



Date: 27 September 2022

SARS-CoV-2 Variants of Concern Update

This document provides an overview of currently circulating SARS-CoV-2 variants as well as newly identified variants. Characteristics of these variants are monitored and reported including: growth advantage/ transmissibility; disease course/ viral dynamics; clinical features (symptoms and severity); immune evasion, vaccine effectiveness and therapeutics effectiveness; and detection/testing.

All viruses, including SARS-CoV-2, change over time. Most of these changes have little to no impact on the properties of the virus, but some may affect properties such as: how easily it spreads, the associated disease severity, the performance of vaccines, therapeutic medicines, diagnostic tools, or the performance of other public health and social measures.

A selected sub-set of topic areas are comprehensively updated in each issue of this document. The dates stated for section updates relate to when a comprehensive update was performed, although additional data might have been added in the interim. New information included since the previous update is provided in red text.

This issue has been consolidated and condensed. Out-dated information has been removed as necessary.

Structure of Report

- **Section 1: Key new information**
- **Section 2: Public Health Risk Assessment of circulating variants**
- **Section 3: Evidence base**
- **Section 4: References and appendices**



Circulating variants across Aotearoa New Zealand:

The Institute of Environmental Science and Research (ESR) reports there are five (sub)variants that each make up 2% or more of the sequenced community samples in Aotearoa New Zealand in the period of 3 to 16 September:

- BA.5 ~91% of sequenced community samples
- BA.4 ~3% of sequenced community samples
- BA.4.6 ~3% of sequenced community samples
- BA.2 ~2% of sequenced community samples

For further information regarding the genomic report produced by ESR, please refer to the following. ([link](#))

Current overall variant risk status:

There is no strong evidence of large increases in transmissibility or disease severity associated with the most recent variants (those after BA.5). The frequency of BA.4.6 is being closely monitored in New Zealand.



Executive Summary

Section updated: 27 September 2022

The pandemic remains in a phase of variants with lower disease severity and moderate immune escape. There are currently no new variants that are considered highly likely to change this situation, but the expectation in the short term is that new Omicron variants with a slight growth advantage will continue to emerge. The development of new Omicron variants, alongside waning immunity, could result in a further wave of infection in the medium (3-6 months) term internationally and in New Zealand.

SARS-CoV-2 Omicron now has numerous subvariants with large numbers of mutations in differing locations in the genome. Internationally, Omicron (including its subvariants¹) is the only widely circulating Variant of Concern (VoC, as designated by the WHO). (1, 2) However, whole genome sequencing efforts are falling globally, reducing the ability of surveillance to detect VoCs as they emerge.

BA.5 is the dominant variant internationally. BA.5 is also the dominant variant in New Zealand with a stable prevalence of between 85 – 90% throughout August and early September 2022. Omicron variants identified in New Zealand with a prevalence of more than 2% in mid-September 2022 include BA.2, BA.4, BA.4.6 and BA.5. The variants detected at the New Zealand border are currently similar to those detected in the community, and no variants are overrepresented in hospital surveillance data. New Zealand will continue to monitor variant trends using whole genome sequencing and wastewater testing.

None of the current Omicron variants have demonstrated a clinically relevant increase in disease severity relative to the number of cases. Vaccination, including boosters, remains effective at decreasing the risk of hospitalisation and death from Omicron. It remains difficult to predict the impact of variants here in Aotearoa New Zealand based on overseas trends as our infection history and hybrid-immunity differ from other countries.

There has been a decrease in the effectiveness of monoclonal antibodies over time. There has been no observed change in the efficacy of antivirals. The performance of tests for COVID-19 has not changed.

¹ Includes BA.1, BA.2, BA.3, BA.4, BA.5 and descendent lineages.



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Section 1 Key updates

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Growth advantage/transmissibility

- BA.4.6 has an estimated growth advantage of 6.55% per week (95% CrI²: 5.53 – 7.57) compared to BA.5 in the UK. (3)
- Over an average 2.3 days of exposure to the index case, the unadjusted risk of Omicron transmission to all close contacts of index cases was 29% (95% CI: 26-31%). Unvaccinated index cases had a 36% (30-42%) risk of transmitting to close contacts, while vaccinated index cases had a 27% (24-30%) risk of transmitting to close contacts. (4)

Immune evasion, vaccine effectiveness

- People who have had a SARS-CoV-2 infection after vaccination have higher neutralising antibody (nAb) levels compared to those who are vaccinated but have not been infected.
- nAb titres wane at slower rates for people who have had a SARS-CoV-2 infection after vaccination compared to those who are vaccinated but have not been infected.

Disease course / Clinical features (symptoms and severity)

- A systematic review and meta-analysis assessing the incubation period associated with different SARS-CoV-2 variants published in August 2022 found that the mean incubation period for COVID-19 cases caused by the Omicron variant was 3.42 days.
- Further evidence supports the observation that the Omicron variant tends to be associated with less severe clinical outcomes compared to Delta.

Therapeutics effectiveness

- Pfizer have initiated a Phase II trial testing Paxlovid in immunocompromised patients. The trial will compare 5-, 10-, and 15-day courses of the oral antiviral to investigate the effect of longer dosing in reducing the incidence of rebound infections. Results from this study are expected September 2023.
- Research published in the New England Journal of Medicine reports that three antivirals (Paxlovid, molnupiravir, and remdesivir) retain efficacy against the dominant Omicron sublineages BA.5 and BA.2.75. (5)
- Two pre-prints have assessed the neutralising abilities against Omicron variants and reported that Evusheld has markedly reduced potency against the emerging Omicron sublineage BA.4.6 in *in vitro*

² 95% Credible Interval



studies. (6, 7) Although this is preliminary data, it indicates that Evusheld may not be as effective against this variant which may be significant if this becomes a dominant variant. BA.4.6 has a slight growth advantage compared to other variants but is not currently a dominant variant in New Zealand. (8) However, this variant is showing steady growth in US and UK therefore is being monitored domestically. (8, 9)

Detection/testing

- Currently there is some emerging evidence that suggests a clinically relevant decrease in the performance of RATs for detection of the Omicron variant. (10, 11) Comparability between studies is limited by difference in study design and objectives. For these reasons it is difficult to compare the results between studies and evidence of reduced sensitivity may not be indicative of device performance.

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 documents

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

- WHO: Weekly epidemiological update on COVID-19 – 7 September 2022 (2)
- UK Health Security Agency: SARS-CoV-2 Variants of Concern and Variants under Investigation in England, Technical Briefing 45, 9 September 2022 (3)

The WHO Weekly Epidemiology Update on 7 September 2022 (2) reported that:

- The number of sequences submitted to GISAID continues to decline and 99% of submitted sequences (globally) between 5 August and 5 September 2022 were the Omicron variant. Among Omicron sequences submitted between 22 August and 28 August, BA.2 lineages represented 3% of sequences, while BA.4 lineages represented 4% and BA.5 lineages represented 87%.
- The WHO reported that 'BA.2.75, an Omicron descendent lineage under monitoring, still shows a relatively low (0.9% and 1.2% in weeks 33 and 34 respectively) prevalence globally, but a number of countries have observed recent increasing trends.'



Section 2: Summary of Variants

Public Health Risk Assessment BA.5

Note: BA.4 and BA.5 have identical spike protein. Many results for these subvariants are reported as combined results on the basis of characterisation using S Gene Target Failure (SGTF).

Updated: 27 September 2022

	Overall Risk Assessment*	Confidence level **	Assessment and rationale
Overall growth advantage	Increased risk	High	<p>Evidence of a growth advantage compared to BA.2.</p> <p><i>As at 22 September 2022, BA.5 is the predominant variant in New Zealand.</i></p> <p>BA.5 has a reported growth advantage of 11.2% over the previously dominant variant BA.2. The growth in BA.5 observed in the whole genome sequencing of individual testing is consistent with the growth observed in wastewater. As cases of BA.5 were increasing and displacing BA.2 in May and early June, the estimated growth rate of BA.5 for New Zealand was approximately 9% per day or 7 day doubling time. (12) This is consistent with growth advantages observed internationally.</p>
Transmissibility	Insufficient data	Insufficient data	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 BA.5 compared to prior Omicron variants, and BA.5 may have increased infectivity. (13)
Immune evasion	Increased risk	High	<p>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, but this is subject to revision. Growth advantage is likely mostly due to immune evasion properties, rather than changes to intrinsic transmissibility.</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.(14-16)</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.(17-19)</p>
Vaccine Effectiveness	Low	Low/ Moderate	<p><i>Vaccine effectiveness (VE):</i> Insufficient data for robust assessment of vaccine effectiveness but early data suggest there no indicators of a large change in VE against symptomatic infection from BA.2 to BA.5.(17, 20). One study has observed a decrease in VE against hospitalisation between BA.2 and BA.5, comparing people who had received the booster (3 dose with prior infection) to unvaccinated (with prior infection). No difference was seen for VE mortality. (21) The current epidemiological data, whilst incomplete, is consistent with the neutralisation findings.</p>
Severity	Possible increase in risk of hospitalisation	Low/ Moderate	<p>Booster vaccination reported to be associated with a lower risk reduction against BA.5 of hospitalisation (77%) and death (88%) compared to the risk reduction for BA.2 of 92% and 94% respectively.</p>
Therapeutics	Low	Moderate	<p>One <i>in vitro</i> study shows increased resistance to Evusheld compared to BA.2, (22) whilst another shows it retains activity. (23)</p> <p>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. (24)</p>
Testing	Insufficient Data	Insufficient data	
Overall Assessment			<p>There is an increase in overall risk from the previous predominant variant, BA.2. BA.5 is more transmissible compared to BA.2 and is the variant associated with the current wave of cases in New Zealand.</p>



*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 (Centaurus)

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	Overall risk assessment*	Confidence level **	Assessment and rationale
Overall growth advantage	Increased Risk	Moderate	<p>Evidence of a growth advantage compared to BA.5.</p> <p>Prevalence in community cases to 2 September in New Zealand is 2% and of border cases is 5%.</p> <p>There is evidence that BA.2.75 has a growth advantage against BA.4/5 in some countries (India, Austria, Singapore).</p> <p><i>There are too few samples of BA.2.75 internationally or in New Zealand to determine if the observed growth advantage observed overseas will be replicated in New Zealand. The data requires continued close monitoring.</i></p>
Transmissibility	Insufficient data	Insufficient data	<p><i>There is no direct data on intrinsic transmissibility and there is no current ability to measure this directly from surveillance data</i></p>
Immune evasion	No change in risk	Low	<p><i>No evidence of increased immune evasion.</i></p>



			<p><i>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.</i></p> <p><i>Laboratory data: Neutralisation studies found that BA.2.75 was similar or slightly less able to neutralise antibodies produced after BA.2 infection and vaccination, compared to BA.4 or BA.5. (25-29) Potentially higher receptor binding compared to other Omicron lineages. There are no data on the ability of BA.2.75 to neutralise antibodies produced after BA.5 infection.</i></p>
Severity	Insufficient data	Insufficient data	<p>No evidence of a change in severity compared to BA.5</p> <p><i>Too few cases have been detected internationally or in New Zealand to evaluate severity. Lab and animal studies suggest mixed results for binding compared to BA.5, (29) but overall pathogenicity similar to BA.5. (30)</i></p>
Therapeutics	Insufficient data	Insufficient data	
Testing	Insufficient data	Insufficient data	
No change in risk			

*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.4.6 (Aeterna)

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	Overall risk assessment*	Confidence level **	Assessment and rationale
Overall growth advantage	Increased risk	Low	Evidence of a growth advantage compared to BA.4/5. BA4.6 prevalence has slowly increased in NZ, now accounting for approximately 4% of genomes tested in the two weeks to 2 September.
Transmissibility	Insufficient data	Insufficient data	
Immune evasion	No change in risk	Low	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. (6)
Severity	Insufficient data	Insufficient data	
Therapeutics	Increased risk	Low	Some indication that Evusheld is less effective for this variant. (6)
Testing	Insufficient Data	Insufficient Data	
	No change in risk		



Other New and Circulating Variants

Updated: 27 September 2022

Pango lineage	Other label	Earliest documented samples	International Detection	Detection in NZ
BA.4.6	Not yet designated	USA, May 2022. (31)	Detected in GISAID in the past 12 weeks (as at 13 September) across 19 different countries including the UK. (9)	Detected in 2 weeks to 8 September
BA.2.10.X	Not yet designated	India, 02 July 2022. (BA.2.10.1) (32)	Detected in GISAID in the past 12 weeks (as at 9 August), predominantly in India. (32)	Not detected in 2 weeks to 8 September
BA.5.2.1	Not yet designated	China, 08 July 2022 (33)	Detected in GISAID in the past 12 weeks (as at 13 September) across 19 different countries including the UK. (9)	Not detected in 2 weeks to 8 September
BA.2.75	Omicron sub-lineage BA.2.75	India, 02 June 2022	Detected in GISAID in the past 12 weeks across 15 different countries including the UK (as at 13 September). (9)	Variant of Interest as of 07 July 2022 (34)
BA.4	Omicron sub-lineage BA.4	South Africa, January 2022. (35)	Detected in the UK in the past 12 weeks as at 28 August. (3)	Detected in 2 weeks to 8 September
BA.5	Omicron sub-lineage BA.5	South Africa, February 2022. (35)	Dominant globally as at 13 September. (9)	Detected in 2 weeks to 8 September
BA.2.12.1			Not detected in the UK in the past week as at 28 August. (3)	Not detected in 2 weeks to 8 September
BA.2	Omicron		Detected in the UK in the past 12 weeks as at 28 August. (3)	Detected in 2 weeks to 8 September
BA.3	-	South Africa (36)	Not detected in the UK in the past week as at 28 August. (3)	Not detected in 2 weeks to 8 September



Previously Circulating Variants

Updated: 27 September 2022

Pango lineage	Other label	International Detection	Latest Detection NZ Community	Latest Detection NZ Border
BA.1	Omicron	Not detected in the UK in the past week as at 28 August. (3)		
Delta and Omicron recombinant lineages (UK)	-	Detected in the UK in the past 12 weeks as at 22 July.(37)		
AY.119.2/BA.1.1 Recombinant		Not detected in the UK in the past 12 weeks as at 22 July.(37)		
XD Recombinant (Delta x BA.1)		Not detected in the UK in the past 12 weeks as at 22 July.(37)		
XE Recombinant (BA.1 x BA.2)		Detected in the UK in the past 12 weeks as at 22 July.(37)		
AY.119.2/BA.1.1 Recombinant		Not detected in the UK in the past 12 weeks as at 22 July.(37)		
BA.1/BA.2 Recombinant (with unique mutation C3583T)		Detected in the UK in the past 12 weeks as at 22 July.(37)		
XF Recombinant		Not detected in the UK in the past 12 weeks as at 22 July.(37)		
B.1.617.2 and sub-lineages	Delta	Detected in the UK in the past 12 weeks as at 22 July.(37)	March 2022	March 2022
B.1.1.7	Alpha	Detected in GISAID, but not in the UK, in the past 12 weeks as at 22 July.(37)		



New signals

Section updated: 27 September 2022

The risk of clinically significant emerging variants is considered to be high, according to the WHO. (38) The WHO has expressed concern in early April, some countries have significantly reduced SARS-CoV-2 testing. They caution that unless robust surveillance systems are retained, countries may lose the ability to accurately interpret epidemiological trends, implement the appropriate measures necessary to reduce transmission and monitor and assess the evolution of the virus. (39) [Details of BA.4.6, BA.5 and BA.2.75 can be found above in the risk assessment.](#)

BQ.1.1

- An Omicron subvariant that is most closely related to the BA.5 subvariant. First flagged on 26 August 2022 with sequences from the USA, UK and Japan. (40)
- Spike protein mutational profile is the same as BA.5 with the following mutations: R346T, K444T and N460K.
- One BQ.1.1 *in vitro* study showed increased resistance to Evusheld and bebtelovimab. (41)

BA.2.3.20

- A BA.2 and Delta recombinant that has a growth advantages over BA.5. (41) Variant has been detected in three countries distant from one another has rare 2-nucleotide mutation S:A484R. First detected in the United States and has since been detected in Singapore. (42)

BJ.1

- Detected on the 29 July 2022, is a BA.2 sub-lineage with 14 additional mutations in the spike protein, this variant has been mostly detected in India (70% of all BJ.1 cases) and has also been detected in Singapore, South Korea, Austria and the United States of America. (32, 43)

BA.2.10.X

- BA.2.10.X (also referred to as BA.2.10.1, BA.2.10.4 or BA.2.10+) is an Omicron subvariant, that has been identified due to its large collection of mutations. There is no observed evidence for phenotypic changes (transmission, severity, immune evasion), and there are very few reported cases of this variant to date.(32)

BA.2.75.2

- A pre-print study has found BA.2.75.2 to be resistant to neutralisation by Evusheld (tixagevimab and cilgavimab), but has remained sensitive to bebtelovimab. (44)
- Serum from blood donors in Sweden was on average five-fold less effective at neutralising BA.2.75.2 compared to BA.5. (44)
- BA.2.75.2 is carrying additional mutations, R346T, F486S, and D1199N that due to its growth advantage are suggestive of more extensive escape from neutralising antibodies than previous Omicron variants. (44)

BA.5.2.1

- A new subvariant of the Omicron BA.5 lineage detected in China on the 8 July 2022.(33) The first confirmed case of BA.5.2.1 was detected in Shanghai, with more cases since identified



across multiple provinces in China.(33) There is limited scientific evidence around transmission potential, disease severity and other properties of this variant.



Section 3: Evidence Base: Omicron

Growth advantage/ transmissibility

Section updated: 27 September 2022

Omicron is more transmissible and has a higher secondary attack rate than Delta

- A study estimated that Omicron (B.1.1.529) had a growth advantage that corresponds to a 5.4-fold (95% CI = 3.1–10.1) weekly increase in cases compared with Delta. (45)
- Data from Denmark (to 18 Dec 2021), the effective reproduction number of Omicron is 3.19 (95%CI 2.82–3.61) times greater than Delta under the same epidemiological conditions. (46)
- Data from Texas, USA, indicated a case-doubling time for Omicron of 1.8 days, three times faster than for Delta in this area. (47)
- Data from the UK estimated a shorter generation time (interval between infection events) for Omicron with a mean of 1.5-3.2 days (standard deviation [SD] 1.3-4.6 days), compared to a mean of 2.5-4 days (SD 1.9-3 days) for Delta. (48)
- UKHSA analysis of contact-tracing data shows the mean serial interval for BA.1 is 3.72 days (95% CI: 3.62 - 3.80). (49)
- BA.4 and BA.5 are estimated to have had a daily growth advantage of 0.08 (95% CI: 0.08–0.09) and 0.10 (95% CI: 0.09–0.11), respectively, relative to BA.2 in South Africa in May 2022. (50)
- **BA.4.6 has an estimated growth advantage of 6.55% (95% CrI³: 5.53 – 7.57) compared to BA.5 in the UK. (3)**

Household transmission

- Secondary Attack Rate (SAR) of 29% for BA.1 compared with an SAR of 39% for BA.2 across households infected with Omicron. (51)
- SAR for Omicron ranges from 7.6% to 50% depending on country and setting. (52-54)
- **Over an average 2.3 days of exposure to the index case, the unadjusted risk of Omicron transmission to all close contacts of index cases was 29% (95% CI: 26-31%). Unvaccinated index cases had a 36% (30-42%) risk of transmitting to close contacts, while vaccinated index cases had a 27% (24-30%) risk of transmitting to close contacts. (4)**

Other data

- The Omicron variant has a survival time in the environment of 21.1 hours (95% CI: 15.8–27.6) compared to 16.8 hours (95% CI: 13.1–21.1) for Delta. (55) The high environmental stability of Omicron could increase the risk of contact transmission and contribute to its spread. However,

³ 95% Credible Interval



convincing evidence of fomite transmission has not been demonstrated for any variant to date.

- A study found that initial testing of HCWs if they had a household positive case in majority of instances, was sufficient to prevent nosocomial transmission to patients. (56)
- A human challenge study using **wild-type virus** found that a dosage of 10 TCID₅₀ (very low dose) was sufficient to result in an infection. Also, they found that viral shedding occurs in both the nose and throat at high levels irrespective of symptom severity. (57)



Immune Evasion / Vaccine effectiveness

Vaccine Effectiveness in adults – Pfizer

Section updated: 27 September 2022

Please note: Current COVID-19 vaccines authorised in New Zealand are based on the ancestral strain of the SARS-CoV-2 virus (wild type or Wuhan-strain).

Vaccine effectiveness against Omicron related infection, hospitalisation and death is lower than prior variants and may wane more rapidly than for previous COVID-19 variants. (58)

VE against infection

Primary Course (2 doses)

VE against infection with Omicron is estimated at 40- 55% within 14-30 days after 2 doses of Pfizer. (58, 59) However, the VE wanes to levels unlikely to reduce transmission within 5-6 months of the second dose. (59, 60)

Booster (three doses)

VE of one booster (three doses) against Omicron infection is 55-69%. (58, 59) The VE against Omicron infection wanes to 50% (95% CI: 46.5; 53.1) after four months for individuals aged 18-59 years. (59)

Second booster (four doses)

VE relative to a first booster dose against Omicron infection is estimated between 30-45% 7-30 days after the second booster. (61, 62) and 33-65% in the period of 2-6 weeks after the second booster. (63, 64)

Two studies estimated a decline in relative VE down to 10-22% from 8-10 weeks after receiving the second booster. (63, 64)

Note: Many countries have only recently began implementing a second booster dose for specific population groups, so data are still emerging about potential benefits and risks. Currently, most studies are in groups that received a second booster first (e.g. elderly and immunocompromised). Additionally, data from studies can be difficult to interpret separately for just 'Pfizer' as many studies combine Pfizer and Moderna datasets, as both are mRNA vaccines.

VE against symptomatic infection

Primary Course (2 doses)

VE against Omicron variant causing symptomatic has been estimated at 42% (95% CI: 15-60) based on meta-analysis. (65) However, this does not account for time since vaccination.

First booster (three doses)

Two-dose vaccine effectiveness against Omicron variant causing symptomatic infection has been estimated at 42% (95% CI: 15-60) based on meta-analysis. (65) However, this does not account for time since vaccination.

Second booster (four doses)



A study on efficacy showed relative VE 7 to 30 days after receiving the second booster dose was approximately 55% (95% CI, 53 to 58) against symptomatic Omicron infection compared to one booster dose. (61)

VE against severe disease / hospitalisation

Primary course (2 doses)

Data from multiple countries indicate that vaccine effectiveness is between 62% - 70%, from 2 weeks after receiving the second dose. (60, 66) A US study with mRNA vaccines reported a higher VE of 81%. (67) After 5-6 months the VE declined to 44% (CI 95%, 30-54%) (60), whereas a Danish study reported an VE of 66% after 4 months. (59)

First booster (3 doses)

VE of one booster (three doses) against Omicron related hospitalisation is estimated to be 83%. (58, 68-73)

Data from multiple countries (UK, South Africa, USA, Denmark, and Hong Kong) show high vaccine effectiveness (VE) of 89% - 92% against hospitalisation for people aged 18-59 years >2 weeks after receiving a booster including for those people aged 65 years or older. (59, 66, 67, 74, 75)

After 10 or more weeks the VE against Omicron related severe disease/hospitalisation has been estimated to wane to 75-83%. (74, 75) and further wanes to approximately 50% after >3 months. (66, 67, 76).

Second booster (4 doses)

Compared to people vaccinated with one booster dose of Pfizer, the relative VE against infection of a fourth dose peaks at 64% (62-66%) during the third week (77).

Relative VE against Omicron related severe disease is estimated at between 58% - 77% 2-6 weeks after second booster dose with no signs of waning by the 6th week. (61, 63, 64), increasing to 87% after 7-10 weeks. (64, 77) For people aged 60+ year relative VE peaked after 3-4 weeks at an adjusted rate of 52%. (63)

Adjusted VE against BA.4/5 related hospitalisation is estimated to be 60% (95%CI, 42-73%) up to three months after receiving the second booster and 56% (95% CI, 41-46%) after >3 months. (78)

VE against death

Primary course (2 doses)

Qatar: VE against Omicron-related severe, critical or fatal COVID-19 infection for two doses of Pfizer was estimated to be 73.5% (95% CI, 60.5 - 82.2%). (68)

First booster (three doses)

Qatar: relative VE (compared to the primary course) against any severe, critical, or fatal COVID-19 for a Pfizer booster dose was estimated at 100.0% (95% CI: 71.4-100.0). (79)

Hong Kong: relative VE (compared to the primary course) against Omicron (BA.2) related mortality for 20-59 years was 83% (-29-98%), 60-69 years 82% (20-96%), 80+ years 66% (-1.3-89%). (76)

Second booster (four doses)

A study on efficacy indicates that relative VE 14 to 30 days after receiving the second booster dose was 76% against Omicron related death compared to one booster dose. (61)



The relative VE (compared to third dose) of a fourth dose of mRNA vaccine against all-cause mortality in long-term care facilities residents in Sweden declined to 27% 61-126 days post vaccination. (80)

World Health Organization review of vaccine efficacy

A WHO weekly epidemiological report (14 August 2022) included an updated summary of evidence on Omicron, including for vaccine effectiveness. (81)

The WHO notes that results of vaccine effectiveness (VE) studies should be interpreted with caution because estimates vary with the type of vaccine administered and the number of doses and scheduling (sequential administration of different vaccines). (81)

Some key points from the WHO interpretation of results of VE for the Omicron variant include:

- To date, 37 studies from 15 countries have assessed the duration of protection of six vaccines against the Omicron variant.
- Findings from these studies show reduced VE of primary vaccine series against the Omicron variant than has been observed for previous variants, for all outcomes (severe disease, symptomatic disease, and infection).
- However, in the majority of studies, VE estimates against the Omicron variant remain higher for severe disease.
- VE estimates against symptomatic disease and infection within the first three months of primary series vaccination tended to be lower than those against severe disease, and VE decreased more substantially over time.
- Booster vaccination substantially improves VE for all outcomes, but studies that assess VE of booster vaccination beyond 6 months are needed to evaluate the duration of protection are not yet available.

Omicron: Immunological response to vaccination

Section updated: 27 September 2022

Immunological response to vaccine in adults, T-cells & B cells

A longitudinal study in vaccinated UK health care workers showed that immune response varies based on previous infection and vaccination. (82)

- The study found that different infection histories alongside different timings of vaccination had an impact on immune response against Omicron.
- The study results most relevant to the New Zealand population (vaccinated, and either infection naïve or post-Omicron infection) were that Omicron infection in vaccinated people resulted in some enhancement of neutralising antibody and T-cell response against Omicron, but this enhancement was less than that observed against earlier variants (Alpha and Delta).
- The study cohort contained only vaccinated participants, so the magnitude of immune response to Omicron infection could not be compared to the response in people naïve to any SARS-CoV-2 antigen exposure.
- The study investigators hypothesise that previous order of exposure to SARS-CoV-2 antigens (through vaccination or infection) results in immune imprinting, which affects response to subsequent SARS-CoV-2 exposures.



Neutralising antibody (nAb)

Neutralisation studies provided initial data predicting lower vaccine effectiveness against Omicron (BA.1) than for previous variants. (83-88) BA.2 does not appear to have a greater capacity for immune evasion by antibody neutralisation than BA.1. (89-91) These data have now been superseded by effectiveness data.

Neutralising antibody against BA.5

Neutralisation titres from studies suggest that vaccine-induced neutralising antibody levels against BA.4 and BA.5 are lower than against BA.1 and BA.2 in serum from triple dosed vaccinated individuals, but data remain limited: (23, 92) One study compared the neutralisation of BA.4/5 28 days after a third dose of Pfizer (BNT162b2) and found antibody titres were reduced 3.2-fold compared to both BA.1 and BA.2. (23)

A follow-up study of 700 participants who received a second booster of Pfizer (four months after first booster) found a 26% multiplicative decay per week of neutralising antibodies and 14% of immunoglobulin G (IgG). (93) A pre-print (July 2022) compared the levels of neutralisation titres of antibodies against SARS-CoV-2 variants after three and four doses of vaccination of Pfizer or Moderna. (94) In this study a fourth dose increased neutralisation titres by 5.6-fold against BA.4/BA.5 compared to levels after a third dose only. However, even after the fourth dose, the titres were significantly decreased against BA.4/BA.5 compared to against BA.2 and the original Wuhan variants which were 2.5-fold and 16.4-fold higher respectively.

It is not yet clear how these neutralising antibody levels relate to vaccine efficacy (i.e. there is no established correlate of protection).

Analysis of whole-blood samples of 100 volunteers confirms that boosters can achieve higher levels of nAb blocking (blocking activity of a sample against the binding of the viral spike protein to the human receptor) against VOCs than that achieved by the initial two-dose vaccination. (95) There is significant variability in the percentage of nAb blocking against Omicron infection from after two doses of mRNA vaccine, with a range of 0.0% to 39.4%. The nAb blocking increased to a median of 88.1% one month after the first booster and waned to a median of 70.7% (CI: 95%, 66.4-82.8%) after three months. (95)

This shows that the booster can achieve higher levels of nAb blocking of VOCs than that achieved by the initial two-dose vaccination. (95) However, fast waning of nAb titres compared with the wild type (WT) or Delta, suggest that long-lasting nAb response against more immunologically diverse VOCs may be difficult to achieve while boosting with the current mRNA vaccines based on the WT virus. (95)

Vaccination and breakthrough infection

Neutralising-antibody (nAb) titres after an mRNA booster against all Omicron subvariants waned more substantially in those participants who did not have breakthrough infections than in those who had a breakthrough infection. (96) A longitudinal cohort of health care workers from Ohio State University who received three doses of mRNA vaccine (Moderna and Pfizer) showed that neutralising-antibody titres against BA.4/5 waned at a 30-day decay rate of 19.55% for the 'vaccination only group', compared to 12.12% for those with three doses and a previous SARS-CoV-2 infection, indicating lower durability of protection for boosted, infection naive people. (96)

Similarly, SARS-CoV-2 infection after vaccination was found to boost the neutralising antibody response compared to vaccination alone. (97) A longitudinal cohort study of 110 participants found that vaccinated participants (2-4 doses of mRNA vaccine) recovered from infection have higher spike specific IgG and RBD antibody levels compared to infection-naive group'. (97)



Cell-mediated responses

While data remain preliminary, an increasing number of studies indicate that vaccination provides a durable T-cell response to Omicron infection. (92)

Immunopathological characteristics

Omicron breakthrough patients had a more robust IFN- γ response (critical for viral clearance) and lower concentration of proinflammatory cytokines at the acute phase of infection. They also had lower frequency of immature neutrophils indicating milder inflammatory response. (98) It has been reported that BA.4/BA.5 has an increased ACE2 affinity compared to other variants (Wuhan, BA.1 and BA.2). This likely causes an increased binding half-life, which may contribute to the growth advantage of BA.4/BA.5 by enhancing cell entry. (23)

Omicron: Reinfection

Section updated: 27 September 2022

Reinfection after previous infection with a “pre-Omicron” variant

- Several studies have estimated the effectiveness of previous infection with a pre-Omicron variant (e.g. Delta) against reinfection with Omicron. Effectiveness estimates range from 15% to 61.9% (18, 60, 99, 100), but it is often unclear in studies when the previous infection occurred relative to the study period, making it difficult to determine whether this variability is due to waning of effect. Effectiveness against hospitalisation/death was 87.8%. (101, 102)
- A study using Johns Hopkins SARS-CoV-2 genomic surveillance data from March 2020 and July 2022 found that a majority of observed reinfections (95%) were caused by the Omicron variant and reinfection can occur in vaccinated and immunocompetent people. (103) While over 90% of infections were symptomatic, only 4% of cases were hospitalised which indicates that confirmed reinfections increased with the Omicron variant but were generally associated with mild infections. (103)

Reinfection after previous Omicron infection

- Infection with previous Omicron variants provides protection against subsequent Omicron infection. Previous Omicron infection is estimated to provide between 76% and 94% protection against symptomatic BA.4/5 infection (time period not reported, but likely within 3 to 5 months since previous infection). (17, 18)
 - A study in Qatar (conducted approximately 5 months after first Omicron wave (104)) estimated the effectiveness of a previous Omicron infection against symptomatic BA.4/BA.5 reinfection was 76.1% (95% CI: 54.9-87.3%), and against any BA.4/BA.5 reinfection was 79.7% (95% CI: 74.3-83.9%).(18)
 - A Danish study (conducted approximately 3 months after first Omicron wave (104)) estimated the effectiveness of a previous Omicron infection on BA.5 infection among triple-vaccinated individuals.(17) Prior omicron infection was highly protective against BA.5 (94%, 95%CI 92-95).(17)



Disease course

Viral dynamics

Section updated: 27 September 2022

Median or mean incubation period 3-4 days, maximum incubation unclear (6-8 days reported). Omicron may have a shorter serial interval than Delta.

Incubation period -The time from infection until symptoms develop

- A systematic review and meta-analysis assessing the incubation period associated with different SARS-CoV-2 variants was published in August 2022. The mean incubation period for COVID-19 cases caused by the omicron variant was 3.42 days (95% CI, 2.88-3.96 days), based on 5 studies with a total of 829 patients. (105) This is shorter than the Alpha, Beta, and Delta variants.
- A German Study (August 2022) has reported a decreased interval between onset of symptoms in the primary and secondary cases in a household for Omicron compared to preceding variants.(106) For Omicron, there was an average of 3.85 days between symptom onset compared to 4.8 with WT. See table below. (106)

	Time in days	Lower 95% CI	Upper 95% CI
Wildtype	4.80	4.74	4.85
Alpha	4.50	4.46	4.54
Delta	4.21	4.18	4.24
Omicron	3.85	3.76	3.94

Table 1: Mean time from symptom onset of primary case in households and symptom onset of secondary case, by variant; Germany, 2020-2022.

Single exposure event data (assumes participants infected at event):

- Incubation periods are short, ranging from 0 to 8 days, with a mean or median incubation period of around 3 days (107-110)

Human challenge studies (non-Omicron, novel transmission data)

- Incubation period of 2 to 4 days after inoculation with **wild-type virus**. (57) Viral load (VL) rose steeply and peaked around day 4-5.

Serial Interval - The time from infection in one person to infection in the next person

- The mean serial interval ranges from 2.5 to 4.8 days. (52, 110-112)

Latent period - The time from infection until the case becomes infectious

Human challenge studies (non- omicron, novel transmission data)

- Viral shedding by qPCR became quantifiable in throat swabs from 40 hours post-inoculation, significantly earlier than in the nose, where initial viral quantifiable detection occurred at 58 hours post-inoculation. (57)

Duration of infectiousness

- Studies for several countries (Japan, Switzerland, Singapore) among predominately vaccinated people show that for vaccinated people, viral RNA from Omicron samples was highest 3-6



days after diagnosis or symptom onset and then decreased gradually, with a marked decrease 8-10 days after diagnosis or symptom onset. (98, 113, 114)

- One study found positive viral cultures were obtained from day 2 of infection, but samples obtained on day 5 were negative. (98)

Duration of illness

- Time to resolution of symptoms varies. In one small study, 21 of 33 attendees at a gathering tested positive soon after. At the end of follow-up (12-14 days after exposure event), five individuals still reported symptoms, while the rest (16 individuals) reported symptoms lasting 1 to 9 days. (107)
- A study based on data from the UK ZOE COVID app found that the duration of acute symptoms was shorter during Omicron prevalence than during Delta prevalence, with the average presentation of Omicron being 2 days shorter than that of Delta. (115)
- A recent study describing a cross-sectional survey in Israel found that among 199 young, healthy, and mostly vaccinated soldiers, the median time of symptom resolution was 4 days. (116)

Symptomatology

Section updated: 27 September 2022

Asymptomatic Disease

- Data suggests a substantial proportion of Omicron cases may be asymptomatic – estimates range from 25-54%. (60, 117)
 - UK data reported from the Real-time Assessment of Community Transmission-1 (REACT-1) survey (Round 17; 99% Omicron cases) found a substantial proportion (approximately 25%) of positive tests were in asymptomatic people. (118) Of note, the vaccine status of individuals within this group was not included in the report.
 - A study from Korea investigated the clinical and epidemiological characteristics of 40 patients with Omicron (42.5% were fully vaccinated) and found that half of the patients (19, 47.5%) were asymptomatic, while the others had mild symptoms. (119)

Symptoms of Omicron

Upper Respiratory Tract Symptoms

- Upper respiratory symptoms predominate in most individuals. The most common symptoms reported are: cough; runny/stuffy nose; fever; muscle pain; fatigue; headache and sneezing. (108, 120-123) The COVID Symptoms Study reports that headache and sneezing are also common symptoms of Omicron infection. (123) A study from Japan reported that cough (47.3%) and sore throat (32.9%) were the most common COVID-19 related symptoms in the early phase of SARS-CoV-2 infection during the Omicron variant wave. (124)
- A sore throat has been reported more in Omicron cases than Delta, with reports ranging from 25% - 53% of cases. (98, 119, 125) UKHSA states that the findings relating to reports of sore throat could be incidental and suggests that sore throat may not be a specific predictor of Omicron infection, as another recent study led by Oxford University and the Office for National



Statistics (126) found increased reports of sore throat in both PCR-positives and symptomatic PCR-negative cases. More data are required to understand which symptoms may be used to identify Omicron infections.

- Loss of taste and smell has been reported less in Omicron cases than Delta, (60, 125) with the UKHSA reporting 13% of Omicron cases compared to 34% of Delta cases.(60, 125) **In a large UK study drawing on data from the ZOE app (matched for age, sex and vaccination dose), loss of smell was less common in participants infected during a period of Omicron prevalence than during Delta (16.7% vs 52.7%, odds ratio [OR] 0.17; 95% CI 0.16–0.19, p<0.001). (115)**

Lower Respiratory Tract Symptoms

- **There appears to be less involvement of the lower respiratory tract associated with Omicron infection compared to Delta. (115)**
- A study from Canada of 1,063 cases of Omicron (confirmed or suspected) found that only 10% reported shortness of breath. (122) **Similarly, in a study conducted in Japan during the B.1.1.529 Omicron variant wave between January and May 2022, 9.9% of participants who tested positive reported dyspnoea. (124)**
- Omicron cases have been reported as less likely to develop pneumonia (3.4 vs 16.1%, p=0.005). (98)

Symptoms in Children

- Symptoms reported in paediatric cases in South Africa have included fever, vomiting, diarrhoea and convulsions. (127)

Effect of vaccination on symptomatology

- Data suggests no difference in symptoms between vaccinated and unvaccinated cases of COVID-19 infection but milder and of shorter duration in vaccinated cases (data likely to include both Omicron and Delta cases). ([link](#))

Symptoms	Percentage of people with this symptom within 35 days of a positive PCR, among those people with a Ct value under 30	
	January 2022	May 2022
Any symptoms	61.27	59.71
No symptoms (asymptomatic)	38.73	40.29
Classic symptoms (cough, fever, shortness of breath, loss of taste, loss of smell)	49.46	51.73
Loss of taste or smell	11.1	11.89
Gastrointestinal symptoms (abdominal pain, nausea or vomiting, diarrhoea)	14.46	13.9
Cough	40.49	46.34



Fatigue (weakness)	34.13	37.14
Headache	36.63	34.54
Sore throat	35.71	37.64
Fever	21.12	22.77
Loss of smell	7.58	8.01
Muscle ache (myalgia)	23.25	22.82
Loss of taste	9.14	9.6
Shortness of breath	11.53	11.19
Nausea or vomiting	8.19	7.7
Abdominal pain	6.23	4.66
Diarrhoea	5.46	6.39

The above table is taken from the 22 June 2022 edition of UK COVID-19 Infection Survey. (128)

Severity

Overall, Omicron appears to be associated with a milder course of illness and more favourable outcomes compared to previous variants.

- The WHO carried out a large analysis of South African data, comparing the clinical severity and outcomes between 17,693 hospitalised patients during the ‘Omicron period’ compared with 16,749 patients during the ‘Delta period’. (129) Their analysis suggests evidence of reduced severity and lower mortality for the Omicron variant compared to Delta. 28.1% of Omicron patients had severe disease, compared with 49.2% of the Delta patients. 3.7% of the Omicron cohort and 7.7% of the Delta cohort had critical disease. In an adjusted analysis, Omicron was associated with a lower odds of developing severe or critical disease (OR: 0.43; 95% CI: 0.41–0.46 and $p < 0.001$) compared to Delta. Additionally, Omicron was associated with lower risk of in-hospital mortality. However, the WHO cautions that their analysis should not be seen as supporting the ‘mild variant’ narrative.
- A retrospective cohort study SARS-CoV-2 infection which included 118,078 persons with COVID-19 in California found that infection with the Omicron variant was associated with approximately 50% lower risk of severe clinical outcomes compared to the Delta variant. (130)

BA.4/BA.5-specific clinical features (symptoms and severity) information

The BA.4/5 wave has been associated with a rise in hospitalisation both internationally and in New Zealand. While an increase in the number of cases has been demonstrated, there has been little evidence to support a significant change in severity compared to the previous predominant mutation, BA.2. (131-133)

- UK, US, Portugal, China and many more countries reported a steady increase in hospitalisations and deaths from May 2022 to July 2022, aligning with the BA.5 wave. (134, 135)
- On 22 July 2022, the [CDC](#) reported that hospitalisation rates in the US were rising due BA.5 infections. This variant accounted for 78% on infections, which rose from 550 hospitalisations per



day at the end of May to over 2200 per day in the second week of July. This has since started to drop. (136)

- South Africa reported a similar rate in hospitalisation due to BA.4/BA.5 and BA.1. (133)

Hospitalisation

Hospitalisation frequency for Omicron relative to Delta

Adjusted for vaccination status (important for understanding basic differences in severity as it can remove differences in vaccine effectiveness from assessment, though residual confounding for vaccination status may still occur):

- Risk of hospitalisation/severe disease was found to be lower for Omicron than Delta in multiple countries (Sweden, Norway, the US, France, Scotland⁴, the UK, Canada⁵, Portugal), with estimates ranging from 40-73%. (137-147)
- A study from South Africa showed that much of the severity reduction observed for Omicron relative to Delta was due to prior infection and vaccination. Intrinsically reduced virulence accounted for a ~25% reduced risk of hospitalisation/death compared to Delta. (148)
- A large study using data from Spain included 48,874 cases during the delta period and 560,658 during the Omicron period. (149) During the Delta period, on average, 3.8% of the detected cases required hospitalization for COVID-19. This percentage dropped to 0.9% with omicron [RR of 0.46 (95% CI: 0.43 to 0.49)].
- However, a US study found a relative increase in emergency department visits (86%) and hospitalisations (76%) from Omicron compared to the Delta period, though this was due to the higher volume of cases and there was a relative decrease in the length of stay in hospitals (-27%). (150)
- Danish data (151) stratified rather than adjusted by vaccination status:
 - Among those with <2 doses: 43% lower risk of hospitalisation
 - Among those with 2 doses: 29% lower risk of hospitalisation
 - Among those with 3 doses: 50% lower risk of hospitalisation
- Unadjusted for vaccination status (provides indication of burden on healthcare at the level of vaccination in country where study conducted):
 - Reduction in hospitalisation of 38% for emergency department attendance or admission, and 62% for admission (54)
 - Reductions in hospitalisation compared to Delta range from 36% to 53% depending on country. (151-153)

⁴ adjusted for age, sex, socioeconomic status, vaccination status and clinical risk factors.

⁵ adjusted for vaccination status and region



Paediatric hospitalisation

- Both the UK and South Africa saw a rapid increases in paediatric COVID-19 cases and hospitalisations in late 2021, mirroring high community transmission of the Omicron variant, with the UK seeing a 3-fold increase in 2 weeks. (60, 127)
- In the UK, the most rapid rise was among children under 5 years, however some small reviews of Omicron admissions in infants found those admitted were not severely unwell, and less severe than previous waves. (60, 154, 155)
- A US study of children under 5 years found a significantly lower risk for severe clinical outcomes in the 3-day time-window following initial Omicron infection compared to Delta. (156) Risk for an ED visit was 18.83% (vs 26.67%), hospitalisation was 1.04% (vs 3.14%), ICU admissions was 0.14% (vs 0.43%), and mechanical ventilation was 0.33% (vs 1.15%).
- Another US study found during the Omicron wave, paediatric acute upper airway infections have increased with more developing severe disease, suggesting Omicron replicates more efficiently in the conducting airways. (157)
- **Although Omicron infections have led to a rise in hospitalisation rate in under 5-year-olds, there has been an estimated 1/3 reduction in hospitalisation rate of over 12-year-olds. The study however, did not assess severity of hospitalised cases. (158)**

Risk factors for hospitalisation with Omicron

- A UK study found the age range of individuals admitted with Omicron to 29 December 2021 was 0 to 100 years (median: 45.5 years); 496 (60.9%) were aged 40 years or more; 30.8% were aged 70 years or more. (143)
- Public Health Scotland data reported on hospital admissions for COVID-19 (week of 22-28 December 2021) shows approximately 44% were in people 60 plus years of age, and 21% of admissions were in people aged 80 plus. (159)
 - Most cases of COVID-19 at this time in Scotland were Omicron but the proportion of cases of the Omicron variant for each age-group hospitalised are not reported.

Time to hospitalisation with Omicron

Currently, there are no studies to date that have investigated this.

Time in hospital with Omicron

- Hospital stays from Omicron infection range from 1 to 6 days. This varies depending on country and demographic but the mean time in hospital tends to be 3 to 4 days. (47, 152, 160) Overall, hospital stays for Omicron infections are significantly shorter compared to that of Delta infections. (144, 145, 161)

ICU admission

Severe/ICU/ventilated frequency

- ICU admission from Omicron infection is around 70-74% lower than from Delta infection. (144, 152)



- In a large Spanish study, the risk of ICU admission dropped from 0.8% of detected cases during Delta predominance, to 0.1% during Omicron predominance [RR 0.25 (95% CI: 0.21 to 0.28)]. (149)
- South African data: Among *hospitalised* individuals, after controlling for factors associated with severe disease⁶, the odds of severe disease did not differ between S-Gene Target-Failure (SGTF, interpreted as Omicron) infected individuals compared to non-SGTF individuals diagnosed during the same time period (aOR 0.7, 95% CI 0.3-1.4). (162) Compared to earlier Delta infections, after controlling for factors associated with severe disease⁷, SGTF-infected individuals had lower odds of severe disease (aOR 0.3, 95% CI 0.2-0.5).
- The risk of needing ventilatory support among patients with Omicron infection is significantly lower than for Delta. (47, 152, 160)

Death

Death frequency for Omicron relative to Delta

Studies have found a 73-86% reduction in death relative to Delta, however, the extent of the reduction was attenuated when prior infections and vaccination are also considered. (148)

- In South Africa, the Hazard Ratio was 0.72, and an adjusted reduction to relative risk to Delta was 28%. (148)
- In a WHO analysis of South African data, 15% of hospitalised Omicron patients died. (129)
- The odds of death in a Portugal study were 0.14 (95% CI: 0.0011-1.12), representing a reduction in the risk of death of 86% for Omicron compared with Delta. (145)
- US: Unadjusted hazard ratios for mortality associated with Omicron variant infection was 0.09 (95% CI : 0.01-0.75)(152) but unadjusted ratios could be confounded by many factors, and the short follow up time might bias results.
- UK data in long term care facility residents: Reduced risk of death within 28 days of a new diagnosis in the Omicron dominant period (1.1 deaths / 1000 person-days, 95% CI: 0.6-2.2) compared to the pre-Omicron period (3.8 deaths / 1000 person-days, 95% CI: 2.8-5.2).(146)

Time to death

UK data: median time from Omicron specimen date to death was 5 days (range 0 to 14). (143) Note that specimen date might not reflect date of symptom onset.

⁶ Controlled for factors known to be associated with severity (age, presence of comorbidity, sex, province and healthcare sector) and adjusted for the number of days between the date of specimen collection and date of hospital admission, known prior SARS-CoV-2 infection and SARS-CoV-2 vaccination status.

⁷ Controlled for factors known to be associated with disease severity (age, presence of co-morbidity, sex, province and healthcare sector), and adjusted for number of days between date of specimen collection and date of hospital admission, known prior SARS-CoV-2 infection and SARS-CoV-2 vaccination status.



Therapeutics

Section updated: 27 September 2022

Therapeutic use for treatment of COVID-19

- Most people can safely manage their own COVID-19 symptoms at home. However, for people with risk factors for severity or comorbidities, different therapeutic options may provide improved outcomes for the patient.
- The Ministry of Health has an overview [about COVID-19 therapeutics](#) and [advice for healthcare professionals](#) websites.
- Therapeutic options currently include antiviral medications (Paxlovid, remdesivir, molnupiravir), anti-SARS-CoV-2 monoclonal antibodies (Evusheld, sotrovimab), immunomodulators (baricitinib, tocilizumab) and anti-inflammatory drugs (dexamethasone, budesonide) available as EUA for COVID-19 management. (163) The utility, effectiveness and need for each of these options is different between individuals, and criteria for each is specific, based on disease severity and individual risk factors.
- The emergence of new variants produces challenges to the therapeutics as adaptive mutations can completely alter the viral genome and pathogenic potential. New variants that become VOC are often associated with increased virulence, pathogenicity and transmissibility which may help them evade the immune response and have decreased response to current therapeutics. (22, 163)

Therapeutics in relation to BA.4 and BA.5

- Many monoclonal antibodies showed reduced efficacy against Omicron variants relative to Delta. (164)
- Additionally, although many of the newer Omicron subvariants are derived from BA.2, there are significant mutations in the spike protein. (22) It has been established that this reduces the sensitivity to vaccine-induced neutralising antibodies. (165, 166) As a result, it becomes likely that these variants will also have reduced sensitivity to therapeutic monoclonal antibodies. (22)
- Evusheld is a long-acting antibody combination (tixagevimab and cilgavimab) derived from the B cells of individuals previously infected by SARS-CoV-2. There are conflicting data supporting its effectiveness against BA.4/5.
 - A [press release](#) by AstraZeneca (who manufacture the drug) reports data from multiple sources showing neutralising activity against BA.2, the global dominant variant currently, and all other variants tested to date (May, 2022). One study, (23) based at the University of Oxford, has *in vitro* data showing that Evusheld retains neutralisation efficacy against Omicron variants including BA.4 and BA.5.
 - In contrast, another study reported that BA.4/5 showed an increased resistance to Evusheld compared to the BA.2 variant. This was estimated to be a decreased neutralization of approximately 20-fold.(22)
 - 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. (24)



- Two pre-prints have assessed the neutralizing abilities against Omicron variants and reported that Evusheld has markedly reduced potency against the emerging Omicron sub lineage BA.4.6 in *in vitro* studies. (6, 7)
 - The BA.4.6 variant appears to make up a relatively low proportion of cases globally, with a small amount of growth advantage reported. This appears to be resulting in a ‘slow’ creep in growth rather than becoming quickly dominant. (9)
 - BA.4.6 only represents 3% of all domestic cases that have undergone WGS, and this number has remained relatively consistent over the past month making it still an effective therapeutic where indicated. (8)
 - This suggests that Evusheld is likely to retain a high efficacy for over 95% of COVID-19 cases, as global prevalence of BA.4.6 remains low.
- A preprint study suggested that among the therapeutic antibodies authorized for clinical use, only bebtelovimab (LY-COV1404) retains full potency against both BA.2.12.1 and BA.4 and BA.5.(167)
- Research published in the New England Journal of Medicine reports that three antivirals (Paxlovid, molnupiravir, and remdesivir) retain efficacy against the dominant Omicron sublineages BA.5 and BA.2.75. (5)

Rebound after therapeutics

“Rebound” (the return of COVID-19 symptoms after an infected person has finished medication) has been reported after use of both Paxlovid and molnupiravir. (168, 169)

- A pre-print, using data collected in the USA during Omicron dominance (January to June 2022) has reported on three types of rebound associated outcomes: COVID-19 infection (coded as lab-test confirmed presence of “SARS coronavirus 2 and related RNA”), symptomatic COVID-19, and COVID-19 hospitalisations (169)
- This was reported after seven and 30 days for Paxlovid and molnupiravir. The percentage of rebound for each outcome is captured in the table below.

Time after Treatment	Rebound Infection Severity	Paxlovid	Molnupiravir
7 days	COVID infection	3.53%	5.86%
	Symptomatic COVID-19	2.31%	3.75%
	COVID-19 Hospitalisations	0.44%	0.84%
30 days	COVID infection	5.40%	8.59%
	Symptomatic COVID-19	5.87%	8.21%
	COVID-19 Hospitalisations	0.77%	1.39%

- The low rates of hospitalisation reported above suggest that rebound infections are generally not severe. Therefore, the study speculates that treatment with a further antiviral course is might not be beneficial.



- Additionally, the difference between COVID-19 hospitalisation after Paxlovid and molnupiravir treatment was not found to be statistically significantly different. However, the cohort treated with Paxlovid were younger than the molnupiravir treated cohort (average age of 56 vs. 62 years, respectively) which may account for the slightly lower rate of hospitalisation.
- One limitation of the report was that the severity of the initial infection was not reported.

Rebound infections after the use of oral antivirals has indicated that the broad administration of stand-alone therapeutics may not be the most effective treatment against SARS-CoV-2. The use of multiple agents with different mechanisms of action, as in the modern treatment of HIV may be necessary to maximise the longevity of therapeutic. (168)

Pfizer have [initiated a Phase II trial](#) testing Paxlovid in immunocompromised patients. The trial will compare 5-, 10-, and 15-day courses of the oral antiviral to investigate the effect of longer dosing in reducing the incidence of rebound infections. Results from this study are expected September 2023.



Detection

PCR

Section updated: 16 May 2022

Most observational studies have relied on SGTF as a proxy for Omicron, which identifies BA.1 but not BA.2. Therefore, caution is required when interpreting comparative analyses which use S-gene target results as the only determinant of Omicron and Delta.

BA.2 lineage generally does not have the spike deletion at 69-70 that causes S-gene target failure (SGTF). (143) It is nicknamed the “stealth” version of Omicron as it cannot be detected using PCR tests that detect SGTF ([link](#))

This has implications on using PCR tests that detect SGTF as a proxy for rapidly detecting Omicron cases. It should be noted that as at 30 March 2022, the UKHSA reported that 0.16% of BA.2 samples sequenced had the deletion at position 69-70. (170)

Rapid Antigen Tests (RATs)

Section updated: 27 September 2022

PCR testing remains the gold standard for SARS-CoV-2 diagnostics, however the longer turnaround time and restricted use in laboratory settings is unsuitable for large scale testing. Rapid antigen tests (RATs) are now the primary diagnostic tool in New Zealand, due to their fast turnaround time, lack of specialist equipment and ability to be self-administered from home.

The performance of a RAT is generally measured against two outputs, sensitivity and specificity. These are defined as the following:

- sensitivity: a measure of how well the test identifies true positives (i.e., result is identified by test as positive and are positive)
- specificity: a measure of how well the test identifies true negatives (i.e., result is identified by test as negative and are negative).

Aotearoa New Zealand has [approved a number of point of care test \(POCT\) devices](#). were approved based on clinical performance study design and results that meets the following thresholds:

- Overall $\geq 80\%$ sensitivity and $>98\%$ specificity (recommended by WHO, ECDC, TGA, and European Commission MDCG) compared to the gold standard RT PCR
- Or
- $\geq 90\%$ sensitivity for Ct values <25

Detection of Omicron by Rapid Antigen Tests

Accurate diagnostic tools are essential in pandemic management, however reliably detecting emerging variants is a challenge. Many of the RATs were developed prior to the emergence of new variants and are based on the reference sequence of the 2019 Wuhan-hu-1 virus. (104) Although nucleocapsid proteins are the most common antigen detected by RAT devices, (104) the spike protein receptor is also a common target for detection. (163) New variants have increasing numbers of mutations in the nucleocapsid proteins and spike protein regions which may limit the reliability of diagnostic tools. (104)



The FDA has cautioned that RAT devices may have reduced sensitivity to Omicron since its emergence towards the end of 2021. However, it should be noted that it is challenging to compare across studies given that the initial data on RAT performance were collected in clinical settings by healthcare workers, and as such real-world data may not match the reported performance. Sensitivity is also highly variable between different RATs and is strongly correlated with viral load and symptomatology.

For many RATs, the sensitivity was above 80% when initially tested in clinical settings. Studies suggest that sensitivity to Omicron in RAT devices is lower than in previous variants with reported sensitivities ranging from 27.5%-63%. (22, 104, 164) However, this data is currently limited due to issues with comparability across studies, settings and devices. **Currently there is some emerging evidence that suggests a clinically relevant decrease in the performance of RATs for detection of the Omicron variant. (10, 11) Comparability between studies is limited by difference in study design and objectives. For these reasons it is difficult to compare the results between studies and evidence of reduced sensitivity may not be indicative of device performance.**

All RATs available in New Zealand have been and will continue to be screened for acceptable performance. RATs are still recommended as the best method of POCT in New Zealand however, test performance will require ongoing review as new variants arise. (171)

Emerging evidence indicates that serial rapid antigen testing may become vital for early detection of new omicron variants. (172) Serial testing is the process where an individual is tested multiple times over a period of a few days to increase the chances of detecting COVID-19 which a single test might have missed. This is commonly used in asymptomatic patients to overcome limitations of poor sensitivity. A recent study showed that serial rapid antigen testing every three days was found to be more effective at case detection than RT-PCR testing. (172) This is due to the rapid turnaround time of RATs compared to PCR tests, enabling rapid isolation and is a lower cost method of case identification. RATs are likely to remain central in testing strategies despite reduced sensitivity to new variants.



Section 4: Appendices

Glossary

AstraZeneca vaccine	AZD1222 or ChAdOx1
Pfizer/BioNTech vaccine	Comirnaty or BNT162b2
Global Initiative on Sharing Avian Influenza Data (GISAID)	This is a consortium that promotes and provides open access to SARS-CoV-2 genomic sequence data. Its original purpose was for sharing data on avian (bird) flu.
Immune escape	The ability of the virus to evade our body's immune response. See also Immune response.
Immune response	The response of our immune system to an infection or antigen. It includes development of specific antibodies to the virus and also cell-mediated responses (triggered by T cells).
Mutation	Small change made to the pattern of nucleotides that make up the virus. These occur as the virus spreads and replicates. Most do not confer a benefit to the virus.
Naming mutations	Mutation nomenclature (i.e., how they are named), describes what occurred at a specific location of the genome. For example, the 'E484K' mutation means that at the position 484, the amino acid changed from glutamic acid (E) to lysine (K). When a deletion occurs, the location is provided (e.g., deletion 144).
N-terminal domain	Part of the spike protein of the SARS-CoV-2 virus.
R₀, Basic Reproductive number	The basic reproductive number R ₀ (R-naught), is a measure of how contagious a pathogen is. It is the average number of people who would become infected from one infected individual in a population where everyone is susceptible (that is, a population that has not previously encountered the disease or received vaccination).
R_{eff}, Effective reproductive number	The 'effective R' (R _{eff}) is the average number of secondary cases per infectious case in a population made up of both susceptible and non-susceptible people. . In general, whenever R _{eff} is less than 1(that is, an infected person goes on to infect less than one person on average) then the incidence of the disease would be expected to decrease.
Secondary attack rate	The probability that infection occurs among a specific group of susceptible people (for example, within a household) after known contact with an infectious person.



Serial interval	The time from symptom onset of a case to symptom onset in their identified contacts.
SGTF / SGTP	"The Omicron genome (lineage BA.1) contains the spike deletion at position 69/70 which is associated with S-gene target failure (SGTF) in some widely used PCR tests. Such PCR tests evaluate the presence of 3 SARS-CoV-2 genes: Spike (S), nucleocapsid (N) and ORF1ab. SGTF is defined as a PCR test where the N and ORF1ab genes are detected (with Ct values less than or equal to 30) but the S-gene is not. SGTF patterns can be used to assess the spread of Omicron lineage BA.1. The Omicron lineage BA.2, VOC-22JAN-01, does not generally contain the spike gene deletion and is S-gene target positive (SGTP)." (170)
Variant	Viruses with mutations are referred to as variants of the original virus. New variants of SARS-CoV-2 have been emerging as the virus has spread and evolved.
Variant of Concern (VOC)	<p>WHO definition: A SARS-CoV-2 variant that meets the definition of a VOI (see below) and, through a comparative assessment, has been demonstrated to be associated with one or more of the following changes at a degree of global public health significance:</p> <p>Increase in transmissibility or detrimental change in COVID-19 epidemiology; OR</p> <p>Increase in virulence or change in clinical disease presentation; OR</p> <p>Decrease in effectiveness of public health and social measures or available diagnostics, vaccines, therapeutics.</p>
Variant of Interest (VOI)	<p>WHO definition: A SARS-CoV-2 variant:</p> <p>with genetic changes that are predicted or known to affect virus characteristics such as transmissibility, disease severity, immune escape, diagnostic or therapeutic escape; AND</p> <p>Identified to cause significant community transmission or multiple COVID-19 clusters, in multiple countries with increasing relative prevalence alongside increasing number of cases over time, or other apparent epidemiological impacts to suggest an emerging risk to global public health.</p>
Variant under Investigation (VUI)	<p>UKHSA definition: SARS-CoV-2 variants, if considered to have concerning epidemiological, immunological or pathogenic properties, are raised for formal investigation. At this point they are designated Variant Under Investigation (VUI) with a year, month, and number. Following a risk assessment with the relevant expert committee, they may be designated Variant of Concern (VOC).</p>



Abbreviations

CDC: Centers for Disease Control and Prevention

Ct: Cycle Threshold

E: Glutamic Acid

GISAID: Global Initiative on Sharing Avian Influenza Data

ICU: Intensive Care Unit

IPC: Infection Prevention and Control

L: Lysine

mRNA: messenger RNA

N: Nucleocapsid (Protein)

NPI: Non-pharmaceutical intervention

PCR: Polymerase Chain Reaction

RBD: *Receptor binding domain (of the virus spike protein)*

RAT: *Rapid Antigen Test*

R_{eff}: 'Effective R', the effective reproductive number

R₀: 'R-naught', the baseline reproductive number

RNA: *Ribonucleic Acid*

S: *Spike (Protein)*

UKHSA: *UK Health Security Agency*

UAI: *Upper Airway Infection*

VE: *Vaccine effectiveness*

VTG: *Variant Technical Group*

WHO: *World Health Organisation*



Useful Links

US CDC – SARS CoV-2 variant classifications and definitions	CDC classification of variants
Outbreak Info	Outbreak Info
WHO - Tracking SARS-CoV-2 variants	WHO Variant Tracking
UK Health Security Agency Technical Briefings (from October 2021 onwards)	Investigation of SARS-CoV-2 variants: technical briefings
Public Health England Technical Briefings	Investigation of SARS-CoV-2 variants: technical briefings



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