507/7/Technical-Briefing-47.pdf)].
67. Wang Q, Iketani S, Li Z, Liu L, Guo Y, Huang Y, et al. Alarming antibody evasion properties of rising SARS-CoV-2 BQ and XBB subvariants. bioRxiv. 2022:2022.11.23.517532. <https://www.biorxiv.org/content/biorxiv/early/2022/11/28/2022.11.23.517532.full.pdf>.
68. Reuters. Factbox: What are the new BQ.1 and BQ.1.1 coronavirus variants, and why it matters 2022 [Available from: <https://www.reuters.com/business/healthcare-pharmaceuticals/what-are-new-bq1-bq11-coronavirus-variants-why-it-matters-2022-11-04/>].
69. World Health Organisation (WHO). Weekly epidemiological update on COVID-19 - 2 November 2022 2022 [Available from: [https://www.who.int/docs/default-source/coronaviruse/situation-reports/20221102-weekly-epi-update-116.pdf?sfvrsn=e2510ada\\_4&download=true](https://www.who.int/docs/default-source/coronaviruse/situation-reports/20221102-weekly-epi-update-116.pdf?sfvrsn=e2510ada_4&download=true)].
70. European Centre for Disease Prevention and Control. Changes to list of SARS-CoV-2 variants of concern, variants of interest, and variants under monitoring 2022 [updated 14 October 2022. Available from: <https://www.ecdc.europa.eu/sites/default/files/documents/Variants%20changelog%2014%20October%2022.pdf>].
71. European Centre for Disease Prevention and Control. Communicable Disease Threats Report: Week 41, 9 - 15 October 2022 2022 [Available from: <https://www.ecdc.europa.eu/sites/default/files/documents/Communicable-disease-threats-report-14-october-2022.pdf>].
72. NSW Health. NSW respiratory surveillance reports - COVID-19 and influenza. Latest surveillance report. Summary of epidemiological week 47 ending 26 November 2022 2022 [Available from: <https://www.health.nsw.gov.au/Infectious/covid-19/Pages/weekly-reports.aspx>].
73. Cornelius Roemer RH, Nicholas Frohberg, Hitoshi Sakaguchi, Federico Gueli, Thomas P. Peacock. SARS-CoV-2 evolution, post-Omicron [Available from: <https://virological.org/t/sars-cov-2-evolution-post-omicron/911/1>].
74. Sheward DJ, Kim C, Fischbach J, Muschiol S, Ehling RA, Björkström NK, et al. Omicron sublineage BA.2.75.2 exhibits extensive escape from neutralising antibodies 2022 [2022.09.16.508299]. Available from: <https://www.biorxiv.org/content/biorxiv/early/2022/09/16/2022.09.16.508299.full.pdf>.
75. University of Edinburgh, Centre for Genomic Pathogen Surveillance, University of Oxford, bluedot, University of Cambridge, University of Sydney. Lineage list [Available from: [https://cov-lineages.org/lineage\\_list.html](https://cov-lineages.org/lineage_list.html)].
76. Fast growing BR.2 with ORF8:S67F, at least 130 samples, Australia, USA and Japan #1292 2022 [Available from: <https://github.com/cov-lineages/pango-designation/issues/1292>].



77. NSW Government. NSW respiratory surveillance reports - COVID-19 and influenza, Latest surveillance report Summary of epidemiological week 44 ending 5 November 2022 2022 [Available from: <https://www.health.nsw.gov.au/Infectious/covid-19/Pages/weekly-reports.aspx>.
78. Centers for Disease Control and Prevention (CDC). COVID Data Tracker: Variant Proportions 2022 [Available from: <https://covid.cdc.gov/covid-data-tracker/#variant-proportions>.