



Date: 19 August 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.

Nomenclature systems for naming and tracking SARS-CoV-2 genetic lineages have been established by GISAID, Nextstrain and Pango. To assist with public discussions of variants, an expert group convened by WHO recommended using letters of the Greek Alphabet, i.e., Alpha, Beta, Gamma, Delta etc.

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.

Key recent documents

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

- World Health Organization (WHO): Weekly epidemiological update on COVID-19 – 10 August 2022 [1]
- WHO: Weekly epidemiological update on COVID-19 – 17 August 2022 [2]
- ECDC: Communicable Disease Threats Report, Week 32, 7-13 August 2022 [3]



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Key new information

- The number of sequences submitted to GISAID continues to decline and 99% of submitted sequences (globally) between 15th July and 15th August 2022 were the Omicron variant. Among Omicron sequences submitted between 31st July and 6th of August, BA.2 lineages represented 3% of sequences, while BA.4 lineages represented 8% and BA.5 lineages represented 74%. Only one case of Delta was submitted during this time period. [2]
- The WHO reported that 'There is now a large diversity within the Omicron VOC, an expected phenomenon that is the result of the accumulation of mutations as part of the virus replication process and/or immune pressure from the host. More than 200 descendent lineages of Omicron have emerged; these variants are being monitored by WHO'. [2] New signals covered in this edition of the SARS-CoV-2 Variants of Concern Update are BA.2.10.X, BA.4.6, BA.2.75, BA.5.2.1, and BA.2.12/BA.2.12.1
- Multiple new subvariants are being monitored on the basis of the number or site of mutations or an observed growth advantage in specific populations. At present, no new subvariants of Omicron have demonstrated concerning features, although the effectiveness of some therapeutics is likely to be decreased.
- The time from exposure to symptom onset has progressively declined for each new variant over the course of the pandemic. The mean incubation period for the wildtype variant was 4.80 days, for Alpha 4.50, Delta 4.21 and Omicron 3.85.
- Rebound infection of SARS-CoV-2 has been reported after treatment of oral antivirals. This has been reported after use of both Paxlovid and Molnupiravir. The low rates of hospitalisation reported above suggest that rebound infections are generally not severe. [4]



Overview of variants

Section updated: 17 August 2022

As of 17 August 2022, Omicron¹ was the only circulating Variant of Concern (VoC) as designated by the WHO. [2] There were no currently circulating Variants of Interest as designated by the WHO at that time. Omicron subvariants under monitoring include BA.4, BA.5, BA.2.12.1 and BA.2.75. ([link](#))

There has been one recently designated variant in the UK (BA.2.75), designated by the UK Health Security Agency (UKHSA) Variant Technical Group (VTG) on 22 July 2022. [5]

Table 1 includes European Centre for Disease Prevention and Control (ECDC) classifications. The ECDC uses the label 'variant of concern' when clear evidence is available for a variant indicating a significant impact on transmissibility, severity and/or immunity that is likely to have an impact on the epidemiological situation in the EU/EEA.

The latest ECDC for 12 August 2022, has de-escalated the following variants: [3]

- BA.1 was de-escalated from VoC to de-escalated variant.
- BA.3 was de-escalated from variant under monitoring (VUM) to de-escalated variant.

Whole genome sequencing efforts are falling globally, potentially obscuring surveillance of VoCs as they emerge and become more prevalent.

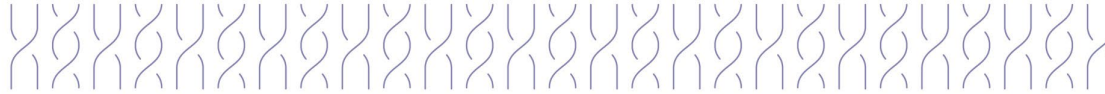
The WHO Weekly Epidemiology Update on 10 August 2022 reported that:

'BA.5 descendent lineages (BA.5.X) are increasing in diversity, with additional mutations in spike and non-spike regions. WHO continues to monitor all lineages, including descendent lineages of VOCs, to track an increase in prevalence and change in viral characteristics.' [1]

Furthermore, the WHO Weekly Epidemiology Update on 17 August 2022 reported that:

'There is now a large diversity within the Omicron VOC, an expected phenomenon that is the result of the accumulation of mutations as part of the virus replication process and/or immune pressure from the host. More than 200 descendent lineages of Omicron have emerged; these variants are being monitored by WHO, depending on the specific genetic constellations of mutations, indications of a rise in prevalence in a specific location or geographic spread, as well as any evidence of phenotypic changes.' [2]

¹ Includes BA.1, BA.2, BA.3, BA.4, BA.5 and descendent lineages. It also includes BA.1/BA.2 circulating recombinant forms such as XE.



Overview of SARS-CoV-2 variants of public health interest

Table updated: 17 August 2022

Table 1: Overview of SARS-CoV-2 variants of public health interest

Pango lineage	WHO label	UKHSA label	UKHSA designation	ECDC designation	Earliest documented samples	Distribution
BA.4.6	Not yet designated	Not yet designated	Not yet designated	Not yet designated	USA, May 2022. [6]	Detected in GISAID in the past 12 weeks (as at 16 August) in North/South America, Europe, Asia and Oceania. Cases are most frequent in the USA. [7]
BA.2.10.X	Not yet designated	Not yet designated	Not yet designated	Not yet designated	India, 02 July 2022. (BA.2.10.1) [8]	Detected in GISAID in the past 12 weeks (as at 9 August), predominantly in India. [8]
BA.5.2.1	Not yet designated	Not yet designated	Not yet designated	Not yet designated	China, 08 July 2022 [9]	Detected in GISAID in the past 12 weeks (as at 16 August) across 19 different countries including the UK. [7]
BA.2.75	Omicron sub-lineage BA.2.75	V-22JUL-01	Variant	Variant of Interest as of 07 July 2022 [10]	India, 02 June 2022	Detected in GISAID in the past 12 weeks across 15 different countries including the UK as at 18 July. [11]
B.1.1.529/ BA.4	Omicron sub-lineage BA.4	V-22APR-03	Variant	Variant of Concern as of 12 May 2022 (previously variant of interest) [12]	South Africa, January 2022. [13]	Detected in the UK in the past 12 weeks as at 22 July.[5, 14] Dominant in South Africa along with BA.5. [12]
B.1.1.529/ BA.5	Omicron sub-lineage BA.5	V-22APR-04	Variant	Variant of Concern as of 12 May 2022 (previously variant of interest) [12]	South Africa, February 2022. [13]	Dominant globally as at 13 July. [11]
BA.2.12.1			Signal in monitoring			Detected in the UK in the past 12 weeks as at 22 July.[5]



Pango lineage	WHO label	UKHSA label	UKHSA designation	ECDC designation	Earliest documented samples	Distribution
B.1.1.529/BA.2	Omicron	VOC-22JAN-01	Variant of concern (<i>previously a variant under investigation</i>)	Variant of Concern [15]		Detected in the UK in the past 12 weeks as at 22 July.[5]
BA.3	-	-	Signal in monitoring (<i>previously Variant in monitoring</i>)	Variant under monitoring [15]	South Africa [15]	Detected in the UK in the past 12 weeks as at 22 July.[5]
B.1.1.529/BA.1	Omicron	VOC-21NOV-01	Variant of concern	Variant of Concern[15]		Detected in the UK in the past 12 weeks as at 22 July.[5]
Delta and Omicron recombinant lineages (UK)	-		Signal in monitoring (<i>previously Variant in monitoring</i>)		United Kingdom, Feb-2022 [16, 17]	Detected in the UK in the past 12 weeks as at 22 July.[5]
AY.119.2/BA.1.1 Recombinant			Signal under monitoring			Not detected in the UK in the past 12 weeks as at 22 July.[5]
XD Recombinant (Delta x BA.1)		V-22APR-01	Variant (<i>previously signal under monitoring</i>)		France, Jan-2022 [18]	Not detected in the UK in the past 12 weeks as at 22 July.[5]
XE Recombinant (BA.1 x BA.2)		V-22APR-02	Variant		First case detected on 19 January 2022. [16, 17]	Detected in the UK in the past 12 weeks as at 22 July.[5]
AY.119.2/BA.1.1 Recombinant			Signal under monitoring			Not detected in the UK in the past 12 weeks as at 22 July.[5]
BA.1/BA.2 Recombinant (with unique mutation C3583T)			Signal in monitoring			Detected in the UK in the past 12 weeks as at 22 July.[5]
XF Recombinant			Signal in monitoring			Not detected in the UK in the past 12 weeks as at 22 July.[5]
B.1.617.2 and sub-lineages	Delta	V-21APR-02 (<i>previously VOC-21APR-02</i>)	Variant (<i>previously a variant of concern</i>)	Variant of Concern [15]	India, Oct-2020 [18]	Detected in the UK in the past 12 weeks as at 22 July.[5]



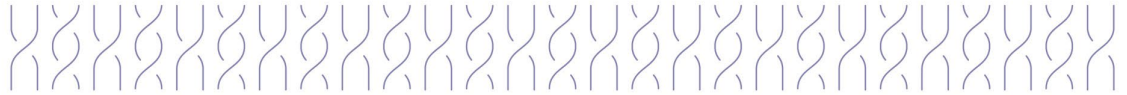
Pango lineage	WHO label	UKHSA label	UKHSA designation	ECDC designation	Earliest documented samples	Distribution
B.1.1.7	Alpha	V-20DEC-01 <i>(previously VOC-20DEC-01)</i>	Variant <i>(previously a variant of concern)</i>	De-escalated variant	United Kingdom, Sep-2020 [18]	Detected in GISAID, but not in the UK, in the past 12 weeks as at 22 July.[5]
B.1.351	Beta	V-20DEC-02	Variant of Concern <i>(last report unclear designation)</i>		South Africa, May-2020 [18]	Not detected in the UK in the past 12 weeks as at 22 July.[5]



Omicron lineages: overview of frequency of detection and genetic features

Section updated: 18 August 2022

- Omicron was first detected in November 2021 causing a rapid resurgence of COVID-19 cases in South Africa. [19] The WHO designated it as the fifth variant of concern of SARS-CoV-2 (Omicron, B.1.1.529). [19]
- The Omicron variant is dominant across the world, displacing the Delta variant. [20] Spread was rapid even in regions with high levels of population immunity. [19]
- Compared to the Alpha, Beta, Gamma, and Delta VoCs, the Omicron variant has the greatest number of mutations; there are 50 mutations accumulated throughout the genome. [21] At least 32 of these mutations are in the spike protein (twice as many as Delta), [21] enabling highly efficient evasion from neutralising antibodies. [20]
- Omicron has continued to evolve, leading to further variants with slightly different genetic constellations of mutations. [22]
- The Omicron variant (B.1.1.529) comprises a number of lineages and sub-lineages. [23]
- Major descendant lineages include BA.1, BA.2, BA.3, BA.4, BA.5.
- BA.2 and BA.3 are evolutionarily linked to BA.1, [19] and BA.4 and BA.5 are evolutionarily linked to BA.2. [24]
- Recombinant lineages include XE, a BA.1/BA.2 recombinant. [18]
- There are a large number of mutations differentiating Omicron variants from other known SARS-CoV-2 lineages. [19]
- BA.1 and BA.2
 - In December 2021, Pango announced designation of two genetically distinct sub-lineages of B.1.1.529 as BA.1 (B.1.1.529.1) and BA.2 (B.1.1.529.2). [25] BA.1 is the original globally distributed lineage, and BA.2 is the new outlier lineage. The prefix BA was then an alias for B.1.1.529. [25]
 - BA.2 was designated a variant under investigation (VUI) by UKHSA on 21 January 2022. BA.2 contains 29 mutations in the spike protein and a deletion at 25-27. Some of the mutations in the spike protein are shared with BA.1. [26]
 - Differentiation of BA.1 from BA.2 requires whole genome sequencing (WGS). 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. The BA.2 genome generally is S-gene target positive, but as of 30 March 2022, the UKHSA reported that 0.16% of BA.2 samples sequenced had the deletion at position 69-70. [24]
 - The BA.2 genome generally is S-gene target positive, but as of 30 March 2022, the UKHSA reported that 0.16% of BA.2 samples sequenced had the deletion at position 69-70. [24]
 - UKHSA is no longer reporting SGTF patterns. UK testing policy on 1 April resulted in a substantial reduction in tests processed through assays which can report SGTF. SGTF is



no longer a reliable representation of variants in the population, and the UKHSA will not be reporting it going forward. [14]

- BA.3
 - BA.3 has the SGTF deletion ($\Delta 69-70$) so can be detected using PCR tests that detect SGTF, and has a combination of mutations found in BA.1 and BA.2 spike proteins.[27]
 - As of 01 June 2022, the proportion of sequences submitted to GISAID that were BA.3 in the past 30 days, has declined to <1%.[28]
- BA.4 and BA.5
 - BA.4 and BA.5 were classified by the VTG on 6 April 2022 as V-22APR-03 and V-22APR-04, respectively. [29]WHO announced that BA.4 and BA.5 had been added to their list of variants for monitoring on 12 April 2022. The ECDC classified both as VoCs on 12 May 2022.[12]
 - BA.4 and BA.5 have many mutations in common with the BA.2 variant, [13] as well as a number of additional mutations. The BA.4 and BA.5 sub-variants tend to be discussed together because the mutations in their spike protein gene are identical (but differ in mutations elsewhere in the genome). [13]
 - Among Omicron sequences submitted to GISAID between 24 and 30 July 2022, BA.4 represented 9% of sequences, and BA.5 represented 70%. [1] The proportion of BA.5 and BA.4 have remained stable globally in the past fortnight.
 - At 22 July 2022, BA.5 is the dominant variant in the UK, with 79% of cases sequenced identified as BA.5 and BA.4 making up just 17%. [5] An updated growth model suggests that the relative growth rate of BA.2.12.1 and BA.4 are both in decline. The relative growth rate of BA.5 has slowed considerably, but its representation is likely still increasing. It is likely that the slowing in BA.5 is due both to it saturating as the dominant variant (relative growth will always eventually saturate) and misclassification of BA.5 sequences as 'other'. [5]
- BA.2.12.1
 - Among Omicron sequences submitted to GISAID between 4 and 10 July 2022, BA.2.12.1 represented 4.5% of cases. This represents a further decrease in proportion that were BA.2.12.1 sequences in the prior 3 weeks. [11]. WHO is now reporting data for BA.2.12.1 combined with other BA.2.X data.
- BA.2.75
 - Detected on GISAID in India on 2 June 2022, subsequently designated by the ECDC as a variant of interest as of 7 July 2022, [10] and by the UKHSA on 22 July 2022. [11]
 - Mutation profile is the same as BA.2 with the following mutations to the spike protein: S:K147E, S:W152R, S:F157L, S:I210V, S:G257S, S:D339H, S:G446S, S:N460K, S:Q493R reversion. [30]
 - Additional mutations outside the spike protein: ORF1a:S1221L, ORF1a:P1640S, ORF1a:N4060S; ORF1b:G662S; E:T11A. [30]

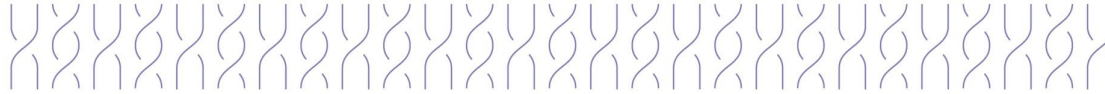


Risk assessment for BA.5 for New Zealand

Section updated: 05 August 2022

Table 2: Risk assessment for BA.5 variant of SARS-CoV-2, 05 August 2022. Assessment based on UKHSA risk assessment for BA.4 and BA.5 (VOC-03-APR2022 and VOC-04-APR2022) from 22 June 2022.[42] Data updated for the context of Aotearoa New Zealand. The risk assessment is revised as new data emerges.

	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>As at August 2022, BA.5 is the predominant variant in New Zealand, with a growth advantage 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. There was an associated overall increase in coronavirus (COVID-19) cases. 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.[31] This is consistent with growth advantages observed internationally.</p>
Growth advantage 1: Transmissibility	Insufficient data	Insufficient data	<p>There is no direct data on intrinsic transmissibility and there is no current ability to measure this directly 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.[32]</p>
Growth advantage 2: 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 demonstrates a moderate drop in neutralising antibodies compared to other Omicron variants BA.1 and BA.2, and protection conferred from vaccination with 3 doses. Less of an impact was observed for samples associated with 'hybrid' protection, e.g., by 'breakthrough' infections after vaccination.[33-35]</p>



			<p><i>Reinfection:</i> There is 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.[36-38]</p> <p><i>Vaccine effectiveness (VE):</i> There is insufficient data for a robust assessment of vaccine effectiveness but in population and survey data there were no early indicators of a large change in VE against symptomatic infection from BA.2 to BA.5.[36, 39]. One study has observed a decrease in VE against hospitalisation between BA.2 and BA.5, comparing cohorts of people who had received the booster (3 dose with prior infection) to unvaccinated (with prior infection). No difference was seen for VE mortality. [40] The current epidemiological data, whilst incomplete, is consistent with the neutralisation findings.</p>
Severity	No change in risk	Moderate	<p>In vitro data suggests realised severity is similar to previous Omicron variants; epidemiological data requires close monitoring</p> <p>There has been an increase in people admitted to hospital with COVID-19 in Aotearoa. There is still limited data on the severity of BA.5.</p> <p>To date, countries which have experienced BA.5 waves have not experienced apparent high severity of disease and hospitalisation rates have tended to remain lower than previous waves. [15, 41, 42] One study suggests greater risk of hospitalisation compared to BA.2 after adjusting for age.[36]</p>
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.

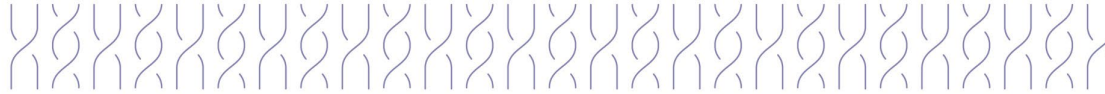
**'Confidence level' indicates the overall quality of data that are available to make the risk assessment: 'High' (high quality, robust data); 'Moderate' (good data with limitations); 'Low' (very little data available). 'Insufficient data' indicates that there are no data of reasonable quality on which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



Risk assessment for BA.2.75 for New Zealand 22 August 2022

Table 3: Risk assessment for BA.2.75 variant of SARS-CoV-2, 22 August 2022. Assessment based on UKHSA risk assessment for BA.4 and BA.5 from 22 June 2022, [link](#). Data updated for the context of Aotearoa New Zealand. The risk assessment is revised as new data emerges

	Overall risk assessment*	Confidence level **	Assessment and rationale
Overall growth advantage	Insufficient data	Insufficient data	<p>No evidence of a growth advantage compared to BA.5.</p> <p>There is some evidence that BA.2.75 has a growth advantage against BA.2 in some countries and may have a slight growth advantage against BA.5 -- likely not enough to cause a wave, but contributes to sustained transmission. There are too few samples of BA.2.75 internationally or in New Zealand to estimate a robust growth rate at this time relative to BA.5. The data requires close monitoring.</p>
Growth advantage 1: Transmissibility	Insufficient data	Insufficient data	There is no direct data on intrinsic transmissibility and there is no current ability to measure this directly from surveillance data.
Growth advantage 2: Immune evasion	No change in risk	Low	<p>No evidence of increased immune evasion.</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><i>Laboratory data:</i> Neutralisation studies found that BA.2.75 was similar or slightly <i>less</i> able to neutralise antibodies produced after BA.2 infection and vaccination, compared to BA.4 or BA.5. [43-47] 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.</p>



Infection severity	Insufficient data	Insufficient data	<p>No evidence of a change in severity compared to BA.5</p> <p>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, [47] but overall pathogenicity similar to BA.5. [48]</p>
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.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.



Characteristics of Omicron

Omicron: Growth advantage/ transmissibility

Section updated: 17 August 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. [19]
- 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. [50]
- Data from Texas, USA, indicated a case-doubling time for Omicron of 1.8 days, three times faster than for Delta in this area. [51]
 - Omicron is more associated with asymptomatic infection and transmission than Beta and Delta. [52]
 - Contact tracing data show a greater proportion of transmission happening outside the household for Omicron than for Delta. [53]
- 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. [12]
- UKHSA analysis of contact-tracing data shows the mean serial interval for BA.1 is 3.72 days (95% CI: 3.62 - 3.80). [54]
- **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. [55]**

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.[56]
- SAR for Omicron ranges from 7.6% to 50% depending on country and setting. [53, 57, 58]

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. [59] The high environmental stability of Omicron could increase the risk of contact transmission and contribute to its spread. However, 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. [60]
- 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.[61]



Omicron: Disease course/ viral dynamics

Section updated: 16 May 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.

NOTE: Incubation period refers to the time from infection until symptom development. The serial interval refers to the time from illness onset in the primary case to illness onset in the secondary case. The latent period refers to the time from infection until the person becomes infectious (and more likely to test positive)

Incubation period

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 [62-65]

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

- Incubation period of 2 to 4 days after inoculation with **wild-type virus**. [61] Viral load (VL) rose steeply and peaked around day 4-5.

Serial Interval

- The mean serial interval ranges from 2.5 to 4.8 days. [57, 65-67]

Latent period:

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. [61]

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. [68-70]

Duration of illness

- Time to resolution of symptoms varies, and at the end of follow-up, five individuals still reported symptoms, while the rest (16 individuals) reported symptoms lasting 1 to 9 days. [62]
- One study found positive viral cultures obtained from day 2 of infection but were cleared and negative by day 5 of illness. [69]



Omicron: Clinical features (symptoms and severity)

Section updated: 16 May 2022

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, Scotland², the UK, Canada³, Portugal), with estimates ranging from 40-73%. [71-81]
- 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. [82]
- 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%). [83]
- Danish data [84] 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 [53]
 - Reductions in hospitalisation compared to Delta range from 36% to 53% depending on country. [84-86]

Paediatric hospitalisation

- Both the UK and South Africa saw a rapid increase 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. [87, 88]
- 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. [88-90]
- 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.

² adjusted for age, sex, socioeconomic status, vaccination status and clinical risk factors.

³ adjusted for vaccination status and region



[91] 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. [92]
- Although Omicron infections have led to a rise in hospitalisations in under 5 year olds, there has been an estimated 1/3 decrease in hospitalisation of over 12 year olds. [93]

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. [77]
- 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. [94]
 - 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 is no studies to date that have investigated this.

Time in hospital with Omicron

- Hospital stays from Omicron infection range from 1 to 6 days and this varies depending on country and demographic but the mean time in hospital tends to be 3 to 4 days. [51, 85, 95] Overall, hospital stays for Omicron infections are significantly shorter compared to that of Delta infections. [78, 79, 96]

ICU admission

Severe/ICU/ventilated frequency

- ICU admission from Omicron infection is around 70-74% lower than from Delta infection. [78, 85]
- South African data: Among *hospitalised* individuals, after controlling for factors associated with severe disease⁴, 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).[97] Compared to earlier Delta infections, after controlling for factors associated with severe disease⁵, 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. [51, 85, 95]

⁴ 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.

⁵ 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.



Death

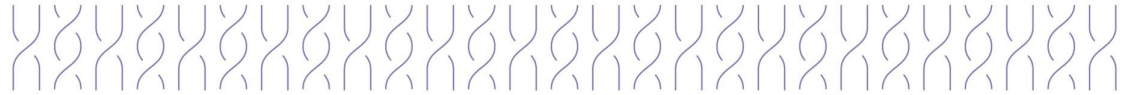
Death frequency relative to Delta

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. [82]

- In South Africa, the Hazard Ratio was 0.72, and an adjusted reduction to relative risk to Delta was 28%. [82]
- 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. [79]
- US: Unadjusted hazard ratios for mortality associated with Omicron variant infection was 0.09 (95% CI : 0.01-0.75)[85] 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).[80]

Time to death

UK data: median time from Omicron specimen date to death was 5 days (range 0 to 14).[77] Note that specimen date might not reflect date of symptom onset.



Symptomatology

Timing of symptom onset of Omicron compared to other variants

- A German Study (August 2022) has reported a decreased time in the onset of symptoms in a household between the primary and secondary case. This has reduced between all superseding variants with an average of 3.85 days in symptom onset for Omicron. See table below for comparison to Wildtype, Alpha, Delta and Omicron. [98]

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

	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
Omikron	3.85	3.76	3.94

Symptoms of Omicron compared to Delta

- Data suggested a substantial proportion of Omicron cases may be asymptomatic – estimates range from 25-54%. [88, 99]
 - 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. [100] 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. [101]
- The most common symptoms reported are: cough; runny/stuffy nose; fever; muscle pain; fatigue; headache and sneezing.[63, 102-105] The COVID Symptoms Study reports that headache and sneezing are also common symptoms of Omicron infection. [105]
- A study from Canada of 1,063 cases of Omicron (confirmed or suspected) found that only 10% reported shortness of breath. [104]
- Symptoms reported in paediatric cases in South Africa have included fever, vomiting, diarrhoea and convulsions. [87]
- A sore throat has been reported more in Omicron cases than Delta, with reports ranging from 25% - 53% of cases. [69, 101, 106] 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 [107] 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, [88, 106] with the UKHSA reporting 13% of Omicron cases compared to 34% of Delta cases.[88, 106] Additionally, Omicron cases have been reported as less likely to develop pneumonia (3.4 vs 16.1%, p=0.005). [69]



- 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. [108]



BA.2-specific clinical features (symptoms and severity) information

Preliminary analyses show no differences in frequency of hospitalisation for BA.2 compared to BA.1.

- Multiple studies have not reported a difference in frequency of hospitalisations or severity between BA.1 and BA.2. [109-112]
- Data on Omicron in children suggested that symptoms were less severe than previous variants, and paediatric deaths were rare. However, these data were from populations in which a majority were already protected from past infection, vaccination or both.[113]
- A large study of an uninfected and unvaccinated population of children investigated severe outcomes among 1,147 children aged 11 years or below who were hospitalised between 5 February and 28 February 2022 (a BA.2-dominant period). Intrinsic severity of BA.2 in children who had no past COVID-19 or vaccination was determined to be not mild. [113]
 - Children hospitalised during the BA.2 dominant period had higher odds of PICU admissions, mechanical ventilation and oxygen use.
 - BA.2 was reported to be more neuropathogenic than previous SARS-CoV-2 variants, influenza and parainfluenza viruses, resulting in more seizures.

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

Preliminary analyses showed an increase in hospitalisations after the emergence of BA.4/BA.5 internationally and in New Zealand.

- UK, US, Portugal, China and many more countries reported a steady increase in hospitalisations and deaths was seen from May 2022 to July 2022, aligning with the BA.5 wave. [114, 115]
- 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 hospitalisation per day at the end of May to over 2200 per day in the second week of July. This has since started to drop. [116]
- South Africa reported a similar rate in hospitalisation due to BA.4/BA.5 but a similar death rate to BA.1. [41]
- Symptoms of BA.4/BA.5 appear consistent with BA.2 variant, with upper respiratory, cold and flu symptoms including fever and sore throat.



Omicron: Vaccine effectiveness

Section updated: 17 August 2022

Vaccine effectiveness (VE)

Vaccine effectiveness against Omicron related infection, hospitalisation and death is lower and may wane more rapidly than for previous COVID-19 variants.[117]

Vaccine Effectiveness in adults -Pfizer

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).

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. [117, 118] However, the VE wanes to levels unlikely to reduce transmission within 5-6 months of the second dose. [88, 118]

Booster (three doses)

VE of one booster (three doses) against Omicron infection is 55-69%. [117, 118] The VE against Omicron infection wanes to 50% (95% CI: 46.5; 53.1) after four months for individuals aged 18-59 years. [118]

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. [119, 120] and 33-65% in the period of 2-6 weeks after the second booster. [121, 122]

Two studies estimated a decline in relative VE down to 10-22% from 8-10 weeks after receiving the second booster. [121, 122]

Note: Many countries have only recently begun 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. [123] 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. [123] 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. [119]

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. [88, 124] A US study with mRNA vaccines reported a higher VE of 81%. [125] After 5-6 months the VE declined to 44% (CI 95%, 30-54%) [88], whereas a Danish study reported an VE of 66% after 4 months. [118]

First booster (3 doses)

VE of one booster (three doses) against Omicron related hospitalisation is estimated to be 83%. [117, 126-131]

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. [118, 124, 125, 132, 133]

After 10 or more weeks the VE against Omicron related severe disease/hospitalisation has been estimated to wane to 75-83%. [132, 133] and further wanes to approximately 50% after >3 months. [124, 125, 134].

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 [135].

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. [119, 121, 122], increasing to 87% after 7-10 weeks. [122, 135] For people aged 60+ year relative VE peaked after 3-4 weeks at an adjusted rate of 52%. [121]

VE against death

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). [136]

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%). [134]

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. [119]

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. [137]



World Health Organization review of vaccine efficacy

A WHO weekly epidemiological report (22 June 2022) included an updated summary of evidence on Omicron, including for vaccine effectiveness.[138]

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). [138]

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

- To date, 23 studies from ten countries have assessed the duration of protection of five 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 longer duration of protection.



Omicron: Immunological response to vaccination

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

Section updated: 01 July 2022

A longitudinal study in vaccinated UK health care workers showed that immune response varies based on previous infection and vaccination. [139]

- 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

Neutralisation studies provided initial data predicting lower vaccine effectiveness against Omicron (BA.1) than for previous variants. [140-145] BA.2 does not appear to have a greater capacity for immune evasion by antibody neutralisation than BA.1. [146-148] These data have now been superseded by effectiveness data.

Neutralising antibody against BA.5

Section updated: 17 August 2022

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: [149, 150] One study compared the neutralization 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. [150]

A follow-up study of 700 participants who received a second booster of Pfizer (four month after first booster) found a 26% multiplicative decay per week of neutralising antibodies and 14% of immunoglobulin G (IgG). [151] 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. [152] 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).



Cell-mediated responses

While data remain preliminary, an increasing number of studies indicate that vaccination provides a durable T-cell response to Omicron infection. [149]

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. [69] **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.** [150]

Omicron: Reinfection

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% [37, 88, 153, 154], 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%. [155, 156]

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). [36, 37]
 - A study in Qatar (conducted approximately 5 months after first Omicron wave [157]) 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%).[37]
 - A Danish study (conducted approximately 3 months after first Omicron wave [157]) estimated the effectiveness of a previous Omicron infection on BA.5 infection among triple-vaccinated individuals.[36] Prior omicron infection was highly protective against BA.5 (94%, 95%CI 92-95).[36]



Omicron: Effectiveness of therapeutics

Section updated: 15 August 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.[158]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. [158, 159]

Therapeutics in relation to BA.4 and BA.5

- Many monoclonal antibodies showed reduced efficacy against Omicron variants relative to Delta.[160]
- Additionally, although many of the newer Omicron subvariants are derived from BA.2, there are significant mutations in the spike protein.[159] It has been established that this reduces the sensitivity to vaccine-induced neutralising antibodies.[161, 162] As a result, it becomes likely that these variants will also have reduced sensitivity to therapeutic monoclonal antibodies.[159]
- 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, [150] 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.[159]
 - **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. [163]**



- 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.[164]

Rebound after Therapeutics

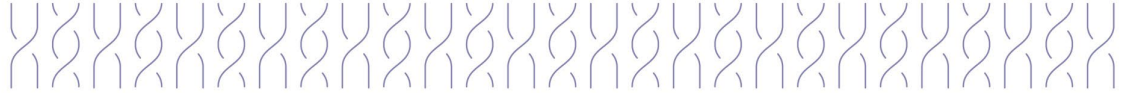
Rebound infection of SARS-CoV-2 has been reported after treatment with oral antivirals. This has been reported after use of both Paxlovid and molnupiravir. [4, 165]

- 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, symptomatic COVID-19, and COVID-19 hospitalisations [4]
- 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. [165]



Omicron: 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).⁽⁷⁷⁾ 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.⁽²⁴⁾

Rapid Antigen Tests (RATs)

Section updated: 16 August 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. ⁽¹⁵⁷⁾ Although nucleocapsid proteins are the most common antigen detected by RAT devices, ⁽¹⁵⁷⁾ the spike protein receptor is also a common target for detection. ⁽¹⁵⁸⁾ New variants have increasing numbers of mutations in the nucleocapsid proteins and spike protein regions which may limit the reliability of diagnostic tools. ⁽¹⁵⁷⁾

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%. (157, 159, 160) However, this data is currently limited due to issues with comparability across studies, settings and devices. Currently there is no evidence that RAT sensitivity is decreased in Omicron variants within the range of tests available in New Zealand.

All RATs available in New Zealand have been and will continue to be screened for acceptable performance.

Emerging evidence indicates that serial rapid antigen testing may become vital for early detection of new omicron variants. [166] 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. [166] 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.

There is no evidence that there is a clinically relevant decrease in the performance of RATs available for testing in New Zealand for detection of the Omicron variant. RATs are still recommended as the best method of POCT in New Zealand however, test performance will require ongoing review as new variants arise. [167]



New signals

Section updated: 19 August 2022

The risk of clinically significant emerging variants is considered to be high, according to the WHO.[168] 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.[169]

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 recently 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.[8]

BA.4.6

- This variant is increasing slowly in the United States and making up ~5 of national cases [6] and 4% of sequenced cases in Canada.[170]
- No severity data are currently available.
- BA.4.6 has been detected in the community in New Zealand at low levels, since late-June.
- 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. [171]
- This this variant appears to have greater resistance to Bebtelovimab but there has been some indication that Evusheld is less effective.[171]

BA.2.75

- BA.2.75 is a novel omicron variant of the BA.2 lineage which has nine new mutations in the spike protein receptors distinguishing it from BA.2.[172] Many of these mutations are located at sites targeted by neutralizing antibodies.
- This variant emerged in India in early May with cases reported in over 17 countries by mid-July 2022. The first two community cases within New Zealand were reported on the 19 July 2022.[173] The World Health Organisation (WHO) has classified BA.2.75 as a variant-of-concern lineage under monitoring on the 7 July 2022.[18]
- Early reports on social media suggest BA.2.75 is more transmissible than other BA.2 subvariants,[174] and in India this variant is competing with the most prevalent strain, BA.5, as of mid-July.[174]
- There is currently no evidence to suggest a change in severity compared to other Omicron variants.
- This variant was found to be moderately more neutralisation resistant to sera from vaccinated/boosted individuals than BA.2 by 1.8-fold but more neutralization sensitive than BA.4/5 (0.6-fold). [172]
- A pre-print states that BA.2.75 shows substantially higher ACE2-binding affinity than BA.5. The BA.2.75 sublineage is less immune evasive (based on humoral immunological data) than BA.4/5 after BA.1/2 breakthrough-infections. [175]



BA.5.2.1

- A new subvariant of the Omicron BA.5 lineage detected in China on the 8 July 2022.[9] The first confirmed case of BA.5.2.1 was detected in Shanghai, with more cases since identified across multiple provinces in China.[9] There is limited scientific evidence around transmission potential, disease severity and other properties of this variant.

BA.2.12 and BA.2.12.1

- New York State Department of Health announced the emergence of two Omicron subvariants in New York State, BA.2.12 and BA.2.12.1 on 13 April 2022, both sub-lineages of BA.2.[176]
 - Estimated to have a 23% – 27% growth advantage above BA.2. New York Department of Health reported no evidence of increased disease severity by these subvariants.[176]
 - The [CDC](#) estimated 36.5% (95% PI 28.9-44.9%) of COVID-19 cases in the United States to be BA.2.12.1 as of 30 April 2022.
- BA.2.12.1 has a substitution mutation at the L452 location (L452Q). This is similar to BA.4/B.5 which have L452R.[177]
 - A mutation to L452 location has arisen independently in other variants including Delta, Epsilon, Kappa. This mutation is linked to immune evasion and cell binding, making it a mutation of interest in new variants.[178]
- BA.2.12.1 has been shown to have increased immune evasion abilities compared to BA.2.[178]
 - BA.2.12.1 has strong neutralising evasion against plasma taken from people with previous BA.1 infection (both 3-dose vaccinated and unvaccinated).[178].
- A preprint study that used sera from both vaccinated and boosted individuals, found BA.2.12.1 to be modestly more (1.8-fold) resistant to neutralization than BA.2.[164]
- Cell culture experiments showed increased replication efficiency of BA.2.12.1 in human alveolar epithelial cells than BA.2, producing viral titres that were 61-fold higher than cells infected with BA.2. [179]



Glossary of Terms

<ul style="list-style-type: none"> • The AstraZeneca vaccine 	<ul style="list-style-type: none"> • AZD1222 or ChAdOx1
<ul style="list-style-type: none"> • The Pfizer/BioNTech vaccine 	<ul style="list-style-type: none"> • Comirnaty/BNT162b2
<ul style="list-style-type: none"> • Global Initiative on Sharing Avian Influenza Data (GISAID) 	<ul style="list-style-type: none"> • 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.
<ul style="list-style-type: none"> • Immune escape 	<ul style="list-style-type: none"> • The ability of the virus to evade our body's immune response. See also Immune response.
<ul style="list-style-type: none"> • Immune response 	<ul style="list-style-type: none"> • The response of our immune system to an infection. It includes development of specific antibodies to the virus and also cell-mediated responses (triggered by T cells).
<ul style="list-style-type: none"> • Mutation 	<ul style="list-style-type: none"> • 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.
<ul style="list-style-type: none"> • Naming mutations 	<ul style="list-style-type: none"> • 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).
<ul style="list-style-type: none"> • N-terminal domain 	<ul style="list-style-type: none"> • Part of the spike protein of the SARS-CoV-2 virus.
<ul style="list-style-type: none"> • R₀, Reproductive number 	<ul style="list-style-type: none"> • The reproductive number R₀ (R-naught), is a measure of how contagious a disease is. It is the average number of people who would catch a disease from one infected individual when there are no control measures in place, e.g., vaccination, lockdowns.
<ul style="list-style-type: none"> • R_{eff}, Effective reproductive number 	<ul style="list-style-type: none"> • The 'effective R' (R_{eff}) is the R observed when control measures are in place. R_{eff} can therefore change depending on the control measures currently enacted in a particular population. In general, whenever R is less than 1, i.e., an infected person goes on to infect less than one person on average, then the prevalence of the disease would be expected to decrease.
<ul style="list-style-type: none"> • Secondary attack rate 	<ul style="list-style-type: none"> • The probability that an infection occurs among persons within a reasonable incubation period after known contact with an infectious person in household or other close-contact environments.



<ul style="list-style-type: none"> • Serial interval 	<ul style="list-style-type: none"> • The time from symptom onset of a case to symptom onset in their identified contacts.
<ul style="list-style-type: none"> • SGTF / SGTP 	<ul style="list-style-type: none"> • "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)." [24]
<ul style="list-style-type: none"> • Variant 	<ul style="list-style-type: none"> • 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.
<ul style="list-style-type: none"> • Variant of Concern (VOC) 	<ul style="list-style-type: none"> • 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: <ul style="list-style-type: none"> • Increase in transmissibility or detrimental change in COVID-19 epidemiology; OR • Increase in virulence or change in clinical disease presentation; OR • Decrease in effectiveness of public health and social measures or available diagnostics, vaccines, therapeutics.
<ul style="list-style-type: none"> • Variant of Interest (VOI) 	<ul style="list-style-type: none"> • WHO definition: A SARS-CoV-2 variant: <ul style="list-style-type: none"> • with genetic changes that are predicted or known to affect virus characteristics such as transmissibility, disease severity, immune escape, diagnostic or therapeutic escape; AND • 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.
<ul style="list-style-type: none"> • Variant under Investigation (VUI) 	<ul style="list-style-type: none"> • 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).



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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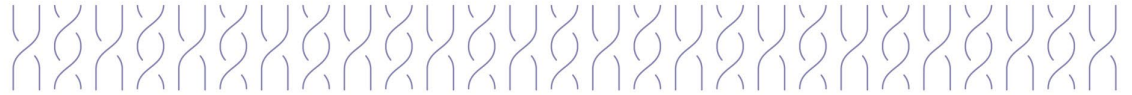
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