SARS-CoV-2 Variant Rapid Risk Assessment Report: XBB.1.5

Assessment completed: January 20, 2023

Background

Omicron variants have increased transmissibility and demonstrated immune evasion when compared to previously circulating variants. This rapid risk assessment compares the public health risk to Canadians posed by Omicron variant XBB.1.5 to those posed by BA.5 (excluding BF.7 and BQ). XBB.1.5 is a sub-lineage of XBB, which is a recombinant of two BA.2 sub-lineages (BA.2.10 and BA.2.75). XBB.1.5 was first detected in the United States in October 2022 and has been detected in 38 countries. According to the World Health Organization (WHO), over 80% of detections are from the US. As of January 16, 2023, the number of XBB.1.5 infections remains low in Canada but is growing at approximately 9% per day. Since November 2022, there have been 126 detections across 8 provinces. This assessment is based on available evidence as of January 17, 2023. This is an evolving situation with new evidence expected.

Risk Statement

The potential 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 number of COVID-19 cases caused by XBB.1.5 will likely increase in Canada, however, it is not known whether XBB.1.5 will become the dominant strain and it is not known whether this will result in an increase in overall COVID-19 incidence. The level of uncertainty in this assessment is moderate to high.

Risk Assessment Summary

Table 1: Risk assessment for variant XBB.1.5 relative to BA.5 (excluding BF.7 and BQ)[a]

Indicator	Risk[b]	Uncertainty	Assessment and rationale[c]
Transmissibility[d]	Elevated	Moderate	XBB.1.5 has mutations that increase transmissibility through improved entry into cells and viral replication. Increases in the US, particularly in the Northeast regions, demonstrate growth advantage of this strain. In Canada, the overall growth advantage of this sub-lineage is approximately 9% per day. Growth estimates are changing quickly as information from other regions, including Canada, becomes available.
Disease severity	Comparable	High	There is no indication that the disease severity of XBB.1.5 is different than that of currently circulating Omicron sub-lineages.
Immune evasion[e]	Elevated	Moderate	XBB* is more immune evasive than earlier Omicron sub-lineages including BA.5, based on studies assessing neutralizing antibody responses.
Therapeutics	Comparable	High	XBB*, like BA.5, is not expected to be susceptible to currently available neutralizing monoclonal antibody therapies. Antiviral treatments are expected to remain effective against Omicron sub-lineages.

[a]BA.5 was used as the reference as it has information available for all comparison attributes.
[b]Risk: Red indicates the assessed variant as elevated risk, yellow is comparable risk, green is reduced risk. Also, see Appendix 2 for risk assessment framework and definitions.
[c]See Appendix 1 for evidence to support assessment.
[d]Selective advantages calculated relative to currently circulating lineages, particularly the most prevalent at the time. Increases of a growth rate over time may be due to decreases in the reference and not necessarily intrinsic jumps in growth by the lineage.
[e]Immune evasion is based on two indicators: immunity after infection and immunity after vaccination.
*Asterisk here is a technical symbol denoting inclusion of the sub-lineages in the overall lineage.

Proposed Actions for Public Health Authorities

These actions are for consideration by jurisdictions according to their local epidemiology, policies, resources, and priorities. Due to the current level of uncertainty associated with XBB.1.5, it is important that the public health response be proportionate to the risk.

Surveillance and Reporting

- Continue to monitor for changes in XBB.1.5 epidemiology, particularly related to growth rate, severity of cases and immune evasion.
- Continue sequencing SARS-CoV-2 to understand circulating strains.
- Continue to share emerging evidence between local, provincial/territorial and federal levels to inform the public health response.

Risk Communication

- Continue regular communication with Canadians and health professionals on the current COVID-19 situation and share associated guidance. When necessary, correct and counter mis- or disinformation.

Public Health Interventions

- Continue public health interventions based on local epidemiology. There are no changes to the federal guidance on individual public health measures, COVID-19 vaccination, infection prevention and control measures and the use of antivirals.

Appendix 1: Supporting Information

Table 2: Indicators and evidence to support risk assessment as of January 17, 2023 (unless otherwise stated).

Indicator	Evidence
Transmissibility	• XBB.1.5 is a sub-lineage of the SARS-CoV-2 lineage XBB.1, a recombinant of Omicron variants BA.2.10* and BA.2.75*. XBB.1.5 has acquired an additional mutation in the spike protein (Receptor Binding Domain mutation 486P). Thus, XBB.1.5 likely is more transmissible than XBB.1 because of the increased ACE2 affinity[1]. **International** • As of January 11, 2023, 5,288 sequences have been reported across 38 different countries. Most of these submissions are from the United States, but there are also increasing numbers of detections in Europe[2]. • As of January 16, 2023, XBB.1.5 is estimated to have a growth advantage (~10% per day) over currently circulating lineages in North America and Europe. However, local growth estimates vary from ~10–20% per day relative to lineages circulating in those US states or EU countries[3]. • From data posted on January 13, 2023, the US CDC estimates the current proportion of XBB.1.5 to be 11.5% for the week ending December 24, 2022. Projections for the week ending January 14, 2023, suggest XBB.1.5 will comprise 43.0% of sequences in the US. There is large geographic variation noted, with 2 regions in the northeastern US projecting that XBB.1.5 will comprise over 80% of sequences and 5 other regions projected at between 8-16% of sequences for the week ending January 14, 2023[4]. **Domestic** • As of January 16, 2023, there are 126 detections of XBB.1.5 in Canada reported to PHAC dating back to November 20, 2022. Most of them are reported from Ontario. • Ontario has reported that the proportion of XBB.1.5 is increasing and that projected prevalence will be 22.2% by January 18, 2023. XBB.1.5 has been detected in multiple health regions[5]. • By January 16, 2023, XBB.1.5 is projected to be 7% of sequences reported to the Public Health Agency of Canada. • The overall growth advantage of this sub-lineage relative to all other currently circulating strains in Canada is ~ 9% per day (6-10%, 95% CI).
Disease Severity	**International** • The ECDC assessment of the XBB.1.5 sub-lineage stated that there is no indication that infections from XBB.1.5 differ in severity from currently circulating Omicron lineages[6]. • The WHO reports that severity data is unavailable and assessments are ongoing. However, XBB.1.5 does not carry any mutation known to be associated with potential change in severity (such as S:P681R)[2]. • 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 Omicron sub-lineages[7]. **Domestic** • As of January 12, 2023, there are 18 COVID-19 cases associated with XBB.1.5 in the national case surveillance database, with 4 hospitalizations, no ICU admissions, and no deaths.
Immune Evasion[a]	**Neutralizing antibody responses** • Currently, most studies evaluating immunity from a prior SARS-CoV-2 infection include individuals with hybrid immunity (immunity obtained from vaccination and SARS-CoV-2 infection), as a result there are fewer studies conducted on those who have only infection-acquired immunity. • Preliminary in-vitro evidence suggests that XBB* sub-lineages are the most antibody-evasive SARS-CoV-2 sub-lineages identified to date and XBB.1.5 is shown to be

Indicator	Evidence
	similarly immune evasive as XBB.1 in 3 pre-prints. Two studies show that XBB.1.5 resists neutralizing immune responses from individuals with hybrid immunity (including prior BA.5 or BA.2 infection after 2-4 doses of monovalent mRNA vaccines)[1,8]. Additional data demonstrates XBB.1.5 resists neutralizing immune responses from individuals infected with BA.4/5 (most of whom were unvaccinated), vaccinated with 3 doses of the monovalent vaccine, and vaccinated with a bivalent booster after 2 to 4 monovalent doses (most received 3 monovalent doses)[9]. • Nine additional studies have evaluated neutralization of XBB* variants by sera from individuals with 3 different immune backgrounds (vaccination and/or infection): (1) vaccinated with 3-4 doses of the original monovalent mRNA vaccine, (2) vaccinated with a bivalent booster, or (3) breakthrough infection with BA.2 or BA.4/5. ○ Evidence suggests that XBB* highly resists neutralizing immune responses induced either by the original monovalent mRNA vaccines or by a combination of vaccination and infection-derived immunity (i.e., hybrid immunity) to a greater degree than BA.5[10, 11, 12, 13, 14] ○ XBB* also resists neutralization to immunity induced by the bivalent boosters to a greater extent than BA.4/5[12, 15, 16, 17, 18]. However, most of these studies suggest bivalent boosters elicit somewhat higher neutralizing antibody titers against XBB* than a monovalent vaccine booster. **Cellular responses** • No studies assessing T-cell immunity are available for XBB.1.5 specifically. However, recent in-vitro studies suggest that CD8+ and CD4+ T-cell responses against XBB are largely conserved[19]. • A pre-print retrospective study from Singapore evaluated the protective effectiveness (PE) of a previous SARS-CoV-2 infection among those who received monovalent mRNA vaccination (2-3 doses) against a BA.4/5 and XBB reinfection (specific sub-lineage not reported)[20]. PE against an XBB reinfection was lower than PE against BA.4/5 reinfection regardless of the prior infecting variant (PE from a prior BA.2 infection among those with 3 mRNA doses was 78% against a BA.4/5 infection versus 51% against XBB infection). There is no data on vaccine effectiveness against XBB.1.5 infection or severe outcomes as well as no data on protective effectiveness from a prior infection against XBB-related severe outcomes.
Therapeutics	• Paxlovid (nirmatrelvir/ritonavir) and Remdesivir seem to retain their activity against SARS-CoV-2 Omicron[21]. It is unknown currently if the same holds true for the recombinant XBB.1.5. • Limited in-vitro data on the activity of COVID-19 mAbs is available against XBB.1.5. • A preprint listed on the Stanford University coronavirus antiviral & resistance database suggests that tixagevimab/cilgavimab (Evusheld) and sotrovimab have reduced or no activity against XBB.1.5[1]. They also demonstrate that XBB.1 and XBB.1.5 show comparable mAb evasion. • In an in-vitro study, Evusheld and Sotrovimab had decreased in activity against XBB compared to BA.5[22]. Evusheld and Sotrovimab may not be effective against XBB.1 and XBB when compared to the ancestral (original) SARS-CoV-2 strain[11]. • The product monograph for Evusheld reports a reduction in susceptibility to XBB compared to BA.5. • No Canadian in-vitro data is available on the activity of COVID-19 antivirals against XBB.1.5. • No Canadian data on the clinical effectiveness of COVID-19 therapeutics (antivirals or monoclonal antibodies [mAbs]) is available for XBB.1.5.

Indicator	Evidence

Sub-lineage Group	mAbs tested	Viral type	Fold-change[b]	Reference strain	Source
XBB.1.5	Sotrovimab	Pseudovirus	1	XBB.1	Yue et al.[1]
XBB.1.5	Tixagevimab/ cilgavimab	Pseudovirus	0.9	XBB.1	Yue et al.[1]

Considerations:

- The U.S. Food and Drug Administration (PDF) defines 'no change' in in-vitro activity for mAbs in its authorized fact sheet guidance documents as <5-fold reduction in susceptibility
- Since in-vitro assays are often conducted under controlled conditions, they do not reflect the in-vivo pharmacokinetic properties of the therapeutic under investigation. Therefore, in-vitro studies do not correlate with therapeutic effectiveness or treatment failure.

[a]Immune evasion is based on two indicators: immunity after infection and immunity after vaccination.
[b]Fold-change values provided from the Stanford University coronavirus antiviral and resistance database (>1 indicates decreased activity)
*Asterisk here is a technical symbol denoting inclusion of the sub-lineages in the overall lineage.

Table 3: Contextual information to support risk assessment and proposed actions

Criteria	Considerations
Health Systems Impact including Hospital Capacity and Infection Prevention and Control measures (Capacity: beds, health care workers)	• Hospital and health care capacity in Canada remains strained due to circulating influenza, RSV, and SARS-CoV-2 and other pressures. Infection, prevention and control practices are in place to limit transmission of COVID-19.
Border Measures (Vaccination, Quarantine and Testing)	• Border measures are designed to slow the importation of new variants, while XBB.1.5 has been detected in Canada since November 2022.
Surveillance Capacity	• Wastewater assays in Canada can detect XBB.1.5. • Confirmatory testing volumes have remained relatively stable, but outpatient testing is generally restricted to specific populations and symptomatic patients. Asymptomatic testing is primarily for at-risk populations, including individuals at risk of severe outcomes, and their contacts. As such, surveillance data are not representative of all COVID-19 infections in Canada. • Testing and sequencing strategies may differ across the country.
Public Health Measures	• The current PHAC guidance on public health measures includes the layered use of individual public health measures such as staying home when ill, properly wearing a well-constructed and well-fitting mask in public indoor settings, improving indoor ventilation, performing frequent hand hygiene and proper respiratory etiquette, and cleaning and disinfecting high-touch surfaces and objects, to reduce the risk of infection and spread. • Public health measures recommendations in Canada continue to vary across jurisdictions as provinces and territories experience differing epidemiology and risks as well as transition to the longer-term management of COVID-19. • Most community-based measures such as lockdowns, widespread case and contact management activities, including quarantine and isolation requirements as well as universal masking have ended. Individual risk-based measures are being promoted (e.g., staying home when ill, wearing a mask in certain circumstances, etc.).
Vaccination	• As of January 1, 2023 (most recent available data), 80.6% of the total population has completed a primary series of COVID-19 vaccine. • As of January 1, 2023 (most recent available data), 25.0% of the total population have completed their primary series or received a booster dose of COVID-19 vaccine in the last six months[23].

Appendix 2: Methods

Variant Risk Assessment Framework

The below has been adapted from the Public Health England Risk Assessment Framework (PDF) for SARS-CoV-2 variants of concern and variants under investigation to determine the level of risk posed by the variant. It will serve as a guidance when determining the comparative risk level to the reference variant.

Table 4: Risk comparison of SARS-CoV-2 variants relative to baseline or specific reference variant

Indicator	Reduced Risk	Comparable Risk	Elevated Risk
Transmissibility	Limited person-to-person transmission	Similar transmissibility to baseline or specific reference variant	More transmissible than baseline or specific reference variant
Disease severity	Evidence of less severe clinical picture (asymptomatic or symptomatic) compared with baseline or specific reference variant	Similar clinical picture in terms of hospitalization rates and/or case fatality compared with baseline or specific reference variant, **or** experimental animal data suggesting potential for increased disease severity in humans	More severe clinical picture (hospitalization rates) or higher case fatality compared with baseline or specific reference variant
Immune evasion: Immunity after infection[a]	Evidence of no infection in humans previously infected with the baseline variant, and/or limited reinfection cases found in humans previously infected with any variant, **or** structural data suggesting no antigenic differences	Evidence of limited infection in humans with known prior infection, or evidence of limited functional evasion of immunity after infection, **or** structural data suggesting some antigenic differences	Evidence of frequent infection in humans with known prior infection, or evidence of marked functional evasion of immunity after infection, **or** structural data suggesting significant antigenic differences
Immune evasion: Immunity after vaccination[a]	Evidence that vaccine performance is preserved, **or** structural data suggesting no antigenic difference in vaccine target epitopes	Evidence of limited functional evasion of vaccine derived immunity, **or** structural data suggesting some differences in vaccine target epitopes	Evidence of marked functional evasion of vaccine derived immunity, **or** structural data suggesting significant differences in vaccine target epitopes
Therapeutics	Evidence of increased clinical effectiveness of therapeutics[b] **or** Increased number of effective therapeutics[b] **or** Evidence of increased in vitro activity[c] of a therapeutic	Evidence of comparable clinical effectiveness of therapeutics[b] **or** No change in the number of effective therapeutics[b] **or** Evidence of retained in vitro activity[c] of therapeutics	Evidence of decreased clinical effectiveness of therapeutics[b] **or** Decrease in the number of effective therapeutics[b] **or** Evidence of reduced in vitro activity or loss of in vitro activity[c] of therapeutics

[a]Immune evasion is based on two indicators: immunity after infection and immunity after vaccination. [b]Therapeutic: Refers to a therapeutic procured and available in Canada. [c]Activity: Refers to a variant's *in vitro* fold change in activity for therapeutics reported by the OpenData Portal: SARS-CoV-2 variants and therapeutics. It is not known how *in vitro* data correlate with clinical outcomes.

Criteria for Estimating Level of Uncertainty

Very high uncertainty: Criteria is lack of data or reliable information; results are based on crude speculation only.

High uncertainty: Criteria is limited data or reliable information available; results are based on educated guess.

Moderate uncertainty: Criteria is some gaps in availability or reliability of data and information, or conflicting data; results based on limited consensus.

Low uncertainty: Criteria is reliable data and information available but may be limited in quantity or be variable; results based on expert consensus.

Very low uncertainty: Criteria is reliable data and information are available in sufficient quantity; results strongly anchored in empiric data or concrete information.

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