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EVIDENCE BRIEF

Risk Assessment for Omicron Sub-lineage XBB* (including XBB.1 and XBB.1.5) (as of January 4, 2023)

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Key Messages

- The proportion of XBB.1 (including XBB.1.5) cases in Ontario remained stable at 2.2% (68 cases from December 11 to 17, 2022) and 2.0% (54 cases from December 18 to 24, 2022).
- XBB is among the most antibody-evasive SARS-CoV-2 variants tested (alongside BQ.1.1.10, BA.4.6.3, and CH.1.1), with some reports showing it to be the most transmissible variant that has been detected.
- It is uncertain whether the severity of disease caused by XBB and its sub-lineages (including XBB.1 and XBB.1.5, cumulatively referred to as XBB*) differs from previous SARS-CoV-2 variants. Increases in bivalent booster vaccine uptake and immunity from previous infections may attenuate the risk of severe cases associated with XBB* 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.
- Based on limited evidence of immune evasion by XBB* variants, and waning immunity following vaccination, incomplete COVID-19 booster coverage and uncertain effectiveness of the new bivalent boosters in the Ontario population, basic principles of public health indicate that use of public health measures can mitigate SARS-CoV-2 transmission at both the individual and population level.
- 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]

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 December 9, 2022 and ending January 5, 2023. English-language peer-reviewed and preprint records that provided information on the Omicron XBB sub-lineages were included. This is an update of a previous risk assessment of XBB and XBB.1.[4]

Ontario Risk Assessment

The current risk of XBB* variants with respect to transmissibility, COVID-19 reinfection, and vaccine effectiveness to prevent breakthrough infection is high with a low degree of uncertainty. Increased disease severity is low with a high 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	High
COVID-19 Reinfection	High	Low
Vaccine Effectiveness to Prevent Breakthrough Infection	High	Low
Impact on Testing and WGS* Surveillance	Low	Low

*Whole genome sequencing, WGS

Genomic Features

XBB.1 is a sub-lineage of XBB, and XBB.1.5 is a sub-lineage of XBB.1.[5] Both XBB and XBB.1 are recombinant lineages of BA.2.10.1 and BA.2.75 sub-lineages.[1,6] XBB shows a higher effective reproduction number (R_e), or viral fitness (the capacity for a virus to produce infectious progeny) than its parental lineages due to its recombination breakpoint being located in the receptor-binding domain (RBD) of the spike protein.[7] XBB is characterized by 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] XBB* contains more receptor-binding domain (RBD) mutations at antigenic sites than any other widespread variant.[3]

- Scarpa et al. (2022), performed a genome-based survey (using nextstrain/ncov and GISAID data) to assess the evolutionary potential of the epidemiological trajectory of XBB and XBB.1 compared to their parental lineages.[9] Phylogenomic reconstruction illustrated that XBB and XBB.1 genomes are clustered within the GSAID Clade 21L, with the evolutionarily close genomes of BA.2 and BM.1.1.1 and BJ.1. The authors note the evolutionary rate of XBB (7.6×10-5 subs/sites/years) and XBB.1 (6.3 x 10-4), compared to BM.1.1.1 (1.3×10-3) and BJ.1 (1.4×10-3). The structural comparison between BA.2, XBB, and XBB.1 revealed that the N-terminal domains (NTD) of XBB and XBB.1 possess a more negative charge than BA.2. In addition, the characterizing mutations Y144del and H146Q (that occur near the site of the AXL receptor) possess an overall negative charge. The authors suggest that NTDs have a weaker propensity to interact with the AXL receptor that will affect the interaction with the host immune system. Further, they note that the spike mutations within XBB and XBB.1 suggest a higher growth advantage.

- Beesley et al., analyzed 12.8 million SARS-CoV-2 sequences reported to the GISAID collected between October 2020 and November 2022 to summarize variant transition dynamics across 215 countries and 13 SARS-CoV-2 variant waves.[10] The authors found that three of the newly emerging variants, XBB/XBB.1, BA.2.75 and BQ.1 have transition slopes similar to earlier Omicron sub-variants, though XBB/XBB.1 and BA.1 had higher transition slopes then BA.2.75. The authors also found that transition in countries where XBB/XBB.1 had been established was rapid when compared to prior Omicron variants. Overall, the authors illustrated that variant transition dynamics differ based on locations and are also associated with vaccination rates, prior infection rates, and time since last COVID-19 peak, population demographics and number of co-circulating variants.

Epidemiology

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.

According to GISAID data, as of the week December 12 – 18, 2022, XBB* has a global prevalence of 6.8 % (including XBB.1 and XBB.1.5),[11] this is a slight increase in sequences (667 sequences) from the previous week (December 5 to 11, 2022) where 525 sequences were reported.[11]

Canada

According to GISAID data, the proportion of XBB* cases in Canada has increased from 0.59% of cases (58 sequences from November 4 to December 4, 2022),[12] to 1.78% of cases (105 sequences from December 5, 2022 to January 5, 2023).[13]

The proportion of XBB.1 (including XBB.1.5) cases in Ontario remained stable at 2.2% (68 cases from December 11 to 17, 2022) and 2.0% (54 cases from December 18 to 24, 2022). XBB* was not included in the most recent Ontario NOWCAST projected prevalence and relative growth rate estimates.[14]

In Ontario, hospital admissions were similar (+/- 10%) this week (December 25 to December 31, 2022) compared to last week (December 18 to December 24, 2022).[15] There were 329 hospital admissions reported this week, compared to 358 last week. There were 25 deaths reported this week, compared to 68 last week. Hospital admission and death counts, particularly for more recent weeks, may increase since these outcomes are lagging indicators.

United Kingdom (UK)

According to GISAID data, the proportion of XBB* cases in the UK increased from 3.76% of cases (519 sequences from November 4 to December 4, 2022),[16] to 5.55% of cases (653 sequences from December 5, 2022 to January 5, 2023).[17]

Hospital admission rates for COVID-19 are increasing in the UK. Between December 12 and 18, 2022, COVID-19 hospital admission rates were 9.56 per 100,000 people.[18] This is an increase from the previous week, December 5 to 10, 2022, where COVID-19 hospital admission rates were 6.61 per 100,000 people.[18]

United States (US)

In the US, estimated proportions of XBB and XBB.1.5 among circulating variants the week of January 1 to 7, 2023 were 4.9% (95% Prediction Interval [PI]: 4.0–6.1%) and 27.6% (95% PI: 14.0–46.5%), respectively.[19] This is a decrease for XBB from the previous week (December 25 to 31, 2022), when it was estimated to be 5.3% (95% PI: 4.2–7.0%) and an increase for XBB.1.5 which was estimated to be 18.3% (95% PI: 9.1–32.8%) the previous week.[20] During the same periods, BQ.1.1 (the variant previously comprising the largest proportion of cases) decreased from 36.7% (95% PI: 31.3–42.5%) to 34.4% (95% PI: 26.7–43.0%).[19,20]

Hospital admission rates for COVID-19 are increasing in the US. From December 27, 2022 to January 2,2023, COVID-19 hospital admission rates increased 17% from the prior week, December 20 to 26, 2022.[21]

Europe

The January 9, 2023 ECDC assessment of the XBB.1.5 sub-lineage notes it's estimated to have a large growth advantage over previously circulating variants in Europe (113%), although the estimates are associated with high uncertainty.[22]

XBB.1.5 has been detected in several EU/EEA countries and there is a possibility that this variant could have an increasing effect on the number of COVID-19 cases in the EU/EEA, but not within the coming month as the variant is currently only present in the EU/EEA at very low levels.[22]

Transmissibility and Infectivity

Yue et al. (2022), examined the binding affinity of XBB.1.5 compared to BQ.1.1 and XBB/XBB.1.[23] The authors suggest that the significant growth advantage of XBB.1.5 over XBB.1 is the higher ACE2 binding affinity through the S486P mutation, while retaining high immune evasion capacity.

Immunogenicity

Evidence suggests XBB is among the most antibody-evasive strains tested (alongside BQ.1.1.10, BA.4.6.3, and CH.1.1), compared to other circulating Omicron sub-lineages.[6,7,24-26] Key findings from select studies are summarized below.

- Yue et al. (2022), used vesicular stomatitis virus (VSV)-based pseudeovirus neutralization assays to analyze convalescent plasma.[23] Plasma from BNT162b2 or mRNA-1273 vaccinated individuals who had a BA.5 breakthrough infection exhibited a 50% neutralization titer (NT50) against XBB.1 and XBB.1.5 that was decreased 31- and 27-fold, respectively, compared to B.1.

- Examining the R346T mutation, Davis-Gardner et al. (2022), tested serum samples obtained from participants who had either one or two monovalent boosters (BNT162b2 or mRNA-1273) or bivalent boosters to determine the neutralization efficiency of the booster vaccines against Omicron variants, including XBB, comparing neutralizing activity in serum samples using the focus reduction neutralization test (FRNT) in a Vero E6/TMPRSS2 cell line .[27] They tested at three different times with three different cohorts: 1) 7 to 28 days after one monovalent booster (n=12), 2) 6 to 57 days after second monovalent booster (n=1), and 3) 16 to 42 days after bivalent booster (n = 12). In all three cohorts, neutralization activity was lower against the Omicron tested strain, with XBB having the lowest neutralization activity. Those who received BA.5 containing bivalent boosters (BNT162b2 or mRNA-1273) had better neutralizing activity against all Omicron variants than those who received one or two monovalent boosters.

- In a phase 2/3 trial, Chalkias et al. (2022) aimed to examine safety and immunogenicity of a COVID-19 bivalent mRNA booster.[28] They compared 50-µg mRNA-1273.222 (with 25-µg each ancestral Wuhan-Hu-1 and Omicron BA.4/BA.5 spike mRNAs) to 50-µg mRNA-1273, which were administered as second boosters in adults who previously received a 2-dose primary series and one booster dose of mRNA-1273. The study used pseudoviruses containing the SARS-CoV-2 full-length spike proteins of ancestral SARS-CoV-2, or Omicron variants BA.4/BA.5, BQ.1.1 or XBB.1. Authors assessed the day 29 cross-neutralization against XBB.1 in mRNA-1273.222 recipients as well as recipients of the BA.1 bivalent booster vaccine mRNA-1273.214. In recipients without prior infection, XBB.1 titers rose 12-fold and 4-fold, compared to pre-booster levels, for mRNA-1273.222 and mRNA-1273.214, respectively. Compared to corresponding BA.4/BA.5 titers, XBB.1 titers were 12-15 fold lower for both vaccines, illustrating a greater potential for immune escape.

- Sullivan et al., systematically reviewed recent primary research studies that reported neutralization of XBB.1 by plasma from vaccinated individuals with or without COVID-19 or after a recent Omicron infection alone, within six months.[29] Among their observations, Sullivan et al. found that while there was a 75-fold reduction in neutralization by sera from individuals with 2-4 vaccine (mRNA BNT162b2) doses plus a breakthrough infection (cohort referred to as VaxCCP) against XBB.1 compared to an ancestral strain (WA-1), more than 89% of the boosted VaxCCP samples were able to neutralize XBB.1.

- Wang et al., evaluated the neutralization of XBB and XBB.1 using sera from cohorts with different sources of SARS-COV-2 immunity, and compared it to neutralization of the ancestral strain D614G to assess antibody evasion.[30] Cohorts included individuals with three doses of the original COVID-19 mRNA vaccines (n=15) or four doses (n=19), termed three shots wild-type (WT) and four shots WT, respectively, one dose of the bivalent COVID-19 mRNA vaccine after three doses of the original vaccine (n=21), termed three shots WT plus bivalent, and those who had a BA.2 or BA.4/5 breakthrough infection after vaccination (n=14, n=20), both termed BA.2 or BA.4/BA.5 breakthrough. The authors found that compared to D614G, the geometric mean 50% inhibitory dose (ID50) titers against XBB and XBB.1 were <70-fold and <71-fold lower, respectively, in the three shots WT cohort, <145-fold and <155-fold lower, respectively, in the four shots WT cohort, <209-fold and <162-fold lower in the three shots WT plus bivalent cohort, <103-fold and <135-fold lower in the BA.2 breakthrough cohort, and <86-fold and <96-fold in the BA.4/5 breakthrough cohort. The authors concluded that SARS-CoV-2 breakthrough infections among vaccinated individuals induce a better antibody response compared to vaccination alone across all cohorts.

Disease Severity

- According to the WHO TAG-VE, the early evidence as of October 27, 2022, does not suggest substantial differences in disease severity for XBB (and XBB sub-lineages) infections compared to other sub-lineages.[1]

- A January 9, 2023 ECDC assessment of the XBB.1.5 sub-lineage stated that there is currently not enough information available to assess any change in infection severity associated with the variant.[22]

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 remain active against this variant.

- Imai et al. (2022), assessed the efficacy of therapeutic mAbs against BQ.1.1 and XBB, isolated from patients, using a 50% focus reduction neutralization test ($FRNT_{50}$) titer of the monoclonal antibodies using a live-virus neutralization assay.[31] XBB showed several additional mutations in its RBD compared to BA.2. As such, the mAbs REGN10987 (imdevimab), REGN10933 (casirivimab), COV2-2196 (tixagevimab), COV2-2130 (cilgavimab), and S309 (the precursor of sotrovimab) did not neutralize the BQ.1.1 or XBB isolates even at the highest $FRNT_{50}$ value tested. LY-CoV1404 (bebtelovimab) had no efficacy against BQ.1.1 or XBB. Both combinations (imdevimab/casirivimab and tixagevimab/cilgavimab) of mAbs tested failed to neutralize either BQ.1.1 or XBB. For the XBB sub-variant, the IC_{50} values for remdesivir, molnupiravir, and nirmatrelvir suggest retained *in vitro* activity for these antiviral agents.

- Touret et al. (2022), compared the neutralizing potential of mAbs (REGN10987 (imdevimab), REGN10933 (casirivimab)) against clinical isolates BA.2.75.2, BQ.1, BQ.1.1 and XBB, using BA.2 and BA.5 as controls, alongside B.1.617.2.[32] Authors found a complete loss of detectable neutralizing activity with the four variants and imdevimab and no activity with casirivimab, making it impossible to calculate effective concentration. Sotrovimab has a modest decrease against XBB *in vitro* and cilgavimab has lost neutralizing activity against XBB variants. Bebtelovimab lost all neutralizing activity against XBB.

- Yue et al. (2022), investigated XBB.1 and XBB.1.5 susceptibility to therapeutic mAbs, the combination tixagevimab/cilgavimab as well as bebtelovimab.[23] Both of these mAb treatments could not neutralize XBB.1.5. Sotrovimab is still weakly active against XBB.1.5.

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 several instances have already been detected in Ontario.

Implications for Public Health Practice

- A gradual increase in COVID-19 case numbers has been observed in Ontario since late November 2022. Percent positivity was 16.5% the week of December 25 to 31, 2022, up from 14.9% the previous week.[15] Based on current epidemiological trends, as well as the lack of data on XBB* disease severity and evidence of high XBB* transmissibility, community-based public health measures and increasing booster vaccination update can help protect Ontarians, reduce the risk of further strain on the health system, and limit disruption to essential services.

- Use of public health measures will reduce the risk of SARS-CoV-2 and other respiratory virus transmission at both the individual and population level. Consideration should be given to the least restrictive and most equitable measures.

    - Layers of protections in addition to vaccination 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 hand hygiene and respiratory etiquette.

- Though integral to the COVID-19 response, the limitations of vaccines are more evident in the context of variants that evade vaccine and infection-acquired immunity, such as XBB*. Evidence to inform the effectiveness of the new BA.1 and BA.4/5 bivalent vaccines against XBB*is still emerging. A COVID-19 pandemic strategy that relies entirely on immunity from current vaccines and past infection will be limited in its ability to affect transmission and the number of cases, whereas public health measures such as masking, ventilation, and staying home when sick will continue to be effective.

- 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,[33-37] as well as the current surge in severe pediatric respiratory diseases and 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.[15]

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