SCIENCE & TECHNICAL ADVISORY | RŌPŪ TOHUTOHU I TE PŪTAIAO ME TE HANGARAU

MINISTRY OF HEALTH
MANATŪ HAUORA

COVID-19 Omicron Update

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COVID-19 Omicron Update

Date: 22 February 2022

About this update

The Omicron variant is the focus of this update. Information is emerging at pace. New information included since the previous update is provided in red text.

Key points of new Omicron data

- Omicron is the dominant variant globally, with all other variants continuing to decline across all 6 WHO regions. BA.1 is currently the predominant Omicron sub-lineage globally. However, the relative prevalence of BA.2 to BA.1 is continuing to increase.
- As of 14 February, BA.2 predominates (>50%) in 10 countries. Increasing predominance of BA.2 is now anticipated, given the apparent increased transmissibility of BA.2 compared to BA.1. Data on BA.2 is now summarised in a table at the beginning of this update.
- The updated UKHSA Risk Assessment for BA.2 of 9 February 2022 states that it is plausible that the growth advantage seen with BA.2 is due to increased transmissibility **and/or shorter serial interva**l, given "the lack of apparent immune evasion" (presumably relative to BA.1).
- Serial interval data for BA.2 & BA.1: The average time from symptom onset of a case to symptom onset in their identified contacts (mean serial interval) is reported as 3.27 days for BA.2, about half a day shorter than for BA.1 (3.72 days), based on UKHSA preliminary analysis of contact-tracing data. For BA.2, 95% of serial intervals are expected to be less than or equal to 7.56 - 8.4 days after primary case symptom onset, similar to that expected for BA.1 at 8.21 - 8.57 days.
- Estimates of the proportion of Omicron infections that are asymptomatic range from 25-54%. UK COVID-19 Infection Survey data reports the frequency of loss of taste/smell has reduced markedly, while there has been an increase in the frequency of sore throat.
- UK data from the COVID-19 Infection Survey also suggest that the incidence of Omicron reinfection is much higher since Omicron became dominant:
    - There were more reinfections among COVID-19 Infection Survey participants in one month, since Omicron became the dominant variant (764 reinfections), than in the previous 18 months (586 reinfections).
    - The reinfection rate for COVID-19 Infection Survey participants was reported as increasing from 11.7 to 180.3 per 100,000 people since Omicron became the dominant variant (proportion vaccinated not specified).
    - Earlier data from the COVID-19 Infection Survey reported in January included that unvaccinated people were approximately twice as likely to be re-infected than people who had their second vaccine 14 to 89 days previously (data from both Delta-dominant and Omicron-dominant periods).
- There have been no sequence-confirmed BA.2 reinfections after BA.1 infection detected in UK data to date.
- A new Delta X Omicron Recombinant variant has been identified in the UK and is being monitored by UKHSA. News sources report a small number of cases. The significance of this variant is not yet known.

Predominance of Omicron and its sub-lineages

The Omicron variant comprises four lineages including B.1.1.529, BA.1, BA.2 and BA.3. These have been monitored under the umbrella term 'Omicron'. Omicron is the dominant variant globally, with all other variants continuing to decline across all 6 WHO regions. [1] The WHO Weekly Epidemiological Update on 15 February 2022 reports GISAID data showing Omicron accounted for 98.3% of sequences uploaded to GISAID in the most recent 30-day period reported.[1] Delta accounted for 1.7% of sequences and Lambda less than 0.1% in the same period. BA.1 accounted for 96.4% of Omicron sequences submitted to GISAID as of 31 January 2022. [2] The relative prevalence of BA.2 to BA.1 is now increasing. [1]

The Omicron BA.2 lineage was designated a variant under investigation (VUI) by UKHSA (not yet listed separately by WHO) on 21 January 2022 due to an increasing number of cases reported from sequencing. It is a sub-lineage of Omicron (B.1.1.529) that was designated by Pangolin on 6 December 2021.[3] 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. (link) BA.2 was designated a variant under investigation (VUI) by UKHSA on 21 January 2022 due to increasing numbers of sequences in the UK and internationally. (link) UKHSA published a risk assessment for BA.2 on 26 January 2022 [4] and this was updated on 9 February 2022. [5] WHO reports that the prevalence of the Omicron lineage BA.2 among sequenced Omicron cases globally submitted to GISAID has been steadily increasing, and that as of 14 February 2022, 10 countries have reported a predominance of BA.2 (>50%). [1] These countries include: Bangladesh, Brunei Darussalam, China, Denmark, Guam, India, Montenegro, Nepal, Pakistan, Philippines. WHO notes significant differences between regions, with the South-East Asia Region reporting the highest prevalence of BA.2 among Omicron sequences (44.7%) and the Region of the Americas reporting the lowest prevalence (1%). [1] The increased prevalence of BA.2 is attributed to increased transmissibility and increasing predominance of the BA.2 lineage is anticipated. Data on BA.2 is now summarised in a table at the beginning of this update.

Omicron BA.2

Characteristic	Data
Growth advantage/ transmissibility	**There is evidence of a growth advantage of BA.2 relative to BA.1. WHO have stated that a relative increase in BA.2 has been observed in multiple countries. BA.2 may have between 30-50% greater transmissibility compared to BA.1.** BA.2 has now been reported in 57 countries and there has been a relative increase in BA.2 sequences according to WHO.[2] WHO reports that the weekly proportion of BA.2 relative to other Omicron sequences rose to over 50% in the period 20 December 2021 to 1 February 2022 in several countries, [2] and as at 14 February 2022, BA.2 predominated in 10 countries. [1] In the UK, BA.2 accounts for an increasing proportion of S-gene positive (SGTP) tests. ESR reporting indicates that 21 cases of BA.2 had been confirmed in Aotearoa New Zealand as of 12.00 am, 31 January 2022. UKHSA states that there is evidence of a growth advantage for BA.2 compared to BA.1 in more than one country. [4] The growth rate advantage observed in England, in areas where there are sufficient cases to assess, is supported by increased household SARs in preliminary UK data. [4] The UKHSA Risk Assessment of 26 January 2022 noted that given the high SAR observed for BA.2 and "lack of apparent immune evasion" (presumably relative to BA.1), it is plausible that a change in transmissibility is contributing to the growth advantage. [4] In the latest UKHSA Risk Assessment (9 February 2022), the potential role of the shorter serial interval for BA.2 in conferring the growth advantage is noted. [5] Scientists from Heidelberg University have shared data on Twitter which suggests a BA.2 growth advantage over Delta of approximately 20% per day and a BA.1 growth advantage over Delta of approximately 15% per day.(link) Data from the UKHSA [6] and Denmark [7] suggests BA.2 may have 30-50% greater transmissibility than BA.1. Household transmission UKHSA reported that the crude SAR for BA.2 is 30% higher, compared to BA.1 for household contacts. [6] Analysis of routine contact tracing data showed SAR for household contacts as 13.4% (10.7%-16.8%) for BA.2 and 10.3% (10.1%-10.4%) for BA.1. [6] SAR analysis was not adjusted for vaccination status and only included close contacts named by the original case to NHS Test and Trace, (household members, face-to-face contact, people within one metre of the case for one minute or longer, or people within 2 metres for 15 minutes). [6] Non peer-reviewed analysis from the Danish Statens Serum Institut suggests a 50% increase in transmissibility for BA.2 compared to BA.1, with the estimated SAR of 29% for BA.1; and 39% SAR for BA.2 across households infected with Omicron. [7]
Disease course/Viral dynamics	**Preliminary UK data gives a mean serial interval for BA.2 of 3.27 days, with 95% of serial intervals expected to be less than or equal to 7.56 - 8.40 days after primary case symptom onset.** Serial interval UKHSA preliminary analysis of contact-tracing data shows the mean serial interval for BA.2 is 3.27 days (95% CI: 3.09 - 3.46), around half a day shorter than BA.1 (3.72; 95% CI: 3.62 - 3.80). [8] Similarly, BA.2 has a shorter median serial interval (2.68 days 95% CI: 2.50 - 2.87) compared to BA.1 (3.27 days; 95% CI: 3.17-3.36). For BA.2, 95% of serial intervals are expected to be less than or equal to 7.56 - 8.4 days after primary case symptom onset. This is similar to BA.1, with 95% of serial intervals expected to be less than or equal to 8.21 - 8.57 days after primary case symptom onset. [8]

Characteristic	Data
Clinical features (symptoms and severity)	**There are insufficient data to determine the severity of BA.2 infections. Preliminary analysis from Danish Statens Serum Institut shows no differences in frequency of hospitalisation for BA.2 compared to BA.1** Danish Statens Serum Institut has stated that preliminary analysis shows no differences in hospitalisations for BA.2 compared to BA.1 and that analyses are ongoing. [9] There continue to be insufficient data to assess the severity of BA.2. [5]
Immune evasion/vaccine effectiveness/therapeutics	**Based on early data BA.2 does not appear to have a greater capacity for immune evasion than BA.1.** Neutralisation assays UKHSA states that a preliminary pseudovirus neutralisation study does not suggest a difference in neutralisation between BA.2 and BA.1, using sera from vaccinated individuals. [4] Vaccine effectiveness Preliminary analysis from the UKHSA found no statistical difference in the vaccine effectiveness for BA.2 compared to BA.1.[6] Analysis included Pfizer, Moderna and AstraZeneca vaccines (combined data). After 2 doses, vaccine effectiveness was 9% (7 to 10%) and 13% (-26 to 40%) respectively for BA.1 and BA.2, after 25+ weeks. This increased to 63% (63 to 64%) for BA.1 and 70% (58 to 79%) for BA.2 at 2 weeks following a booster vaccine. [6] UKHSA will continue to analyse this data. Reinfection UKHSA Technical Briefing 11 February 2022 reports that there have been no detected sequence-confirmed BA.2 reinfections after BA.1 infection in their data to date. [8]
Detection	**Most observational studies have relied on SGTF as a proxy for Omicron, which would only consider 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.** Unlike BA.1, the BA.2 lineage does not have the spike deletion at 69-70 that causes S-gene target failure (SGTF).[3] Because of this, it is being called the "stealth" version of Omicron as it cannot be detected using PCR tests that detect SGTF, such as Thermo Fisher's TaqPath. (link) This has implications on using PCR tests that detect SGTF as a proxy for rapidly detecting Omicron cases. Data is emerging for BA.2. Most observational studies have relied on SGTF as a proxy for Omicron, which would only consider 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.

Omicron – B.1.1.529 variant and sub-lineages

(note: specific data on the BA.2 sub-lineage is reported in the table above)

Characteristic	Data
Growth advantage/ transmissibility	**Omicron is more transmissible and has a higher secondary attack rate than Delta** Using data from Denmark (to 18th Dec 2021), the effective (instantaneous) reproduction number of Omicron is 3.19 (95%CI 2.82–3.61) times greater than that of Delta under the same epidemiological conditions. [10] In Canada, initial modelling estimates of R_{eff} for Omicron is 1.5 (90%CI 0.78–2.34). [11] Data to 20 December 2021 reported by UKHSA show that, relative to Delta, Omicron is currently more concentrated in young adult age groups (20 to 29) and is less prevalent in children. [12] Of the 1,063 cases in one region of Canada, 59% of 1,063 cases were 18-24 years old and 27% were 25-39 years old, corresponding with the main outbreak environments being in post-secondary education and food/beverage settings. [11] Scientists from Heidelberg University have shared data on Twitter which suggests a BA.1 growth advantage over Delta of approximately 15% per day.(link) Data from a US health provider in Houston, Texas, indicated a case-doubling time for Omicron of 1.8 days, three times faster than for Delta in this area. [13] Preprint data from South Africa found Omicron was more associated with asymptomatic infection and transmission than Beta and Delta. [14] In England, contact tracing data show a greater proportion of transmission happening outside the household for Omicron than for Delta. [12] Emerging data from the UK estimated a shorter generation time (interval between infection events in an infector-infectee pair) for Omicron during late November to December 2021, 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. [15] This translated to a transmission advantage of 160%-210% for Omicron. However, the study is subject to bias from factors such as differences in the populations the variants were present in, differences in immune escape between variants, and using test to test distribution as a proxy for the generation time distribution.

Characteristic	Data
	UKHSA preliminary analysis of contact-tracing data shows the mean serial interval for BA.1 is 3.72 days (95% CI: 3.62 - 3.80). [8] BA.1 has a median serial interval of 3.27 days (95% CI: 3.17-3.36). For BA.1, 95% of serial intervals are expected to be less than or equal to 8.21 - 8.57 days after primary case symptom onset. [8] Household transmission Non peer-reviewed analysis from the Danish Statens Serum Institut estimates a SAR of 29% for BA.1 (compared with an SAR of 39% for BA.2) across households infected with Omicron. [7] South Korea [16]: secondary attack rate in a small study of 25 households was 50.0% Danish data [17]: • Overall, household SAR was 31% for Omicron and 21% for Delta. • Household SAR for unvaccinated individuals was 29% for Omicron and 28% for Delta. • Household SAR for fully vaccinated (defined according to each vaccine) individuals was 32% for Omicron and 19% for Delta. • Household SAR for booster-vaccinated individuals was 25% for Omicron and 11% for Delta. UK data [12]: The UKHSA Technical Briefing 33 (23 December 2021) reported that household SAR was 13.6% (95% CI: 13.1-14.1) for Omicron and 10.1% (95% CI: 10.0-10.2) for Delta. SAR in non-household settings was 7.6% (95% CI: 7.2-8.0) for Omicron and 2.8% (95% CI: 2.7-2.9) for Delta. However, this data has not been stratified by vaccination status. Other data Japan [18]: A study investigated the differences in viral environmental stability between the SARS-CoV-2 Wuhan strain and all VOCs on plastic and skin surfaces. The Omicron variant has the longest survival time of 21.1 hours (95% CI: 15.8–27.6) compared to 16.8 hours (95% CI: 13.1–21.1) for Delta. The high environmental stability of Omicron could increase the risk of contact transmission and contribute to its spread. Canada [19]: 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. On initial testing 196 of 475 HCWs were positive and were quarantined. Only 42 (15%) of 279 HCWs that were initially asymptomatic and allowed to work became positive a median of 4 days after the initial test, but no further transmission was detected. Absence of symptoms at initial evaluation (OR 3.8, 95% CI 2.5-5.7) and having received a third vaccine dose more than 7 days before (OR 1.88, 95% CI 1.3 – 2.8) were associated with increased odds of remaining negative. Non-omicron, novel transmission data: A human challenge study (n=36) using pre-alpha **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.[20]
Disease course/Viral dynamics	**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): • Faroe Islands [21]: Observed incubation period was short, ranging from 2 to 6 days, with a mean incubation period of 3.24 days (95% CI 2.87-3.60). All had had 3 doses of Pfizer (2 primary, and booster in last 2.5 months) • Norway [22]: Estimated incubation period was 0 to 8 days, median of 3 days (interquartile range: 3–4). [22] Almost all participants interviewed had received 2 doses of an mRNA vaccine. The incubation period was consistent with another study (median 3 days for both Delta and Omicron variants) • USA [23]: Incubation period (6 cases only) of approximately 3 days (73 hours, range = 33–75 hours). [23] • Netherlands [24]: Mean incubation period 3.2 days (SD = 2.2 days) for SGTF cases (Omicron BA.1) Human challenge studies (non- omicron, novel transmission data) • Incubation period of 2 to 4 days after inoculation with **wild-type virus.** [20] Viral load (VL) rose steeply and peaked around day 4-5. Serial Interval • Spain [25]: The mean serial interval was significantly shorter for Omicron (4.8 days) versus Delta (5.4 days), corresponding to a difference of -0.6 (95% CI: -1 to -0.15). • Netherlands [24]: Within households, a mean serial interval of 3.4 days was observed for SGTF (proxy for Omicron) and 3.9 days for non-SGTF (proxy for Delta) cases.

Characteristic	Data
	• South Korea [16]: mean: 2.5-4.3 days, and median was 3-4 days (based on small sample size of 12 transmission pairs). • Belgium [26]: overall Omicron mean 2.75 days (SD=2.54). Within household mean 2.8 (SD=2.6), between household mean 2.72 (SD=2.44) <u>Latent period:</u> Human challenge studies (non- omicron, novel transmission data) • Viral shedding by qPCR became quantifiable in throat swabs from 40 hours (95% CI [40,52]) (~1.67 days) post-inoculation, significantly earlier than in the nose (p=0.0225, where initial viral quantifiable detection occurred at 58 hours (95% CI [40,76]) (~2.4 days) post-inoculation. [20] Viral load (VL) rose steeply and peaked around day 4-5. <u>Duration of infectiousness</u> Data predominantly from **vaccinated** people: • Japan [27]: Preliminary data from the National Institute of Infectious Diseases suggest that the amount of viral RNA in specimens from Omicron infections (19 vaccinated and 2 unvaccinated cases) was highest 3-6 days after diagnosis or symptom onset and then decreased gradually, with a marked decrease 10 days after diagnosis or symptom onset. A similar trend was seen for viral isolates, with no infectious virus detected in the respiratory samples 10 days post diagnosis or symptom onset. • Switzerland [28]: A study investigating viral shedding dynamics included a small number of Omicron breakthrough infections (n=18) and showed similar infectious viral titres in nasopharyngeal samples for breakthrough Omicron and Delta (n=17 for this comparison) infections. Samples were gathered in the first 5 days post symptoms. • US [29]: Preliminary data from a longitudinal study (National Basketball Association's [NBA] occupational health programme) in a largely vaccinated cohort suggest that Omicron may have a lower peak viral load (Ct 23.3 for Omicron vs Ct 20.5 for Delta) and shorter clearance time (5.35 days for Omicron vs 6.23 days for Delta) than Delta. However, the rate of clearance (3.13 Ct/day for Omicron vs 3.15 Ct/day for Delta) and total mean duration of infection is similar (10 days for Omicron vs 11 days for Delta). These data are only from a small number of infections, so more is needed to understand the viral dynamics of Omicron and how they are affected by vaccination. • Singapore [30]: Ct value at presentation was significantly higher for Omicron compared with Delta infections (20.7 [IQR 17.9 – 28.5] vs. 19.1 [15.4 – 21.1], p<0.001). Pattern of viral shedding was comparable for Omicron and Delta, with an increase in viral load over the first 2-3 days of illness, and significant decline from Day 8. Trough and illness onset median Ct values were similar for Omicron between those with primary vaccination or booster vaccination doses. • Switzerland[31, 32]: A small study in Delta (n=17) and Omicron patients (n=18) found that Delta and Omicron have comparable genome copies (p=0.3345) but Omicron patients had slightly but not significantly lower infectious viral titres compared to Delta patients (p=0.1033). Human challenge studies (non- omicron, novel transmission data) Some clinical participants still shed culturable virus ~10 days after symptom onset but the sample size is small (n=36). [20] <u>Duration of illness</u> • Faroe Islands [21]: Time to resolution of symptoms varied, and at the end of follow-up, five individuals still reported symptoms, while the rest (16 individuals) reported symptoms lasting 1 to 9 days. • Singapore [30]: Negative viral cultures were obtained starting from day 2 of illness and no positive viral cultures were obtained for patients beyond day 5 of illness or with Ct values >26 based on 14 patients. • For time to hospitalisation and death, see "severity" section above. Data on the disease course remains limited at present, with few quantitative studies to date.
Clinical features (symptoms and severity)	**Severity – data to date indicates hospitalisation and death rates are lower than Delta, taking into account vaccination status and risk for severe disease.** **Hospitalisation** <u>Hospitalisation frequency for Omicron relative to Delta</u> Adjusted for vaccination status (important for understanding basic differences in severity as it can remove differences in vaccine effectiveness from assessment. However, residual confounding for vaccination status may still occur): • A preprint Swedish study (N= 1 384 531) comparing Omicron period vs Delta found that risk of severe disease was lower with Omicron by 40% for unvaccinated and 71% less for vaccinated individuals. Also, the risk for severe COVID-19 remained high among unvaccinated, first-time-infected cases of both sexes during the Omicron period in the age group 65+, and also among males in the age group 40-64 years with two or more comorbidities. [33] • US study comparing healthcare utilisation in high transmission periods of Omicron vs Delta found a relative increase in ED visits (86%) and hospitalisations (76%) compared to the Delta period due to the higher volume of cases but a relative decease in the length of stay in hospitals (-27%). [34]

Characteristic	Data

	• A preprint US study comparing Omicron period vs Delta period found that among hospitalised omicron patients (41% vaccinated) they were less likely to require ICU or die. [35]
	• A Norwegian study (n= 91005) found that cases infected with Omicron were 73% lower risk of hospitalisations compared with delta infection. [36]
	• A preprint study from France looked at 39 Hospitals in the Paris area to measure the risk of ICU admission. It found risk of hospitalisation with Omicron was reduced by 64% compared to Delta. [37]
	• Canadian data: risk of hospitalisation or death was 54% lower (Hazard Ratio =0.46, 95% CI: 0.27-0.77)[1]. [38]
	• Scottish data: risk of hospitalisation 68% lower (observed/expected ratio of 0.32, 95% CI: 0.19-0.52).[2] [39]
	• UK data: risk of presentation to emergency care or hospital admission 50% lower than with Delta (Hazard Ratio 0.53, 95% CI: 0.50 to 0.57). The risk of hospital admission from emergency departments was approximately 67% lower than with Delta (Hazard Ratio 0.33, 95% CI: 0.30-0.37).[3] [40]
	• A pre-print 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 hospitalization/death compared to Delta. [41]
	• A US study in veterans found that infection by Omicron has a 45% (95% CI: 26-58) lower likelihood of resulting in hospitalisation than infection by Delta. [42]
	• UK data in long term care facility residents: risk of hospitalisation much lower, 10.8% for Delta and 4.0% for Omicron (Hazard Ratio 0.50, 95% CI: 0.29-0.87). [43] This paper by Krutikov and colleagues, part of the VIVALDI study, is also reported in the UKHSA Technical Briefing 35. [6]
	• Portugal data: risk of hospitalisation lower, 1.6% for Delta and 0.2% for Omicron (Hazard ratio 0.25, 95% CI: 0.15-0.43). [44]
	• Danish data [45] stratified rather than adjusted by vaccination status:
	  ○ Among those with <2 doses: 43% lower risk of hospitalisation (RR = 0.57, 95% CI: 0.44-0.75)
	  ○ Among those with 2 doses: 29% lower risk of hospitalisation (RR = 0.71, 95% CI: 0.60-0.86)
	  ○ Among those with 3 doses: 50% lower risk of hospitalisation (RR = 0.50, 95% CI: 0.32-0.76)
	
	Unadjusted for vaccination status (provides indication of burden on healthcare at the level of vaccination in country where study conducted):
	
	• UK data (adjusted to some extent for prior infection): reduction in hospitalisation of 38% (95%CI 31-45%) for emergency department attendance or admission, and 62% (95% CI 50-70%) for admission, [12] or (from a different group analysing same data, with different methods for prior infection) 20-25% lower for attendance at hospital, and 40-45% for hospital admission. [46]
	• US data (unclear if adjusted for vaccination/infection): 53% reduction in hospitalisation (hazard ratio for symptomatic hospital admission relative to Delta was 0.47 (95% CI: 0.35-0.62))[4] [47]
	• Danish data [45]: Overall, 36% lower risk of hospitalisation (RR = 0.64, 95% CI: 0.56, 0.75)
	
	<u>Hospitalisation frequency (not compared to Delta)</u>
	
	UK data:
	
	England: ICU admissions with a valid sequencing result for Omicron increased from 9% week commencing 15 December 2021 to 50% in week commencing 12 January 2022. [6]
	
	England: To 29th December, 815 Omicron hospitalisations had been reported. To the same date, around 650,000 Omicron cases had been reported, but there are lags in hospitalisation reporting and many recent cases are unlikely to have had sufficient observation time to be admitted to hospital (i.e., hospitalisation likely to be underestimated). [40] Some crude data available by day but vary substantially each day, and likely affected by lack of follow up time (people testing positive most recently only followed up for 7 days), and lack of adjustment for age or vaccination status. [46]
	
	Scotland: Did not report as numbers too small. [39]
	
	Canadian data:
	
	Ontario: 29,594 cases to December 25th, of whom 75 (0.25%) hospitalised (or died). Again this is likely to be an underestimate due to very short follow up of those diagnosed later. [38]
	
	US data:
	
	California: 52,297 cases to January 1, 2022, of whom 182 (0.35%) were admitted to hospital with symptoms. [47]

[1] adjusted for vaccination status and region
[2] adjusted for age, sex, socioeconomic status, vaccination status and clinical risk factors.
[3] Controlled for date of specimen and area of residence and further adjusted for age, sex, ethnicity, local area deprivation, international travel, vaccination status. Also adjusted for whether the current infection is a known reinfection, although as reinfections are substantially under-ascertained, the adjustment may not have fully accounted for the effect of reinfections.
[4] adjusted for age, sex, race/ethnicity, and neighborhood-level median household income, as well as clinical risk factors recorded within the prior year (including history of smoking, body mass index, Charlson comorbidity index, and healthcare utilization across outpatient, emergency department, and inpatient settings)

Characteristic	Data
	Indian data: New Delhi: 82 cases to December 23rd, 3 (3.6%) of whom required hospitalisation. This could be biased due to the short follow up time since diagnosis, or underdiagnosis of cases. [48] French data: Marseille: 1,119 cases between November 28 to December 31, 21 (1.9%) of whom were admitted to the hospital. [49] Paediatric data South Africa: Rapid increases in paediatric COVID-19 cases and hospitalisations were reported in the Tshwane District, mirroring high community transmission of SARS-CoV-2 (Omicron variant). [50] US: According to news reports, the CDC says since mid-December the hospital admission rate for those under 5 has increased to more than 4 in 100,000 children, up from 2.5 per 100,000, while the rate among children aged 5 to 17 years is about 1 per 100,000 (link). However, the overall hospitalisation rate among children and teens is still lower than that of other age groups, and they account for less than 5 per cent of average new daily hospital admissions, according to the CDC. A US study in 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. [51] Risk for ED visits was 18.83% (vs 26.67%), hospitalisations was 1.04% (vs 3.14%), ICU admissions was 0.14% (vs 0.43%), and mechanical ventilation was 0.33% (vs 1.15%). UK: Pediatric admissions began to rise from 26 December 2021, with a 3-fold increase in 2 weeks. [3] The rise is most rapid among children under 5 years, and highest in infants aged under 1 year (based on data for all variants, but Omicron represents over 90% of sequenced samples in the UK). A clinical case review of a small number of Omicron admissions in infants found those admitted were not severely unwell. [3, 52] Preliminary data from the UK during the Omicron wave (14 December 2021 to 6 January 2022) indicate less severe outcomes in children aged under 1 year compared to previous waves. [53] In the current wave, 12.7% required oxygen use compared to 22.5% in the first wave of the pandemic. 16% required admission to intensive care (vs 14%), 3.9% required use of mechanical ventilation (vs 5.8%), 1.3% required use of non-invasive ventilation (vs 7.2%), and mean length of stay was 1.9 days (vs 6.6 days). A preprint study from the US states that paediatric acute upper airway infection (UAI) cases have increased during the Omicron variant surge, with many developing severe disease. [54] The retrospective cohort study suggests that Omicron replicates more efficiently in the conducting airways, increasing the risk of a croup phenotype in children as they have smaller airway calibres. The study compares data within the National COVID Cohort Collaborative before and during the rise of Omicron. It was observed that in December 2021, as Omicron became dominant in the US, SARS-CoV-2 positive UAI cases increased to the highest number per month (N = 170) and 1.5% (234/15,806) of hospitalized children with SARSCoV-2, had an UAI diagnosis. Risk factors for hospitalisation with Omicron: In the UK, 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. [40] 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. [55] Of note, 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: no data found. Time in hospital with Omicron: median length of stay reported as 2.8 days but strong potential bias as included only those already discharged at 3 weeks after start of Omicron wave (i.e,. those with longer stays might not be included). [13] A South African study also found median hospital length stay was significantly lower for Omicron than other variants, but possibly suffers from similar bias. [56] Preliminary analysis of South African hospital admissions in Gauteng Province (includes Johannesburg and Tshwane) reported a median hospital stay of 4 days (inter-quartile range 2-6 days) during an Omicron-dominant period. [57] A US study estimated that the median duration of stay for patients with Omicron variant infections experiencing symptomatic hospitalisations was 1.5 (1.3-1.6) days, with 90% of patients expected to complete hospitalisations within 3.1 (2.7-3.6) days, corresponding to a 69.6% (95% CI: 64.0-74.5%) shorter median length of hospital stay compared to patients with Delta infections. [47] However, a key limitation in some of these studies is that longer stays will have been missed for Omicron (biasing median duration downward) due to short follow up times. A US study in veterans found that among COVID hospitalisations, Omicron is associated with a 2-day (95% CI: 1-2) shorter stay than Delta. The average length of stay was 6 days (95% CI: 5-7). [42] A Portuguese study found the length of stay in hospital for Omicron was significantly shorter than for Delta (confounding-adjusted difference[5] -4.0 days (95% CI -7.2 to -0.8). [44] **ICU admission** Severe/ICU/ventilated frequency relative to Delta Adjusted for vaccination status (important for understanding basic differences in severity as removes differences in vaccine effectiveness from assessment. However, residual confounding for vaccination status may still occur):

[5] adjusted for sex, age, previous infection and vaccination status

Characteristic	Data

- South African data: Among *hospitalised* individuals, after controlling for factors associated with severe disease[6], 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). [58] Compared to earlier Delta infections, after controlling for factors associated with severe disease[7], SGTF-infected individuals had lower odds of severe disease (aOR 0.3, 95% CI 0.2-0.5).
- A US study in veterans found that Omicron is associated with a 73% (95% CI: 28-92) lower risk of ICU admission than Delta. [42]

Unadjusted for vaccination status (provides indication of burden on healthcare at the level of vaccination in country where study conducted):

- US data: Unadjusted hazard ratios for ICU admission associated with Omicron variant infection was 0.26 (95% CI: 0.10-0.73), a 74% reduction. [47]

Severe/ICU/ventilated frequency (not compared to Delta)

In Texas, among 862 people who tested positive for Omicron (mainly symptomatic people presenting to healthcare facilities), [13] the maximum ventilatory support required was:

Extracorporeal membrane oxygenation	1 (0.7% of 134 hospitalised, 0.1% of 862 testing positive for Omicron)
Mechanical ventilation	6 (4.5%, 0.7%)
Non-invasive ventilation	9 (6.7%, 1.0%)
High flow oxygen	12 (9.0%, 1.4%)
Low flow oxygen	42 (31%, 4.9%)
Room air (but hospitalised)	64 (48%, 7.4%)

A total of 19.7% (875/4438) of hospital admissions required supplemental oxygen (not further specified) and 6.9% were treated in ICU (308/4438) in an analysis of data from Gauteng Province, South Africa during an Omicron-dominated period. [57]

Californian data: The daily risk of mechanical ventilation among patients (unclear if analysis restricted to hospital inpatients) with Omicron infections was significantly lower than for Delta (0 vs 0.04 per 1000 person-days at risk).[47]
Risk factors for ICU/ventilation: no data.
Time to ICU/ventilation: no data.

Death

Death frequency relative to Delta

UK data: To 29 December 2021, a total of 57 people were reported to have died within 28 days of an Omicron COVID-19 diagnosis (198,348 confirmed cases of Omicron). [40]

South African data: After adjusting for age, sex, comorbidities, and subdistrict, the hazard ratio was 0.27 (95% CI: 0.19-0.38), a 73% reduction relative to Delta, but the extent of reduction was attenuated when prior infections and vaccination were also considered (HR: 0.72, a 28% reduction relative to Delta). [41]

US data: Unadjusted hazard ratios for mortality associated with Omicron variant infection was 0.09 (95% CI : 0.01-0.75) [47] 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). [43]

Portugal data: The odds of death were 0.14 (95% CI: 0.0011-1.12), representing a reduction in the risk of death of 86% for Omicron compared with Delta. [44]

[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.

Characteristic	Data
	Risk factors for death: UK data: Of 57 people who died within 28 days of Omicron diagnosis (to 29th December 2021) the age of those dying ranged from 41 to 99 years. [40] Time to death: UK data: median time from Omicron specimen date to death was 5 days (range 0 to 14). [40] Note that specimen date might not reflect date of symptom onset. **Other severity information** Non-peer reviewed studies (pre-prints) have shown that in hamster and mouse models, Omicron poorly infects the lung, leads to lower viral loads, and produces milder clinical signs of infection compared to those observed with previous strains. [59-61] Data from a study using ex-vivo human lung and bronchus tissue show similar results, with slower Omicron replication observed in the lung and faster in the bronchus compared to previous strains. [62] Clinical symptoms were largely absent in hamsters that were re-infected with Omicron, suggesting that immunity raised against the ancestral strain was protective against Omicron. [60] The characteristics of the antibody-mediated protection observed within this study is of interest while we wait for further studies in humans confirm the relevance of these findings. **Symptoms – Symptoms may be milder in previously infected and/or vaccinated individuals. Recent UK data suggests a substantial proportion of Omicron cases may be asymptomatic – estimates range from 25-54%. The most common symptoms reported are sore throat, cough, runny/stuffy nose, and fatigue. Additional data supports earlier reports that loss of smell and taste is less commonly reported by Omicron cases than for Delta, and that sore throat is more commonly reported.** The most common symptoms reported in early data were: cough; runny/stuffy nose; and fatigue. [11, 22, 63, 64] The COVID Symptoms Study (by health science company Zoe and Kings College London) reports that headache and sneezing are also common symptoms of Omicron infection. [65] Preliminary information 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) A study from Canada of 1,063 cases of Omicron (confirmed or suspected) found that only 10% reported shortness of breath. [11] Symptoms reported in paediatric cases in South Africa have included fever, vomiting, diarrhoea and convulsions. [50] UKHSA Technical Briefing 34 compares Omicron to Delta symptoms. The report provides a recent analysis of NHS Test and Trace data of 182,133 confirmed Omicron cases and 87,920 confirmed Delta cases in the period between 01 December to 28 December 2021. Adjusted odds ratio analysis showed that Omicron cases were less likely to report loss of smell and taste compared to Delta cases (13% of Omicron cases, 34% of Delta cases, odds ratio 0.22, 95% CI: 0.21-0.23). However, Omicron cases were more likely to report a sore throat than Delta cases (53% of Omicron cases, 34% of Delta cases, odds ratio 1.93, 95% CI: 1.88-1.98). Adjustments were made for age group, sex, ethnicity, self-reported vaccination status (two or more doses, one or no dose, or missing data), geographical region of residence, and the week in which symptoms began. 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 [66] 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. 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. [67] The most common symptoms were sore throat (25%), fever (20%), headache (15%), cough (12.5%), and sputum production (12.5%). While these findings are consistent with recent reports of mild symptoms from other sources, given the small size and low median age of the study (39.5), more data are required to understand symptoms and determine the severity of Omicron. A Singapore study compared the symptoms between Omicron and Delta found having sore throat was significantly more common in Omicron patients (sore throat 46.0 vs 23.0%, p=0.005) and less likely to develop pneumonia (3.4 vs 16.1%, p=0.005). Median neutrophil count, C-reactive protein and lactate dehydrogenase levels were lower in Omicron infections. Patients with booster vaccination were significantly older and had higher anti-spike antibody but were similar in clinical and laboratory features including median initial and lowest PCR cycle threshold values. [30] A study from Jordan showed that the most frequent symptoms for Omicron were fever, cough, sore throat, runny nose, joint and muscle pain, and general fatigue. Loss of taste and smell was only reported in 1.2% of patients. [68] Recent 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.[69] Vaccine status of individuals within this group was not included in the report. A preprint study that analysed data from the UK COVID-19 Infection Survey found Omicron infections were associated with fewer lower, and more upper, respiratory tract symptoms. [70]There was a marked reduction in reports of loss of taste/smell, from high levels observed in the Delta period, e.g. 44%/44% on 1 December 2021, to 16%/13% on 31 December 2021. Loss of taste/smell were previously highly specific symptoms. [70] Increases in sore throat were reported, from 45% to 57% in symptomatic PCR-positive infection episodes during December 2021 decreasing slightly to 54% by 15 January 2022. However, data should be interpreted with caution as sore throat also increased from 40% to 43% in symptomatic PCR-negative visits during December 2021 and then decreased to 35% by 15 January 2022. The UK COVID-19 Infection Survey collects data on characteristics of people testing positive for COVID-19, including data on symptoms for those who had strong positive tests - Ct value under 30 (see Table below). These data are provisional, reflect infections reported in the community, and exclude infections reported in hospitals, care homes, or other institutional settings. The below table is taken from the 19 January 2022 edition of this dataset. [71] The Delta variant was dominant in the UK in the November period and Omicron was becoming dominant in the December period.

<table>
<tr><th>Characteristic</th><th>Data</th></tr>
<tr><td></td><td>While the December data provide an indication of the common symptoms of the Omicron variant, Omicron was not dominant for the whole of December, so these data are not a complete representation and further information is required. Recent data from the UK COVID-19 Infection Survey which reported on what can be considered the beginning of the ‘Omicron period’ (20 December 2021 23 January 2022) indicates that approximately 54% of participants did not report any symptoms (within 35 days after first observed positive test), considered asymptomatic. [72]
<table>
<tr><th rowspan="2">Symptoms</th><th colspan="2">Percentage of people with this symptom within 35 days of a positive PCR, among those people with a Ct value under 30</th></tr>
<tr><th>November 2021</th><th>December 2021</th></tr>
<tr><td>Any symptoms</td><td>65.00</td><td>58.16</td></tr>
<tr><td>No symptoms (asymptomatic)</td><td>35.00</td><td>41.84</td></tr>
<tr><td>Classic symptoms (cough, fever, shortness of breath, loss of taste, loss of smell)</td><td>56.86</td><td>48.42</td></tr>
<tr><td>Loss of taste or smell</td><td>30.52</td><td>15.55</td></tr>
<tr><td>Gastrointestinal symptoms (abdominal pain, nausea or vomiting, diarrhoea)</td><td>17.38</td><td>13.31</td></tr>
<tr><td>Cough</td><td>45.65</td><td>39.88</td></tr>
<tr><td>Fatigue (weakness)</td><td>39.96</td><td>32.09</td></tr>
<tr><td>Headache</td><td>40.45</td><td>34.39</td></tr>
<tr><td>Sore throat</td><td>29.62</td><td>32.71</td></tr>
<tr><td>Fever</td><td>25.19</td><td>21.95</td></tr>
<tr><td>Loss of smell</td><td>25.96</td><td>12.29</td></tr>
<tr><td>Muscle ache (myalgia)</td><td>27.83</td><td>23.07</td></tr>
<tr><td>Loss of taste</td><td>25.14</td><td>12.62</td></tr>
<tr><td>Shortness of breath</td><td>13.82</td><td>9.84</td></tr>
<tr><td>Nausea or vomiting</td><td>10.29</td><td>7.35</td></tr>
<tr><td>Abdominal pain</td><td>7.94</td><td>5.84</td></tr>
<tr><td>Diarrhoea</td><td>5.86</td><td>5.42</td></tr>
</table></td></tr>
<tr><td>Immune evasion/vaccine effectiveness/therapeutics</td><td>Vaccine effectiveness (VE) – some protection offered against symptomatic disease, however, VE is reduced compared to Delta. Rapid waning of VE occurs against Omicron but a booster dose restores protection. VE against hospitalisation appears to be 60-70% after a primary vaccine course but declines to ~45% from 25 weeks after second dose. VE against hospitalisation increases to ~90% after a booster dose (including in those over 65 years of age).

Pfizer and BioNTech have begun enrolment for a clinical trial to test the safety, tolerability, and immunogenicity of an Omicron-based vaccine candidate in 1,420 healthy adults aged 18-55 years. (link) Pfizer is hoping to be able to deliver the vaccine in March 2022. (link) However, testing in primates has shown no advantage of an Omicron specific mRNA (Moderna) booster over a booster with the regular Moderna vaccine (link)

VE against infection

A preprint longitudinal cohort study of elderly individuals (n = 37, median age 82 years) found that the proportion of individuals with detectable SARS-CoV-2-neutralizing serum activity against Omicron increased from 0% at 5 months after a primary Pfizer course, to 89% 1 month after a booster dose of Pfizer. [73] At 3-5 months after the booster dose, 81% of participants had a detectable level of neutralising activity against Omicron.

A Danish cohort study has shown VE (Pfizer) against infection of 55% in the month after primary vaccination, [74] VE is significantly lower than for Delta infection and declines rapidly after the first month. [74] Booster vaccination increases VE back to 55%. [74]

A study in the Netherlands also found an increased risk of infection with Omicron compared to Delta in vaccinated and previously infected individuals. [75]

Emerging results from the US indicate that 2-dose VE for Moderna against Omicron infection (determined by S-gene status) was 30.4% (95% CI 5-49) at 14-90 days after vaccination and declines over time. [76] The 3-dose VE was 62.5% (95%CI: 56.2-67.9) against Omicron infection compared with 95.2% (95%CI: 93.4-96.4) for Delta. Among immunocompromised individuals, the 3-dose VE against Omicron infection was very low (11.5%; 95% CI: 0.0-66.5).</td></tr>
</table>

Characteristic	Data

The UKHSA reported unadjusted VE (all vaccines combined) against infection in healthcare workers (SIREN cohort): [3]

- Those with no prior infection: 32% (95% CI: -6-57) after 2 doses and 62% (95% CI: 41-75) after 3 doses
- Those with prior infection: 60% (95% CI: 36-75) after 2 doses and 71% (95% CI: 56-82) after 3 doses

VE for US veterans (aged 65+ years) who received two doses of mRNA vaccines (vaccines not specified) was 25% (95% CI: 20-30) against Omicron infection, rising to 62% (95%CI: 59-65) after an mRNA vaccine booster. [42]

<u>VE against symptomatic disease</u>

VE data from South Africa [77, 78] the UK [3, 12, 39, 40, 79] and Denmark [74] all suggest reduced VE for 2-dose Pfizer vaccine regimens against symptomatic disease caused by Omicron compared with Delta. A booster dose of mRNA vaccine restores rapidly waning protection against symptomatic COVID-19 to levels similar to immediately after the primary course but early data from England suggest waning also occurs after the booster dose (e.g. VE against symptomatic disease dropped to ~50% 10 weeks after a Pfizer booster and ~65% 5-9 weeks after a Moderna booster following primary Pfizer course - see Figure 1). [3, 12, 40] A UK analysis conducted in the elderly aged 65+ years reported similar results. [80] Among those who received a primary course of Pfizer, VE after a Pfizer booster was 65% at 2 to 4 weeks but then dropped to 31% at 10+ weeks. For those who received a Moderna booster, VE was 70% at 2 to 4 weeks, dropping to 57% at 5 to 9 weeks.

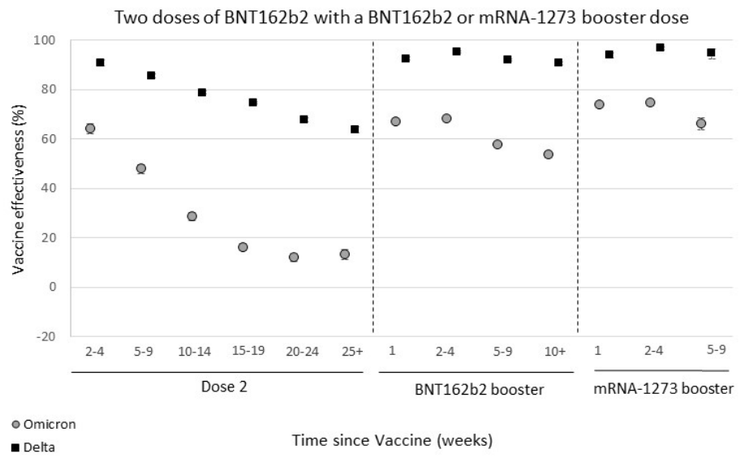

Figure 1: Pfizer vaccine effectiveness against symptomatic disease by period after 2 doses and after a booster. Note this is the updated figure, with more certainty about the data for boosters. [3]

Qatar: VE against symptomatic infection for a Pfizer booster dose relative to the primary course was 50.1% (95% CI: 47.3-52.8). [81]

<u>VE against hospitalisation</u>

UKHSA COVID-19 Vaccine Surveillance Report from 27 January reported estimates from a test-negative case control study:

- Protection against hospitalisation remained high, particularly after 3 doses**.** For a Pfizer booster (after either Pfizer or AstraZeneca primary 2 doses), VE against hospitalisation started at around 90% dropping to around 75% after 10 to 14 weeks. [82]

South African data for VE against hospitalisation:

- VE against hospitalisation for two doses of Pfizer was 70% (95%CI 62-76) during Omicron dominance (Delta dominance (93% [95%CI 90-94]) in South Africa.[83] Data were adjusted for age, sex, previous infection, surveillance week, geographic location, and CDC risk factors.
- Results from another South African study show that VE against hospitalisation for the Janssen vaccine increased over time since the second (booster) dose. [84]

UK data for VE against hospitalisation (all vaccines combined):

- For adults 18+ years, VE was 64% (95% CI: 54-71) 2 to 24 weeks after dose 2, declining to 44% (95%CI: 30-54) at 25+ weeks. VE increased to 92% (95% CI: 89-94) 2+ weeks after a booster dose, declining to 83% (95% CI: 78-87) at 10+ weeks. [3]

Characteristic	Data
	• For elderly aged 65+ years, booster VE was 94% (95% CI: 89-97) 2 to 9 weeks after a booster dose and 89% (95% CI: 80-95) at 10 weeks. VE after two doses was not reported in this analysis. [80] US data: • VE against Omicron-related hospitalisation for two doses of Pfizer was 68% (95% CI: 58−75), and VE for three doses of Pfizer was 89% (95% CI: 84−92). VE against omicron-related hospitalisation after two or three doses remained steady for several months. [85] • VE against Omicron-related ED admission for two doses of Pfizer was 60% (95% CI: 43−72) at <3 months and declined to 41% (95% CI: 32−50) at ≥6 months. [85] • VE against Omicron-related ED admission for three doses of Pfizer was 78% (95% CI: 73−82) at <3 months and declined to 48% (95% CI: 14−69) at ≥3 months. [85] • VE against Omicron-related hospitalisation for mRNA vaccines was 81% 14–179 days after dose 2, 57% ≥180 days after dose 2, and 90% ≥14 days after dose 3. [86] • VE against Omicron-related ED and UC encounters for mRNA vaccines was 52% 14–179 days after dose 2, 38% ≥180 days after dose 2, and 82% ≥14 days after dose 3. [86]. VE against death Qatar: VE against any severe, critical, or fatal COVID-19 for a Pfizer booster dose relative to the primary course was estimated at 100.0% (95% CI: 71.4-100.0). [81] **Use of second booster dose** Israel: Initial news reports of a fourth Pfizer dose (second booster) trial in 150 medical personnel in Israel have noted minor side effects only and no safety signals. The fourth dose was given 4-5 months after the third dose. An additional 25,000 people over 60 years have now had a fourth Pfizer dose. (link) Israel's Health Ministry noted preliminary findings that a fourth dose of COVID-19 vaccine given to people over 60 in Israel made them three times more resistant to serious illness than thrice-vaccinated people in the same age group. The ministry also said the fourth dose, or second booster, made people over 60 twice as resistant to infection than those in the age group who received three shots of the vaccine. The fourth shot for people over 60 increases antibodies to even higher levels than the third, but it "probably" could not completely protect against infection by the highly transmissible Omicron variant. (link) On 25 January 2022, the Advisory Committee on Epidemic Control and the Advisory Board on COVID-19 Vaccination recommended a fourth dose to people under 60 and above 18 in Israel, if 5 months has passed from recovery or third dose administration date. This recommendation still needs to be approved by the Israeli Ministry of Health. (link) This follows the approval of a fourth vaccine dose to immunosuppressed individuals (link). Chile: From January 10, people over 12 years who are immunocompromised will be offered a fourth vaccine dose. From February 7 eligibility for a fourth dose will be extended to people over 55 years who had a 3rd vaccine dose at least 6 months previously. (link) The fourth vaccine regimen has not been specified. Third (booster) doses were Pfizer or AstraZeneca. (link) **Neutralising assays** Neutralisation studies provided initial data predicting lower vaccine effectiveness against Omicron. [87-92] These data have now been superseded by effectiveness data. **Cell-mediated responses** While data remain preliminary, an increasing number of studies indicate that vaccination provides a durable T-cell response to Omicron infection. [87, 93-96] **Immunopathological characteristics** Omicron breakthrough patients had a more robust IFN-y 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. [30] **Prior Infection** A Qatar study estimated effectiveness of prior infection against preventing Omicron symptomatic re-infection at 61.9% (95% CI: 48.2-72.0) after excluding vaccinated individuals. Effectiveness against hospitalisation/death was 87.8% (95% CI: 47.5-97.1), however both vaccinated and unvaccinated individuals were included in this analysis. [97] The UKHSA reported an unadjusted effectiveness of 44% (95% CI: 4-67) against infection in unvaccinated healthcare workers (SIREN cohort) who had a prior infection. [3] The Imperial College London COVID-19 Response Team (Report 49 Updated 20 December 2021) estimated that Omicron was associated with a 5.41-fold (95% CI: 4.87-6.00) higher risk of reinfection than Delta, controlling for vaccination, age, and ethnicity. The relative risks were 6.36 (95% CI: 5.23-7.74) and 5.02 (95% CI: 4.47-5.67) when estimated separately for unvaccinated and vaccinated cases, respectively. It was estimated that the protection prior infection (with most likely a non-Omicron variant) provides against reinfection with Omicron is 19% (95%CI: 0-27%). The data analysed was UKSA and NHS data from PCR-confirmed SARS-CoV-2 cases with no history of recent travel. [98]

Characteristic	Data
	Omicron reinfection UK data from the COVID-19 Infection Survey reported in February 2022 that there were more reinfections in a month when Omicron became the dominant variant (764 reinfections), than in the previous 18 months (586 reinfections). [99] The reinfection rate was reported as increasing from 11.7 to 180.3 per 100,000 people since Omicron became the dominant variant (proportion vaccinated not specified). Earlier COVID Infection Survey reported in January stated that unvaccinated people were approximately twice as likely to be re-infected than people who had their second vaccine 14 to 89 days previously. Of note, this data was drawn from both Delta-dominant and Omicron-dominant periods. [99] UKHSA Technical Briefing 11 February reports that there have been no detected sequence-confirmed BA.2 reinfections after BA.1 infection in their data to date. [8] **Therapeutics - Most monoclonal antibody products including Ronapreve appear ineffective against Omicron – sotrovimab an exception. Oral antivirals and remdesivir are expected to be remain effective, have been shown to be effective in recent *in vitro* studies, and their use is increasing internationally.** Antibody products The FDA (statement of 24 January) have revised authorisations for two monoclonal antibody treatments – bamlanivimab and etesevimab (administered together) and REGEN-COV (casirivimab and imdevimab; Ronapreve). These treatments are not authorised for use at present in any U.S. states, territories, or jurisdictions due to Omicron being estimated to comprise more than 99% of US COVID-19 cases as of January. (Link) *In vitro studies* In a non-peer reviewed study, only three of the tested 24 therapeutic antibody products (product names not revealed) retained their full potency against Omicron and high-level resistance was seen against fifteen. [100] Several other laboratory studies have shown Omicron is resistant to neutralisation by a number of monoclonal antibodies including casirivimab + imdevimab (Ronapreve). [100-105] Several other laboratory studies have shown Omicron is resistant to neutralisation by a number of monoclonal antibodies including casirivimab + imdevimab (Ronapreve). [100-105] Sotrovimab has been shown to retain some neutralisation activity. A preprint from the US found that Regeneron (REGN10933 and REGN10987), and Lilly (LY-CoV555 and LY37 CoV016) monoclonal antibodies were ineffective against Omicron, while Sotrovimab was partially effective. [90] An additional Australian study has also shown that of the mAbs tested, only sotrovimab retained neutralisation activity against Omicron in vitro. [106] *In vitro* data from Japan reported that sotrovimab and also the combination of cilgavimab + tixagevimab (marketed by AstraZeneca as Evusheld) showed some neutralisation activity against Omicron. [107] A preprint from the US found that Regeneron (REGN10933 and REGN10987), and Lilly (LY-CoV555 and LY37 CoV016) monoclonal antibodies were ineffective against Omicron, while Sotrovimab was partially effective. [90] An additional Australian study has also shown that of the mAbs tested, only sotrovimab retained neutralisation activity against Omicron in vitro. [106] *Animal studies* An animal study (mice) from the University of Liverpool investigating the virological efficacy of casirivimab + imdevimab (Ronapreve) showed no reduction in viral RNA in lung and nasal turbinate tissue compared to saline for Omicron but a reduction for Delta. [108] Antivirals Antiviral agents including remdesivir and newer oral antivirals are expected to be effective against the Omicron variant on the basis of their mode of action. *In vitro* studies provide experimental evidence of preserved effect of remdesivir, molnupiravir and Paxlovid against Omicron. A non-peer reviewed cell-culture study showed that the antiviral drugs molnupiravir (Legevrio), Paxlovid, remdesivir, acriflavine, and AT-527 will likely retain efficacy for the omicron variant. [109] An *in vitro* study using live virus collected from nasal swab specimens demonstrated that the activity of the antivirals remdesivir, molnupiravir (specifically, its active metabolite EIDD-19331) and PF-07321332 (nirmatrelvir) was preserved against Omicron. [110] Antiviral assays completed in a Belgian study similarly reported retained effect of remdesivir, EIDD-19331 and nirmatrelvir against all variants studied, including Omicron. [111] Note that the oral antiviral Paxlovid is a combination of PF-07321332 and ritonavir, with the PF-07321332 responsible for blocking viral replication (whereas ritonavir acts to slow the breakdown of PF-07321332). Further *in vitro* studies supported by Pfizer showing that nirmatrelvir is effective against Omicron have also recently been reported as pre-prints. [112, 113] (Link) *In vitro* data from Japan reported in a January 26 NEJM editorial showed preserved effect of remdesivir, molnupiravir and PF-07394814 (active component of Paxlovid) against Omicron. Uraki and colleagues have demonstrated that molnupiravir reduced lung viral titres of Omicron in 4 infected laboratory hamsters. [114] Paxlovid is now authorised for use across the European Union following the granting of a conditional marketing authorisation by the European Commission on 28 January 2022. Link The Therapeutic Goods Administration (TGA) in Australia announced provisional approval for both molnupiravir and Paxlovid on 20 January 2022. (Link)

Characteristic	Data
	The FDA and MHRA have authorised Pfizer's oral antiviral, Paxlovid (USA in those >12 years old, UK 18 years and over with risk of severe disease). [115] (link) The PANORAMIC (Platform Adaptive trial of Novel Antivirals for Early Treatment of COVID-19 in the Community) trial in the UK is currently investigating community use of molnupiravir in the UK and targeting enrolment from over-50 years and younger adults with underlying health conditions. (Link and Link) Singapore has also granted Paxlovid an interim authorisation for use (31 January) and is expecting first deliveries of Paxlovid in February. Link
Detection	**More PCR tests recognised as unable to detect Omicron. Saliva testing might offer advantages for Omicron over nasal swabs. RATs under spotlight but evidence is mixed for reduced analytical sensitivity, including two NZ approved RATs.** **PCR** PCR tests continue to be appropriate for diagnosis of SARS CoV-2. [116] On 23 December, the World Health Organization stated that PCR tests that include multiple gene targets are unlikely to be affected and should continue to be used to detect SARS-CoV-2 infection, including the Omicron variant. [117] However, the FDA has identified three COVID-19 molecular tests (from Applied DA Sciences, Meridian Bioscience and Tide Laboratories) that are not able to detect the Omicron variant because they target genes with deletions in Omicron. [118] ThermoFisher TaqPath PCR test can detect S gene target failure - an early marker to distinguish between Omicron and Delta, pending sequencing confirmation. [116] The PCR proxy marker RNA-dependent RNA polymerase (RdRp) target delay was associated with a lower risk of hospital admission. [119] To account for the changing receptor binding domain of the SARS-CoV-2 spike protein, assays capable of rapidly and accurately identifying variants including Omicron are being reported to have discriminated against a S-gene dropout Delta specimen. [120] A Malaysian study evaluated the Allplex SARS-Cov-2 Master Assay and Variant Assay and found that the assays should detect Omicron (B.1.1.529). [121] Two pre-print studies suggest saliva testing might detect more infections (and possibly earlier) than nasal swabs in PCR testing. [122, 123] **RATs** The performance of four of the RATs currently approved in New Zealand have been reported as not affected by Omicron based on the manufacturers testing. [124-126] UKHSA reports initial laboratory validation of RATs in use by NHS Test and Trace shows similar sensitivity to detect Omicron compared to Delta [54]. A pre-print assessing 10 RATs (only 1 of the four in NZ), also found that all 10 had a sensitivity against Omicron consistent with prior variants. [97] However, a non-peer reviewed study using testing of seven RATs, three of them WHO-EUL approved and two approved for use in New Zealand, using cultured virus found a tendency towards lower sensitivity for Omicron compared to previous variants. [98] One small pre-print found RATs may not detect Omicron in its early phases although PCRs are positive (RATs positive 2 days later than PCR) [93] A pre-print from California assessed the BinaxNOW nasal rapid antigen test and reported decreased sensitivity with higher Ct values, suggesting that repeat testing may be required for those who are at high risk. [99] Sensitivity was 95.2% (95% CI 92-98) for Ct < 30, 82.1% (95% CI 77-87) for Ct < 35, and 65.2% (95% CI 60-70) overall (no threshold). BinaxNOW's clinical sensitivity is influenced by the interaction between viral replication, the dynamics of tissue tropism, and the timing of sampling [100]. A pre-print study investigated the sensitivities of swabs compared to RT-PCR, found separate samples from nasal or throat swabs each detected 64.5% of 34 SARS-CoV-2 cases; combining the contributions of each swab for an individual increased the sensitivity to 88.7% . [127] A pre-print on 6 January 2022 reports a cost-effectiveness analysis of providing government-funded RATs for early detection of COVID-19 in Australia. The authors concluded that '*even only minor reductions in COVID-19 transmission rates due to early isolation would justify the additional costs associated with a policy of government-funded RATs*.' [128]
Effectiveness of infection prevention control/ public health measures	• A new modelling study suggests that in contrast to Delta, infection prevention control settings in South Africa and UK will be insufficient to control the Omicron outbreak in those countries. [129] • A French study discusses the implication of a higher viral load on airborne transmission within the context of COVID-19 with new variants and its implication for health policies. [130] The conclusion from their observations was that the present norms of ventilation, already insufficient, are not respected, especially in a variety of public premises, leading to high risk of contamination. Finally, the researchers insist that public health policy in the field of airborne transmission should be based on a multi parameter analysis, considering the whole complexity of dose evaluation.
Other sub-lineages of interest	**Omicron sub-lineage BA.3 is currently very rare. It has the SGTF deletion (Δ69-70) so can be detected using PCR tests that detect SGTF. There is little data on BA.3.** BA.3 is a sub-lineage of Omicron (B.1.1.529). [131] Preliminary investigation suggests that BA.3 has no specific mutations in the spike protein, but is a combination of the mutations found in BA.1 and BA.2. [132] Similar to BA.1, BA.3 has the SGTF deletion (Δ69-70) which means it can be detected using PCR tests that detect SGTF, such as Thermo Fisher's TaqPath and does not present the same issues as BA.2 discussed above in relation to PCR tests. (link) BA.3 is currently very rare, as of 24 January 2022, 85 sequences in the BA.3 lineage have been detected since the lineage was identified (link) and it is most commonly reported in Poland, South Africa and UK (link).
Delta X Omicron Recombinant	A signal for a Delta x Omicron Recombinant virus is currently under monitoring and investigation in the UK. [133] News reports indicate a small number of cases to date without any concerning features of cases noted. (Link)

Glossary of Terms

The AstraZeneca vaccine	AZD1222 or ChAdOx1
The Pfizer/BioNTech vaccine	Comirnaty/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. 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.
R_0, Reproductive number	The reproductive number R_0 (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.
R_{eff}, Effective reproductive number	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.
Secondary attack rate	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.
Serial interval	The time from symptom onset of a case to symptom onset in their identified contacts.
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)	**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: • 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.

Variant of Interest (VOI)	**WHO definition:** A SARS-CoV-2 variant: • 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.
Variant under Investigation (VUI)	**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

GSAID: Global Initiative on Sharing Avian Influenza Data

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

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

R_0: 'R-naught', the baseline reproductive number

UKHSA: UK Health Security Agency

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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