Risk Assessment for Omicron Sub-lineage BQ.1 and its sub-lineages (BQ.1*) (as of November 9, 2022)

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Key Messages

- The proportion of BQ.1 and BQ.1.1 cases in Ontario are increasing. BQ.1 increased from 5.4% (October 16 to October 22) to 6.5% (October 23 to October 29) while BQ.1.1 increased from 3.3% (October 16 to October 22) to 5.3% (October 23 to October 29). By November 16, 2022, BQ.1 is projected to increase to 17.4% (95% CI: 13.9% - 21.4%) and BQ.1.1 to increase to 21.2% (95% CI: 15.9% - 27.6%).

- The relative contributions of increased transmissibility inherent in BQ.1 and its sub-lineages (indicated as BQ.1*), immune evasion, and waning immunity, is unclear; however, early evidence limited to pre-prints suggests immune evasion may be responsible for increased transmission of BQ.1* relative to BA.5 co-circulating sub-lineages.

- It is highly uncertain whether the severity of disease caused by BQ.1* differs from previous SARS-CoV-2 variants; however, due to increased transmissibility of BQ.1*, the absolute number of severe cases may increase as BQ.1* becomes dominant. Increases in bivalent booster vaccine uptake and immunity from previous infections may attenuate the increase of severe BQ.1* cases.

- An increase in severe COVID-19 cases due to BQ.1* may further impact current capacity issues facing the Ontario healthcare system due to the early and rapid increase of other respiratory viruses (e.g., respiratory syncytial virus (RSV) and influenza) that have caused a surge in pediatric emergency department visits, admissions and intensive care unit (ICU) occupancy.

- Based on limited evidence of immune evasion by BQ.1 and BQ.1.1, 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 be the most effective way to reduce the risk of SARS-CoV-2 transmission at both the individual and population level. With increased time spent indoors during the winter months, 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; and hand hygiene. Consideration should be given to the least restrictive and most equitable measures.
Issue and Research Question

There are multiple PANGO sub-lineages associated with the B.1.1.529 (Omicron) variant of concern (VOC), and the main BA.1, BA.2, BA.3, BA.4, and BA.5 sub-lineages have their own sub-lineages (e.g., BA.1.1, BA.2.12, BA.2.12.1, BA.2.3, BA.2.20, BA.2.9, BA.5.1, BQ.1). Considering the possible changes to transmissibility, severity, and/or vaccine effectiveness (VE) of these sub-lineages compared to other VOCs, it is important to monitor the potential impact they might have in Ontario’s context.

The World Health Organization’s (WHO) Technical Advisory Group on SARS-CoV-2 Virus Evolution (TAG-VE) has flagged BQ.1/BQ.1.1 as an Omicron sub-variant under monitoring, and therefore, necessary to continue monitoring. The Omicron sub-lineage BQ.1 (a sub-lineage of BA.5) was given United Kingdom (UK) Health Security Agency (UKHSA) variant designation on October 28, 2022. This evidence brief summarizes available information and evidence on the Omicron sub-lineages BQ.1 (alias of BA.5.3.1.1.1.1.1) and BQ.1.1 (alias of BA.5.3.1.1.1.1.1.1) that emerged since the last Public Health Ontario (PHO) BQ.1 and BQ.1.1 risk assessments, relevant to Ontario.

Methods

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. PHO performed grey literature searches daily using various news feeds and custom search engines beginning November 1, 2022 and concluding November 9, 2022. English-language peer-reviewed and preprint records that described the Omicron variants BQ.1 and BQ.1.1 were included if identified. Formal critical appraisal of published and preprint COVID-19 literature was out of scope for this PHO risk assessment. This is an update of two evidence briefs on BQ.1 and BQ.1.1.

Ontario Risk Assessment

The current risk of BQ.1 and BQ.1.1 transmissibility, reinfection, and breakthrough infection in Ontario is high with a moderate degree of uncertainty. The risk of severe disease is unknown with a high degree of uncertainty. The risk of impact on testing is unknown with a high degree of uncertainty. The overall risk assessment may change as new evidence emerges (see Table 1).

Table 1. Risk Assessment for Omicron Sub-lineages BQ.1 and BQ.1.1

<table>
<thead>
<tr>
<th>Issues</th>
<th>Risk Level</th>
<th>Degree of Uncertainty</th>
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</thead>
<tbody>
<tr>
<td>Increased Transmissibility</td>
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<td>Moderate</td>
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<tr>
<td>Increased Disease Severity</td>
<td>Unknown</td>
<td>High</td>
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<tr>
<td>COVID-19 Reinfection</td>
<td>High</td>
<td>Moderate</td>
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<tr>
<td>Lowered Vaccine Effectiveness Against Infection</td>
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<td>Moderate</td>
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<tr>
<td>Impact on Testing</td>
<td>Unknown</td>
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</tbody>
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Genomic Features

The genomic characteristics of BQ.1 and BQ.1.1 have been described previously. Of note, within the spike (S) protein, BQ.1 and BQ.1.1 contain the mutations K444T, L452R, N460K, and F486V. BQ.1.1 additionally contains the mutation R346T. It is thought that some of these S protein mutational sites are prone to antibody evasion based on previous broad mutational scanning analyses.

Epidemiology

Global

- From October 3 to 9, 2022, GISAID data indicated a BQ.1* prevalence of 6%. As of October 25, 2022, BQ.1 (and its lineages) are reported from 65 countries with 8,077 sequences.
- From the WHO, comparing the week of October 16 to 22, 2022 to the previous week (October 9 to October 15, 2022), BQ.1* had the largest increase in global cases of the variants monitored by the WHO, rising from 9.4% to 13.4% of cases.
- The most recent UKHSA Technical Briefing reported that, since BQ.1 was first noted, BQ.1 GISAID uploads have increased by more than 75% each week, with updates most commonly coming from the United States (US) and the UK.

Canada

- Based on sequences uploaded to GISAID, in Canada, between October 9 to November 9, 2022, there were 98 sequences of BQ.1 (1.65% of cases) and 170 sequences of BQ.1.1 (2.86% of cases). This is an increase from the previous month (September 8 to October 8, 2022) when there were 188 sequences of BQ.1 (0.85% of cases) and 281 sequences of BQ.1.1 (1.28% of cases).
- In Ontario, the proportion of BQ.1 cases increased from 5.4% (October 16 to October 22, 2022) to 6.5% (October 23 to October 29, 2022) and is projected to increase to 17.4% (95% CI: 13.9% - 21.4%) by November 16, 2022. The weekly relative growth rate of BQ.1 is 1.72 (95% CI: 1.63 - 1.80) times that of BA.5.2.1 (the most prevalent lineage at 18.7% the week of October 23 to October 29, 2022).
- In Ontario, the proportion of BQ.1.1 cases increased from 3.3% (October 16 to October 22, 2022) to 5.3% (October 23 to October 29, 2022) and is projected to increase to 21.2% (95% CI: 15.9% - 27.6%) by November 16, 2022. The weekly relative growth rate of BQ.1.1 is 2.01 (95% CI: 1.86 - 2.17) times that of BA.5.2.1.
- In Quebec, the aggregated data shows the proportion of BQ.1 and BQ.1.1 cases based on random sequencing increased across the weeks of October 9, 2022 (1.7% and 3.8%, for BQ.1 and BQ.1.1 respectively), October 16, 2022 (3.9% and 7.6%, respectively), and October 23, 2022 (7.0% and 11.5%, respectively).
France

- Based on sequences uploaded to GISAID, in France, between October 9 and November 9, 2022, there were 184 sequences of BQ.1 (3.74% of cases), and 1,011 sequences of BQ.1.1 (20.54% of cases). This is an increase in proportion from the previous month (September 8 to October 8, 2022) when there were 173 sequences of BQ.1 (1.41% of cases) and 1,030 sequences of BQ.1.1 (8.39% of cases).

UK

- In the UK, between October 9, and November 9, 2022, there were 608 sequences of BQ.1 (5.31% of cases), and 657 sequences of BQ.1.1 (5.73% of cases). This is an increase in proportion from the previous month (September 8 to October 8, 2022) when there were 386 sequences of BQ.1 (1.85% of cases), and 449 sequences of BQ.1.1 (2.15% of cases).
- The UKHSA, assigned BQ.1 “designated variant status” on October 24, 2022.

Europe

- The European Centre for Disease Control and Prevention (ECDC) designated BQ.1 (and its sub-lineages) as a variant of concern on October 20, 2022. According to ECDC modelling, it is expected that by mid-November to beginning of December 2022, more than 50% of SARS-CoV-2 infections will be due to BQ.1/BQ.1.1.

US

- According to the Centers for Disease Control and Prevention (CDC), the estimated proportions of BQ.1 and BQ.1.1 among circulating variants the week ending in November 5, 2022 were 16.5% (95% Prediction Interval, PI: 13.6%-20.0%) and 18.8% (95% PI: 15.7%-22.4%), respectively. This is an increase from the previous week, when BQ.1 and BQ.1.1 were estimated to be 11.9% (95% PI: 9.9%-14.2%) and 11.3% (95% PI: 9.6%-13.3%), respectively. During the same period, BA.5 (the variant comprising the largest proportion of cases) dropped to 39.9% (95% PI: 36.2%-42.3%), from 50.5% (95% PI: 48.1%-53.5%) the previous week.

Transmissibility and Infectivity

- Although there is limited information on BQ.1* inherent transmissibility, genomic surveillance in various jurisdictions continues to show this sub-lineage and its sub-lineages to be highly transmissible as their relative share of COVID-19 infections has been increasing since early October, 2022.
- Qu et al., used lentivirus pseudotyped with the spike protein from Omicron sub-lineages, and reported BQ.1 and BQ.1.1 exhibited modestly enhanced infectivity in HEK293T-ACE2 cells compared to the ancestral D614G variant. They also reported enhanced fusogenicity and spike protein processing in the BA.4/5-derived sub-lineages they examined, which included BQ.1 and BQ.1.1, driven largely by the N460K mutation. The authors state that these data may indicate a continuing shift towards more efficient plasma membrane-mediated viral fusion and entry pathway.
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### Disease Severity

- Qu et al reported BQ.1 and BQ.1.1 exhibited poor infectivity in lung-derived CaLu-3 cells compared to ancestral D614G. Weak lung tropism demonstrated by previous Omicron sub-variants have been correlated with decreased pathogenicity; however, formal studies of BQ.1* tissue tropism and pathogenicity in vivo are needed.²⁸

### COVID-19 Therapeutics

- Information on activity of therapeutic neutralizing antibodies (NAbs) against BQ.1 and BQ.1.1 is currently limited. Please refer to Risk Assessment for Omicron Sub-lineages BQ.1 and BQ.1.1 (as of October 20, 2022) for a summary of that evidence.³,⁴

- On November 4, 2022, the US Food and Drug Administration (FDA) provided updated neutralizing data for bebtelovimab which indicates reduced activity against certain Omicron sub-variants. While bebtelovimab is not expected to neutralize BQ.1 and BQ.1.1, nirmatrelvir/ritonavir (Paxlovid) and remdesivir (Veklury) are expected to retain activity against these variants.²⁹

### Immune Evasion

- Qu et al., examined sera from three-dose vaccinated health care workers (mRNA-1273 [Moderna], n=3, or BNT162b2 [Pfizer-BioNTech], n=12), hospitalized BA.1- wave patients (n=15), and BA.5-wave patients for their ability to neutralize several sub-lineages, including BQ.1 and BQ.1.1.²⁸ For the sera from three-dose vaccinated healthcare workers, compared to D614G (ancestral SARS-CoV-2), BQ.1, and BQ.1.1 sub-lineages exhibited an 18.7-fold (p < 0.0001), and 22.9-fold (p < 0.0001) lower neutralization sensitivity, respectively. Sera from hospitalized COVID-19 patients infected during the BA.1 wave, compared to D614G, showed that BQ.1, and BQ.1.1 sub-lineages exhibited a 5.3-fold (p <0.01), and 5.0-fold (p <0.05) lower neutralization sensitivity, respectively. Sera from individuals who tested positive for COVID-19 during the BA.4/5 wave of the pandemic, compared to D614G, showed that BQ.1, and BQ.1.1 sub-lineages exhibited a 10.4-fold (p < 0.0001), and 10.7-fold (p < 0.0001) lower neutralization sensitivity, respectively. The authors state that this consistent pattern of strong neutralization resistance exhibited by BQ.1 and BQ.1.1 is largely driven by the N460K mutation and has implications for persistence of both vaccine- and infection-induced immunity.

- Kurhade et al., examined the neutralizing activity of antibodies against six Omicron sub-lineages (BA.5, BF.7, BA.4.6, BA.2.75.2, BQ.1.1 and XBB.1) using sera from individuals who received either four doses of parental mRNA vaccines (BNT 162b2 and/or mRNA-1273 ; 1-3 months post four-doses; n=25), a BA.5-bivalent-booster (one month post-booster; n=29) or have had a previous SAR-CoV-2 infection and also received a BA.5-bivalent booster one month prior (n=23).³⁰ Based on the results, the authors concluded that the BA.5-bivalent booster provides better neutralization against the Omicron sub-lineages than parental mRNA vaccines and that individuals with previous SAR-CoV-2 infection have broader neutralization against Omicron sub-lineages after the BA.5-bivalent booster. The authors reported that BA.2.75.2, BQ.1.1 and XBB.1 showed the greatest evasion of vaccine-elicited neutralization. In the four-dose parental mRNA vaccine group, the BA.5-bivalent-booster group, and the infected-then-bivalent boosted group, the neutralizing GMTs against BQ.1.1-spike viruses were reduced 4.3-, 4.1- and 5.8-fold, respectively, compared to neutralizing GMTs against BA.4/5.


• Miller et al. assessed the ability of BQ.1.1 to evade neutralizing antibodies (NAbs) produced by vaccination as well as previous SARS-CoV-2 infection. In individuals vaccinated and boosted with the monovalent mRNA BNT162b2 and no history of infection (n=16), median BQ.1.1 NAb titers were lower than median WA1/2020 (ancestral SARS-CoV-2) and BA.5 NAb titers by factors of 175 and 3, respectively. In two cohorts of individuals who received either the monovalent mRNA boosters (n=15) or the bivalent mRNA boosters (n=18), with most assumed to have had a SARS-CoV-2 infection at some point, median BQ.1.1 NAb titers were lower than median WA1/2020 and BA.5 NAb titers by factors of 53-80 and 7, respectively. The author’s data showed that BQ.1.1 can escape NAbs produced by vaccination and infection more effectively than BA.5. The authors concluded that these findings provide immunologic context for the rapid increase in BQ.1.1 prevalence in regions where BA.5 is dominant.31

• Davis-Gardner et al., used a live-virus focus neutralization test (FRNT) assay to compare the neutralizing activity of serum from individuals who received one monovalent booster (7-28 days after vaccination; n=12), two monovalent boosters (70-100 days after vaccination, n=12), or the bivalent booster (16-42 days after vaccination, n=12), against SARS-CoV-2 sub-lineages compared to an ancestral SARS-CoV-2 strain.32 Sera from recipients of one monovalent booster, two monovalent boosters, and one bivalent booster exhibited 39-fold, 34.5-fold, and 21-fold reduced neutralization activity against BQ.1.1, respectively, as compared to the ancestral SARS-CoV-2 strain. The authors conclude that recipients of one or two monovalent COVID-19 boosters had a dramatic decrease in neutralization activity against Omicron sub-lineages compared to WA1/2020, and individuals that received the BA.5-containing bivalent booster showed improved neutralizing activity against all Omicron sub-lineages, including BQ.1.1.

Testing and Whole Genome Sequencing (WGS) Surveillance
• The impact of BQ.1 and BQ.1.1 on the performance of current antigen and molecular testing methods is currently unknown, but testing has not been known to be significantly impacted by other Omicron sub-lineages with diverse mutation profiles. No impact is expected on the capability of WGS to detect BQ.1 or BQ.1.1 in the provincial lineage surveillance program as numerous cases have already been identified to date through current testing algorithms.
Implications for Public Health Practice

- In Ontario, for the week of October 30 to November 5, 2022, COVID-19 case numbers amongst those eligible for testing decreased by 19% to 7,959 cases from 9,797 cases the previous week. COVID-19 percent positivity decreased to 14.2% from 17.1% the previous week. Current projections suggest weekly case numbers may decrease over the 2 weeks following November 5, 2022.\(^{33}\)

- Despite current trends of a decrease in the total number COVID-19 cases and percent positivity, very limited data on BQ.1* disease severity suggest increased immune evasiveness and transmissibility potential may result in a rise in the number of severe cases. BQ.1* severity trends should be monitored closely, as an increase in severe cases may contribute to current capacity issues facing the Ontario health care system (i.e., surge in pediatric emergency department visits, admissions and ICU occupancy) due the early and rapid increase in circulation of other respiratory viruses in Ontario (e.g., RSV and influenza).\(^{34}\)

- COVID-19 vaccination remains an essential component of the public health response in the current context, with an emphasis on initiation and completion of a primary series in all (especially under-vaccinated) communities, as well as boosters for eligible individuals.\(^{35}\) Groups at higher risk for severe outcomes should be prioritized.

- 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 (e.g., BQ.1 and BQ.1.1). Growing evidence shows variable antibody cross-neutralization across SARS-CoV-2 variants after an infection, making it difficult to gauge the level of immunity against reinfection by future variants. The new BA.1 and BA.4/5 bivalent vaccines were only recently implemented in vaccination programs, and their effectiveness against BQ.1 and BQ.1.1 (a sub-lineage of BA.5) is still unknown. Therefore, 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 and ventilation will continue to be effective.

- With the transition to colder weather and increasing time spent in indoors, using 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; and hand hygiene.

- 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, the risks associated with post-acute COVID-19 syndrome,\(^{36-39}\) 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.
References


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