

EVIDENCE BRIEF

Risk Assessment for Omicron Sub-lineage XBB and XBB.1 (as of November 2, 2022)

Published: November 9, 2022

Key Messages

- According to the World Health Organization (WHO), XBB may have higher reinfection risk compared to other circulating Omicron sub-lineages.
- According to two preprints, XBB is among the most antibody-evasive strains tested (alongside BQ.1.1.10, BA.4.6.3, and CH.1.1) and is exhibiting the highest level of immune evasion.
- From September 25 to October 22, 2022 there were 6 cases of XBB and 5 cases of XBB.1 found in Ontario.
- The proportion of XBB cases in Canada has grown from 0.04% of cases (5 sequences from September 1, to October 1, 2022), to 0.07% of cases (4 sequences from October 2, to November 2, 2022.
- There is limited evidence to inform the risks of XBB (and XBB.1) with respect to transmissibility, immune evasion, and disease severity. Due to limited data, the risk to Ontario is currently highly uncertain.

Issue and Research Question

XBB and XBB.1 are recombinants of the Omicron sub-lineages BA.2.10.1 and BA.2.75, first reported in India, August 2022.¹ The WHO Technical Advisory Group on SARS-CoV-2 Virus Evolution (TAG-VE), has flagged Omicron variants (such as XBB and XBB.1), as variants of concern, and therefore, necessary to continue monitoring.² The Omicron subvariant XBB received "signals in monitoring" status on Oct 11 and received "designated variant status" on Oct 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 October 4 and ending November 2, 2022. English-language peer-reviewed and preprint records that provided information on the Omicron sub-lineages XBB were included.

Ontario Risk Assessment

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

Table 1.	Risk A	Assessment	for	Omicron	Sub-lineag	es XBE	3 and XBB.1
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Issues	Risk Level	Degree of Uncertainty
Increased Transmissibility	Moderate	High
Increased Disease Severity	Low	High
COVID-19 Reinfection	Moderate	High
Vaccine Effectiveness to Prevent Breakthrough Infection	Moderate	High
Impact on Testing and WGS* Surveillance	Low	Low

*Whole genome sequencing, WGS

Genomic Features

- XBB.1 is a sub-lineage of XBB. Both XBB and XBB.1 are a recombinant lineage of BA.2.10.1 and BA.2.75 sub-lineages.²
- XBB is characterized by the following key mutations in the spike protein: E: T11A, Spike: V83A, H146Q, Q183E, F486S, F490S. XBB contains more receptor-binding domain (RBD) mutations at antigenic sites than any other widespread variant.³

Epidemiology

As of the week October 3 to 9, 2022, from GISAID data, XBB has a global prevalence of 1.3%, increasing to 1.5% as of October 10 to 16, and it has been detected in 35 countries^{2,4}

Canada

- According to GISAID data, the proportion of XBB cases in Canada has increased from 0.04% of cases (5 sequences from September 1 to October 1, 2022),⁵ to 0.07% of cases (9 sequences from October 2 to November 2, 2022).⁶ There are currently not enough data to provide a reliable relative growth advantage estimate.
- From September 25 to October 22, 2022 there were 6 cases of XBB and 5 cases of XBB.1 found in Ontario.⁷ This is an increase of one case for both XBB (5 cases previously) and XBB.1 (4 cases previously) from October 15 to October 22, 2022.⁷ No cases of either XBB or XBB.1 were noted in Ontario January 1 to September 24, 2022.⁷

Global

- XBB was first reported in Singapore in September 2022, but the WHO documents samples of XBB as early as August 13, 2022.⁸
- In Victoria, Australia, a wastewater surveillance and clinical genomic testing program showed the rapid growth of BQ.1 and XBB combined reaching 10% of cases as of October 28, 2022.⁹

Europe and the United Kingdom (UK)

• XBB was first raised as a signal in monitoring in England on October 11, 2022 as part of horizon scanning. It was escalated to a designated variant on October 28, 2022.³ From October 16 to October 24, 2022, 18 UK samples have been uploaded to GISAID out of a global total of 1,104.³

United States (US)

According to GISAID data, the proportion of XBB cases in the US has grown from 0.01% of cases, (10 sequences) from September 1 to October 1, 2022,¹⁰ to 0.11% of cases (23 sequences) from October 2 to November 2, 2022.¹¹

Transmissibility and Infectivity

Early evidence suggests that there may be a higher reinfection risk for XBB, compared to other circulating Omicron sub-lineages.²

- According to two preprints, XBB is among the most antibody-evasive strains tested (alongside BQ.1.1.10, BA.4.6.3, and CH.1.1).^{2,12}
- Cao et al. (2022) examined variants with significant growth advantage over BA.5 (BA.2.3.20, BA.2.75.2, CA.1, BR.2, BN.1, BM.1.1.1, BU.1, BQ.1.1, and XBB) and their receptor-binding domain (RBD) to understand the impact of these mutations on the neutralizing antibody response and antibody therapeutics. The study included plasma from individuals who received 3 doses of CoronaVac (a vaccine currently not used in Canada), with or without breakthrough infection by BA.1, BA.2, or BA.5. They used 50 vesicular stomatitis virus-based spike pseudotyped viruses carrying RBD mutations, and examined the neutralizing activities of therapeutic neutralizing antibodies (NAbs).¹² Authors found that:
 - LY-CoV1404 (Bebtelovimab) was escaped by XBB (and BJ.1, BR.1, BQ.1.1) due to K444N/T mutations and the combination of K444M/G446S or V445P/G446S.
 - COV2-2196+COV2-2130 (Evusheld) was vulnerable to F486, R346, and K444-G446 mutations and evaded by XBB.
 - SA58 and SA55 (NAbs), were examined to understand neutralization efficacy of RBD mutations. SA58 showed reduced neutralization efficacy against XBB while SA55 showed high potency against all tested Omicron sub-lineages (including XBB).
 - The preprint reported that XBB exhibited the strongest resistance to monoclonal antibodies (mAbs) and treatment cocktails (COV2-2196+COV2-2130 and LY-CoV1404) of the SARS-CoV-2 mutant-based pseudoviruses they tested. The authors suggested that it was due to RBD mutations at F486, R346 and K444-G446 that XBB was highly evasive to COV2-2196+COV2-2130.

- Findings stated that XBB escaped most of the RBD NAbs, while showing high angiotensinconverting enzyme 2 (ACE2)-binding capability (noting that SARS-CoV-2 and SARS-CoV transmission occurs via the ACE2 receptor).¹³
- Omicron-specific NAbs from BA.5 breakthrough infections were found to have poor neutralization against XBB.
- Kurhade et al. (2022), examined the neutralizing activities of RBD spike mutations found in six newly emerged sub-lineages (BA.5, BF.7, BA.46, BA.2.75.2, XBB.1 and BQ.1.1). They collected human serum panels from individuals 1-3 months after their fourth dose of ancestral mRNA vaccine (either Pfizer/BioNTech or Moderna) (n=25), 1 month after BA.4/BA.5 bivalent-booster (n=29), and 1 month after BA.4/BA.5 bivalent-booster with previous SARS-CoV-2 infection (n=23).¹⁴
 - In the 4-dose mRNA vaccine group, the neutralizing geometric mean titres (GMTs) against XBB.1 (and BA.4/5-, BF.7-, BA.4.6-, BA.2.75.2-, BQ.1.1) spike viruses were 16.1-, 22.2-, 24.7, 59-, 69.7-, and 102-fold lower than the GMT against the USA-WA1/2020-spike virus (ancestral SARS-CoV-2). This indicates that 4 doses of ancestral mRNA vaccine appeared to not elicit as high a neutralization response against new sub-lineages compared to ancestral SARS-CoV-2, with XBB.1 exhibiting the lowest neutralizing GMT.
 - In the BA.4/BA.5 bivalent-booster group, the neutralizing GMTs against BA.4/5-, BF.7-, BA.4.6-, BA.2.75.2-, BQ.1.1-, and XBB.1-spike viruses were 12.1-, 11.9-, 19.8-, 36.9-, 49.6-, and 103-fold lower than the GMT against the USA-WA1/2020-spike (ancestral SARS-CoV-2). The BA.4/BA.5 bivalent-booster elicited significantly higher neutralizing antibody titers against the recently emerged Omicron sub-lineages compared to the 4^{-d}ose mRNA ancestral vaccine group, but the neutralization against XBB.1 (and BA.275.2 and BQ.1.1) remained low (fluorescent focus reduction neutralization test, FFRNT, below 320) after the BA.4/BA.5 bivalent booster.
 - In the BA.4/BA.5 bivalent-booster and previous infection group, the neutralizing GMTs against BA.4/5-, BF.7-, BA.4.6-, BA.2.75.2-, BQ.1.1-, and XBB.1-spike viruses were 3.7-, 4.7-, 7.8-, 15.7-, 21.6-, and 56.1-fold lower than the GMT against the USA-WA1/2020-spike (ancestral SARS-CoV-2). BA.4/BA.5 bivalent-booster and infection group sera increased neutralizing GMTs against SARS-CoV-2 over the BA.4/BA.5 bivalent-booster (no infection) group. The authors suggested that previous infection significantly increased neutralizing GMTs among BA.5 bivalent-boosted individuals for the tested sub-lineages, with XBB.1 exhibiting the highest level of immune evasion in both individuals with and without a history of previous infection.

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) in infections compared to other sub-lineages.²
- The Indian SARS-CoV-2 Consortium on Genomics (INSACOG), a group of 54 laboratories across India that monitor variants of concern, stated that they have detected no increase in disease severity associated with XBB.¹⁵

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.
- WGS surveillance: No or little impact is expected on the capability of WGS to detect XBB as several instances (11) have already been detected in Ontario.

Implications for Public Health Practice

- According to the WHO's TAG-VE, the overall phenotype of XBB* and BQ.1* do not diverge sufficiently from each other or from other Omicron lineages with immune escape mutations to alter the current public health response.²
- The limited evidence of the newly emerging sub-lineages XBB (on transmissibility, disease severity, COVID-19 reinfection, vaccine effectiveness against breakthrough infection, and testing and WGS), and the growing evidence of XBB exhibiting high immune evasion, suggests that vaccine boosters and other public health measures may be necessary to mitigate the impact of Omicron and future SARS-CoV-2 variants.¹⁶

References

- Singapore. Ministry of Health. Update on Covid-19 situation and measures to protect healthcare capacity [Internet]. Singapore: Government of Singapore; 2022 [cited 2022 Nov 08]. Available from: <u>https://www.moh.gov.sg/news-highlights/details/update-on-covid-19-situation-andmeasures-to-protect-healthcare-capacity.</u>
- World Health Organization (WHO). TAG-VE statement on Omicron sub-lineages BQ.1 and XBB [Internet]. Geneva: WHO; 2022 [cited 2022 Nov 3]. Available from: <u>https://www.who.int/news/item/27-10-2022-tag-ve-statement-on-omicron-sub-lineages-bq.1-and-xbb</u>
- UK Health Security Agency. SARS-CoV-2 variants of concern and variants under investigation in England: technical briefing 47 [Internet]. London, UK: Crown Copyright; 2022 [cited 2022 Nov 3]. Available from: <u>https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_dat</u> a/file/1115077/Technical-Briefing-47.pdf
- World Health Organization (WHO). COVID-19 weekly epidemiological update: edition 116 published 2 November 2022 [Internet]. Geneva: WHO; 2022 [cited 2022 Nov 3]. Available from: <u>https://www.who.int/publications/m/item/weekly-epidemiological-update-on-covid-19---2-</u> <u>november-2022</u>
- CovSPECTRUM. XBB (Nextclade) Canada (from 2022-09-01 to 2022-10-01) [Internet]. Zurich: GISAID; 2022 [cited 2022 Nov 2]. Available from: <u>https://cov-</u> <u>spectrum.org/explore/Canada/AllSamples/from=2022-09-01&to=2022-10-</u> 01/variants?nextcladePangoLineage=XBB&
- CovSPECTRUM. XBB (Nextclade) Canada (from 2022-10-02 to 2022-11-02) [Internet]. Zurich: GISAID; 2022 [cited 2022 Nov 2]. Available from: <u>https://cov-spectrum.org/explore/Canada/AllSamples/from=2022-10-02&to=2022-11-02/variants?nextcladePangoLineage=XBB&</u>
- Ontario Agency for Health Protection and Promotion (Public Health Ontario). Weekly epidemiological summary: SARS-CoV-2 genomic surveillance in Ontario, November 4, 2022 [Internet]. Toronto, ON: King's Printer for Ontario; 2022 [cited 2022 Nov 4]. Available from: <u>https://www.publichealthontario.ca/-/media/Documents/nCoV/epi/covid-19-sars-cov2-whole-genome-sequencing-epi-summary.pdf?sc_lang=en</u>
- World Health Organization (WHO). Tracking SARS-CoV-2 variants [Internet]. Geneva: WHO; 2022 [cited 2022 Nov 3]. Available from: <u>https://www.who.int/activities/tracking-SARS-CoV-2-variants</u>
- Australia. Department of Health. Chief health officer update 28 October 2022 [Internet]. Melbourne: Victorian Government; 2022 [cited 2022 Nov 3]. Available from: <u>https://www.health.vic.gov.au/media-releases/chief-health-officer-update-28-october-2022</u>

- CovSPECTRUM. XBB (Nextclade) United States (from 2022-09-01 to 2022-10-01) [Internet]. Zurich: GISAID; 2022 [cited 2022 Nov 2]. Available from: <u>https://cov-spectrum.org/explore/United%20States/AllSamples/from=2022-09-01&to=2022-10-01/variants?nextcladePangoLineage=XBB&</u>
- 11. CovSPECTRUM. XBB (Nextclade) United States (from 2022-10-02 to 2022-11-02) [Internet]. Zurich: GISAID; 2022 [cited 2022 Nov 2]. Available from: <u>https://cov-</u> <u>spectrum.org/explore/United%20States/AllSamples/from=2022-10-02&to=2022-11-</u> <u>02/variants?nextcladePangoLineage=XBB&</u>
- Cao Y, Jian F, Wang J, Yu Y, Song W, Yisimayi A, et al. Imprinted SARS-CoV-2 humoral immunity induces convergent Omicron RBD evolution. bioRxiv 507787 [Preprint]. 2022 Oct 4 [cited 2022 Nov 3]. Available from: <u>https://doi.org/10.1101/2022.09.15.507787</u>
- Ni W, Yang X, Yang D, Bao J, Li R, Xiao Y, et al. Role of angiotensin-converting enzyme 2 (ACE2) in COVID-19. Crit Care. 2020;24(1):422. Available from: <u>https://doi.org/10.1186/s13054-020-03120-0</u>
- Kurhade C, Zou J, Xia H, Liu M, Chang HC, Ren P, et al. Low neutralization of SARS-CoV-2 Omicron BA.2.75.2, BQ.1.1, and XBB.1 by 4 doses of parental mRNA vaccine or a BA.5-bivalent booster. bioRxiv 514580 [Preprint]. 2022 Nov 2 [cited 2022 Nov 3] Available from: <u>https://doi.org/10.1101/2022.10.31.514580</u>
- 15. India. Department of Biotechnology. INSACOG statement on XBB recombinant lineage [Internet]. New Delhi: Government of India; 2022 [cited 2022 Nov 3]. Available from: https://dbtindia.gov.in/insacog/insacog-statement-xbb-recombinant-lineage
- Grewal R, Nguyen L, Buchan SA, Wilson SE, Nasreen S, Austin PC, et al. Effectiveness of mRNA COVID-19 vaccine booster doses against Omicron severe outcomes. medRxiv 22281766 [Preprint]. 2022 Nov 1 [cited 2022 Nov 2]. Available from: <u>https://doi.org/10.1101/2022.10.31.22281766</u>

Citation

Ontario Agency for Health Protection and Promotion (Public Health Ontario). Risk assessment for Omicron sub-lineage XBB (as of November 2, 2022). Toronto, ON: King's Printer for Ontario; 2022.

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