

EVIDENCE BRIEF

Risk Assessment for Omicron Sub-lineage XBB* (including XBB.1 and XBB.1.5) (as of January 25, 2023)

1st Revision: February 3, 2023

Key Messages

- In Ontario, the proportion of XBB.1.5 increased from 4.9% (January 1 to 7, 2023) to 9.0% (January 8 to 14, 2023) and is projected to increase to 44.2% (95% CI: 37.4% - 51.1%) by February 1, 2023. The proportion of XBB.1 decreased from 1.0% (January 1 to 7, 2023) to 0.9% (January 8 to 14, 2023).
- XBB and its sub-lineages (including XBB.1 and XBB.1.5, together referred to as XBB*) is reported to be one of the most transmissible variants, with early evidence that its transmissibility is enhanced independent of the contribution of immune evasion (e.g., ability to 'hide' or not be easily recognized by circulating antibodies).
- XBB* is among the most immune-evasive SARS-CoV-2 variants tested based on several in vitro studies of human sera.
- Early evidence from one real-world vaccine effectiveness (VE) study, published by the United States (US) Centers for Disease Control and Prevention (CDC), suggests that the COVID-19 bivalent mRNA vaccines provide additional protection against symptomatic XBB/XBB.1.5-related sub-lineage infections.
- It remains uncertain whether the severity of disease caused by XBB* differs from previous SARS-CoV-2 variants.
- Currently available neutralizing monoclonal antibody agents are generally not effective against XBB* based on current evidence. However, antiviral agents such as nirmatrelvir/ritonavir remain active against this variant.
- Using layers of protection, in addition to vaccination, are important and include: staying home when sick or with symptoms of COVID-19; wearing a well-fitted, high quality mask whenever feasible in indoor settings; optimizing indoor air quality; use of outdoor spaces when weather permits; as well as respiratory etiquette and hand hygiene.

Issue and Research Question

XBB and its sub-lineages (referred to as XBB*) are recombinants of the Omicron sub-lineages BA.2.10.1 and BA.2.75, first reported in India, August 2022.^{1,2} The WHO Technical Advisory Group on SARS-CoV-2 Virus Evolution (TAG-VE) has flagged Omicron variants (such as XBB*) as variants of concern and; therefore, necessary to continue monitoring.¹ The Omicron sub-variant XBB received “signal in monitoring” status on October 11, 2022 and received “designated variant” status on October 28, 2022.³ As of January 12, 2023, the European Centre for Disease Prevention and Control (ECDC) has designated XBB.1.5 as a variant of interest.^{4,5}

Methods

Public Health Ontario (PHO) Library Services has been conducting daily searches of primary and preprint literature on Omicron variants and sub-lineages using the MEDLINE database (search strategies available upon request). Preprints are research papers that have not undergone peer-review but are made publicly available to provide the latest data relevant to the rapidly evolving COVID-19 pandemic. Formal critical appraisal of published and preprint COVID-19 literature was out of scope for this PHO risk assessment. PHO performed grey literature searches daily using various news feeds and custom search engines starting January 5 to 25, 2023. An additional therapeutics study was included January 26, 2023. English-language peer-reviewed and preprint records that provided information on the Omicron XBB sub-lineages were included. This is an update of two previous risk assessments of XBB*.^{6,7}

Ontario Risk Assessment

The current risk of XBB* variants with respect to transmissibility and COVID-19 reinfection, is high with a low degree of uncertainty. Vaccine effectiveness to prevent breakthrough infection is moderate with a low degree of uncertainty. Increased disease severity is low with a moderate degree of uncertainty. Impact on testing and WGS surveillance is low with a low degree of uncertainty. The overall risk assessment may change as new evidence emerges (see [Table 1](#)).

Table 1. Risk Assessment for Omicron Sub-lineages XBB*

Issues	Risk Level	Degree of Uncertainty
Increased Transmissibility	High	Low
Increased Disease Severity	Low	Moderate
COVID-19 Reinfection	High	Low
Vaccine Effectiveness to Prevent Breakthrough Infection	Moderate	Low
Impact on Testing and WGS* Surveillance	Low	Low

*Whole genome sequencing, WGS

Genomic Features

The genomic characteristics of XBB* have been described previously.^{6,7} Of note, XBB contains the following key mutations: envelope protein (E) T11A and spike protein (S): V83A, H146Q, Q183E, F486S, and F490S. XBB.1 contains an additional G252V mutation in the spike protein. XBB.1.5 also contains an additional F486P mutation in the spike protein derived from the F486S mutation found in XBB.1.⁸

Wang et al. (2023), sought to characterize mutations in the SARS-CoV-2 E protein across variants, grouping them based on association with level of pathogenicity and therefore likely disease severity.⁹ The authors note that XBB contains the mutation T9I, which has been associated with reduced viral replication and virulence. XBB also contains a new dominant-negative mutation of T11A at a frequency 90.52%, which is associated with reduced cell lethality, cytokine induction and viral production capabilities in vitro. The authors conclude that the XBB mutations they examined suggest weakened pathogenicity of XBB compared to other Omicron sub-variants.

Epidemiology

The epidemiology section provides information on variant severity. Hospitalizations, intensive care unit (ICU) admissions and deaths are lagging indicators, often occurring days or weeks after cases are initially reported to public health, and are subject to reporting lags. Therefore, trends may change and may not be fully representative of the most up-to-date situation. The severe cases i.e., hospitalizations, in the settings described below have not been attributed to XBB* either due to lack of genomic information or due to XBB* still comprising less than half of cases based on surveillance, but in the absence of evidence for severity of XBB*, settings with increasing XBB* prevalence can be closely monitored for severity trends. Differences in vaccine programmes, history of infection, use of public health measures, and other contextual considerations will limit the generalizability of variant epidemiological trends to the Ontario context.

Global

Globally, from October 22, 2022 to January 23, 2023, 8,931 sequences of the XBB.1.5 variant have been reported from 54 countries, with most of these sequences being from the United States (US) (75.0%), the United Kingdom (UK) (9.9%), Canada (3.0%), Denmark (2.0%), Germany (1.5%), Austria (1.3%), and Ireland (1.3%).¹⁰ The WHO TAG-VE revised the confidence level of the XBB.1.5 risk assessment from 'low' (assessed on January 11, 2023) to 'moderate' (assessed on January 25, 2023).¹⁰ According to GISAID data, the proportion of COVID-19 cases that are XBB* has increased over the past four weeks from 6.40% (December 4 to December 10, 2022), 6.72% (December 11 to 17, 2022), 8.47% (December 18 to 24, 2022), to 8.36% (December 25 to December 31, 2022).¹¹

Canada

According to GISAID data, the proportion of COVID-19 cases in Canada that are XBB.1 increased from 0.60% (November 24 to December 24, 2022)¹² to 4.90% (December 25, 2022 to January 25, 2023).¹³ The proportion of COVID-19 cases that are XBB.1.5 increased from 0.47% (November 24 to December 24, 2022)¹⁴ to 3.51% (December 25, 2022 to January 25, 2023).¹⁵

- The Public Health Agency of Canada (PHAC) SARS-CoV-2 Variant Rapid Risk Assessment Report: XBB.1.5 stated that the public health risk posed by XBB.1.5 is driven by incremental increases in transmissibility and immune evasion compared to BA.5; however, disease severity and antiviral therapeutic effectiveness are comparable. The level of uncertainty in their assessment (of XBB.1.5 relative to BA.5) is moderate to high.¹⁶

The proportion of XBB.1.5 in Ontario increased from 4.9% (January 1 to 7, 2023) to 9.0% (January 8 to 14, 2023) and is projected to increase to 44.2% (95% confidence interval [CI]: 37.4% - 51.1%) by February 1, 2023. The weekly growth rate of XBB.1.5 is 1.94 (95% CI: 1.82-2.07) times that of BQ.1.1.¹⁷ The proportion of XBB.1 decreased from 1.0% (January 1 to 7, 2023) to 0.9% (January 8 to 14, 2023).

In Ontario, hospital admissions were trending down this week (January 15 to 21, 2023) compared to last week (January 8 to 14, 2023).¹⁸ There were 279 hospital admissions reported this week, compared to 350 last week. There were 52 deaths reported this week, compared to 69 last week.

Weekly COVID-19 case numbers are down in Ontario 12% from 5,997 (January 8 to 14, 2023) to 5,254 (January 15 to 21, 2023).¹⁸ Percent positivity was 13.4% (January 15 to 21, 2023) compared to 13.9% observed the previous week (January 8 to 14, 2023).¹⁸ Current projections suggest that weekly case numbers may continue the decline observed last week. It remains unclear how increased XBB* prevalence might impact overall COVID-19 epidemiological trends.

United Kingdom (UK)

According to GISAID data, the proportion of COVID-19 cases that are XBB.1 decreased from 2.48% (November 24 to December 24, 2022)¹⁹ to 2.02% (December 25, 2022 to January 25, 2023).²⁰ Over the same time period, the proportion of COVID-19 cases that are XBB.1.5 increased from 0.95%²¹ to 5.30%.²²

Hospital admission rates for COVID-19 are decreasing in the UK. Between January 9 to 15, 2023, COVID-19 hospital admission rates were 6.69 per 100,000 people. This is a decrease from the previous week, January 2 to 8, 2023, where COVID-19 hospital admission rates were 8.94 per 100,000 people.²³

United States (US)

In the US, estimated proportions of XBB and XBB.1.5 among circulating variants the week of January 15 to 21, 2023 were 3.3% (95% Prediction Interval [PI]: 2.7–4.1%) and 49.1% (95% PI: 37.5–60.8%), respectively.²⁴ This is a decrease for XBB from four weeks prior (December 25 to 31, 2022), when it was estimated to be 4.0% (95% PI: 3.3–4.9%) and an increase for XBB.1.5 which was estimated to be 17.1% (95% PI: 9.8–26.7%).²⁵ During the same periods, BQ.1.1 (the variant previously comprising the largest proportion of cases) decreased from 37.3% (95% PI: 33.0–41.7%) to 26.9% (95% PI: 20.9–33.9%).^{24,25} At the regional level in the US, XBB.1.5 was >80% in the Northeast the week of January 15 to 21, 2023 (US Health and Human Services Region 1 and 2: Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island, Vermont, New Jersey, New York, Puerto Rico, and the US Virgin Island).^{26,27}

Hospital admission rates for patients (all ages) with confirmed COVID-19 have been decreasing in the US since January 4, 2023. From January 17 to 23, 2023, COVID-19 hospital admission rates decreased 13.7% from the prior 7-day average, January 10 to 16, 2023.²⁸

Europe

The January 13, 2023 ECDC threat assessment of the XBB.1.5 sub-lineage assessed the overall level of risk to the European Union / European Economic Area (EU/EEA) associated with its spread as low for the general population. They concluded that there are currently no signals that the infection severity of XBB.1.5 is different than that of previously circulating Omicron sub-lineages.⁵

The ECDC's modelling estimated that based on reported proportions of XBB.1.5 in the EU/EEA and its estimated growth advantage compared to previously circulating variants (12% with large uncertainties across the EU/EEA), there is moderate probability that XBB.1.5 will become dominant in the EU/EEA within one to two months.⁵

Transmissibility and Infectivity

Evidence suggests XBB* is among the most antibody-evasive strains tested compared to other circulating Omicron sub-lineages.²⁹⁻³⁴

Qu et al. (2023),³⁵ used lentiviruses pseudotyped with different subvariant S proteins and reported that XBB and XBB.1.5 exhibited increased infectivity in HEK293T-ACE2 cells, with 1.9 times ($p < 0.001$) and 2.2 times ($p < 0.0001$) higher titers, respectively, compared to ancestral D614G infectivity. Unlike other Omicron subvariants examined, XBB and XBB.1.5 infectivity in CaLu-3 cells (lung epithelial cell line) was not significantly different from D614G. Analysis of S protein biological function revealed enhanced XBB.1.5 S protein fusogenicity compared to BA.4/5. Relative to XBB, the XBB.1.5 subvariant and its two single mutants XBB.1 containing G252V and XBB-S486P did not demonstrate obvious differences in S fusogenicity. In addition, XBB.1.5 showed increased S processing (increased S1/S and S2/S ratios) compared to D614G. The authors conclude that XBB.1.5 and XBB have increased infectivity compared to the other Omicron subvariants but formal studies in primary lung epithelial cells and airway tissue is needed, in particular due to their observation that all prior Omicron subvariants exhibited low infectivity in CaLu-3 cells, which correlated with lower pathogenicity, whereas XBB shows a similar infectivity to ancestral SARS-CoV-2.

Immunogenicity and Vaccine Effectiveness

Evidence continues to show that XBB* is among the most antibody-evasive strains tested in vitro, compared to other circulating Omicron sub-lineages.^{6,31,36} Key findings from select studies are summarized below.

- Lasrado et al. (2023),³⁷ assessed neutralizing antibody titers (NAb) in individuals in the US who received a bivalent mRNA booster (n=30), at three weeks and three months post booster, and compared them against NAb titers prior to booster administration.³⁷ At three weeks post-booster, NAb titers to XBB.1 and XBB.1.5 increased, and then at three months decreased 2.1-fold and 1.8-fold, respectively. The authors note that by month three post-booster, NAb titers to XBB.1 and XBB.1.5 declined to almost baseline levels, indicating waning immunity and likely reducing the effectiveness of the bivalent mRNA boosters. They also concluded that since NAb titers to XBB.1 and XBB.1.5 were similar, it suggests the F486P mutation likely confers greater transmissibility but not increased immune escape. Spike-specific T cell responses were assessed by intracellular cytokine staining assays, and showed that median CD4+ T cell responses to XBB.1.5 were 0.065% at baseline and 0.090% at month 3 post-booster, and median CD8+ T cell responses were 0.059% at baseline and 0.106% at month 3 post-booster. The authors also reported evidence that XBB.1.5 does not substantially escape T cell responses after bivalent mRNA boosting.
- Miller et al. (2023),³⁸ assessed neutralizing antibody titers in individuals who had been vaccinated and boosted with the monovalent mRNA vaccine BNT162B2 in 2021 (n=16) and in 2022 (n=15) as well as individuals who received the bivalent booster in 2022 (n=18). Compared to the ancestral WA1/2020 strain, the neutralizing antibody titer against XBB.1 was 435-fold lower in the cohort who received the monovalent booster in 2021, 127-fold lower for the cohort who received the monovalent booster in 2022, and 232-fold lower for the cohort who received the bivalent booster in 2022.
- Qu et al. (2023),³⁵ investigated the sensitivity of XBB.1.5 to neutralizing antibodies from bivalent and monovalent mRNA COVID-19 vaccine recipients in the US, as well as from individuals with a previous infection with BA.4/5 in the US. In the bivalent vaccinated cohort (n=14), the nAb titers against XBB.1.5 were 12.6- and 4.6-fold lower than titers against ancestral D614G and BA.4/5, respectively. In the 3-dose monovalent cohort (n=15), the nAb titers against XBB.1.5 were 24.5- and 3.3-fold lower than titers against D614G and BA.4/5, and 8.2- and 2.6-fold lower in the cohort with previous BA.4/5 infections (n=20). The authors conclude that administration of a bivalent mRNA booster can result in approximately 2-8-fold higher nAb titers when compared to monovalent boosters. Qu et al state that although XBB subvariants exhibited strong immune escape, it was less than that observed for BQ.1.1.

- Vikse et al. (2023),³⁹ evaluated neutralizing antibodies against XBB in serum samples from Norwegians who were fully vaccinated with three doses of monovalent mRNA vaccines only (n=9), along with those who were fully vaccinated with a confirmed breakthrough infection with BA.1/BA.2 (n=10) or BA.5 (n=10). Across all three cohorts, neutralizing titers against XBB were significantly reduced compared to titers against BA.2 and BA.5. The authors observed that titers against BQ.1 were generally similarly reduced relative to XBB titers, except in the case of BA.1/2 breakthrough infections which resulted in XBB and BQ.1.1 ID50 values of 60 and 43, respectively (i.e., higher titers against XBB). Sera from people with breakthrough infections with BA.1, BA.2 or BA.5 generally had higher neutralizing titers against all tested variants, compared to vaccinated-only individuals.
 - An additional 32 serum samples were collected in mid-October 2022, and evaluated for neutralizing titers against BA.5, BQ.1.1 and XBB, in order to get a snapshot of immunity against emerging variants, at that point in time. Only 4/32 had titers >64 against XBB, suggesting very limited immunity against XBB. The authors found that the neutralizing antibody titers ID50 against XBB in the vaccinated-only cohort were 9-fold lower, 60-fold lower in the cohort with BA.1/BA.2 breakthrough infections and 36-fold lower in the cohort with BA.5 breakthrough infections.
- Jiang et al. (2023),⁴⁰ assessed the neutralizing activity of sera from US individuals vaccinated with three monovalent doses and individuals who received a bivalent mRNA vaccine as a fourth dose, against 10 Omicron lineages, including XBB.1.⁴⁰ Three dose-vaccinated sera (n = 16) showed reduced neutralizing activity against XBB and XBB.1 relative to an ancestral SARS-CoV-2 614D, resulting in 324- and 371-fold reduced neutralization. The bivalent vaccine sera (n = 11) showed reduced neutralizing activity against XBB and XBB.1 relative to an ancestral SARS-CoV-2 614D, resulting in 69- and 125-fold reduced neutralization. The authors conclude that the bivalent booster increased neutralizing antibodies against progenitor and contemporary Omicron lineages, and improved antibody breadth against all Omicron lineages. Jiang et al also investigated the role that the RBD and non-RBD spike mutations played in antibody escape by uncoupling mutations identified in lineages with different spike proteins. Based on their findings the authors suggest spike mutations outside the RBD may function synergistically with RBD mutations resulting in the dramatic escape from antibody neutralization shown by XBB.1.
- Link-Gelles et al. (2023),⁴¹ estimated vaccine effectiveness (VE) of the bivalent COVID-19 mRNA vaccines (either Pfizer/BioNTech or Moderna) against symptomatic infection caused by BA.5 and XBB/XBB.1.5 using US population data (n = 29,175). Of note, they used S-gene target presence (SGTP) as a proxy for XBB and XBB.1.5, and of specimens with SGTP and with genomic sequencing results available from December 1, 2022 to January 2, 2023, XBB accounted for 26%, and XBB.1.5 accounted for 33%. Thus, XBB and XBB.1.5 likely comprised approximately 60% of the SGTP specimens when SGTP was used as a proxy for XBB/XBB.1.5 in this study. The authors found that among adults who had received 2-4 monovalent doses, the relative VE of a bivalent booster dose given 2–3 months earlier compared with no bivalent booster in persons aged 18–49 years was 52% against symptomatic BA.5 infection and 48% against symptomatic XBB/XBB.1.5 infection. The authors conclude that the COVID-19 bivalent mRNA vaccines may provide additional protection against symptomatic BA.5-related sub-lineage and XBB/XBB.1.5-related sub-lineage infections in persons who had previously received 2, 3, or 4 monovalent vaccine doses, for at least the three months after vaccination.

Disease Severity

The WHO's January 25, 2023 epidemiological report noted that based on reports from several countries, no early signal of increased severity due to XBB.1.5 has been observed.¹⁰ XBB.1.5 does not carry any mutation(s) known to be associated with potential change in severity (such as S:P681R).⁴² A January 13, 2023 ECDC threat assessment brief on XBB.1.5 stated that there are currently no signals that the infection severity of XBB.1.5 is different than that of previously circulating Omicron sub-lineages.⁵ Key findings from select studies are summarized below.

- Karyakarte et al. (2023),⁴³ reported indicators of severity of COVID-19 cases caused by different variants, including XBB (142/1,039 cases, 13.7%), in India. Compared to BA.2.10*, BA.2.38*, BA.2.75*, BA.5*, and BQ.1 cases, there was no statistically significant difference in the proportion of XBB* cases that were symptomatic. Of 494 COVID-19 patients hospitalized, none of the BA.2.10*, BA.2.38*, BA.5*, or BQ.1 cases died, and 3/85 (3.5%) XBB* cases died ($p=0.105$). The proportion of institutionalized/hospitalized cases also differed across variants with 5.9%, 33.3%, 24.4%, 14.3%, 0.0% and 21.2% of BA.2.10*, BA.2.38*, BA.2.75*, BA.5*, BQ.1 and XBB* cases institutionalized/hospitalized, respectively ($p=0.02$). The authors conclude that the pathogenicity of XBB is comparable to that of other Omicron variants, but note that it remains unclear whether the intrinsic pathogenicity of XBB* or the immunity from vaccination and previous infection is responsible for mild cases in India.
- Wang et al. (2023), reported that the XBB mutations they examined suggest weakened pathogenicity of XBB compared to other Omicron sub-variants. Please see the study summary in Genomics section (above).⁹

Therapeutics

Currently available neutralizing monoclonal antibody (mAb) agents are generally not effective for XBB* based on current evidence. However, antiviral agents such as nirmatrelvir/ritonavir (Paxlovid) and remdesivir (Veklury) remain active against this variant.^{36,44}

- While there are studies which demonstrate some in vitro activity (e.g. binding, neutralization) of monoclonal antibodies against circulating Omicron subvariants including XBB*, the WHO continues to recommend against the use of mABs for treatment of COVID-19 in the 13th version of their Therapeutics and COVID-19 living guideline released on January 13, 2023 based on a review of currently available evidence.⁴⁵⁻⁴⁸
- The WHO has also extended their strong recommendation for the use of nirmatrelvir-ritonavir (Paxlovid) in patients with non-severe COVID-19 at high risk of hospitalization and that pregnant or lactating individuals can be offered nirmatrelvir-ritonavir with the use of shared decision making to weigh the benefits and potential harms.⁴⁸
- As of January 26, 2023 the US Food and Drug Administration (FDA) revised the emergency use authorization (EUA) for tixagevimab-cilgavimab (Evusheld) and as a result, it is not currently authorized for use in the US until further notice by the FDA.⁴⁴ This is because Evusheld is unlikely to provide protection against XBB* (including XBB.1.5) which the CDC Nowcast data show to be responsible for the majority of current infections in the US.²⁴

Impact on Testing and WGS Surveillance

- Antigen testing: There is limited literature on the performance of rapid antigen tests (RATs) with VOCs; however, the majority of VOC mutations occur in the spike protein and RATs used in Ontario target the nucleocapsid protein. Therefore, we expect there to be limited impact on RAT performance for XBB although confirmatory studies are needed.
- Molecular testing: No impact is expected on the capability of molecular tests to detect XBB and XBB* sub-lineages.
- WGS surveillance: No or little impact is expected on the capability of WGS to detect XBB and XBB* sub-lineages as multiple cases have already been detected in Ontario.

Implications for Public Health Practice

Most of the implications for practice remain unchanged from the previous PHO XBB* Risk Assessment.⁷

- A gradual decrease in COVID-19 case numbers has been observed in Ontario since the beginning of January, 2023; however, percent positivity remains high and was 13.4% the week of January 15 to 21, 2023, similar to 13.9% the previous week.
- Clear risk communication to Ontarians regarding current levels of SARS-CoV-2 transmission and COVID-19 disease risk, risk factors for severe COVID-19 disease, protective effects of infection-acquired and vaccine-acquired immunity, emerging evidence for the risks associated with post-acute COVID-19 syndrome,⁴⁹⁻⁵³ as well as the current health system strain, will be important in the context of COVID-19 booster vaccine uptake and use of public health measures such as masking in indoor public settings.
- COVID-19 severity trends in jurisdictions with a high prevalence of XBB* should be monitored closely to help assess risk of severe cases associated with XBB* variants in Ontario.¹⁸

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Summary of Revisions

Page	Revision	Implementation Date
2	Risk Assessment statement was corrected to align with Table 1. The degree of uncertainty for vaccine effectiveness to prevent breakthrough infection was changed from moderate to low.	February 3, 2023

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