

### **EVIDENCE BRIEF**

# Risk Assessment for Omicron Sub-lineage BQ.1 and its Sub-lineages (BQ.1\*) (as of November 30, 2022)

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### Key Messages

- The proportions of COVID-19 cases that are of the BQ.1 and BQ.1.1 lineage continue to increase in Ontario, although current trends indicate a decrease or stabilization in the total number COVID-19 cases and percent positivity. The proportion of COVID-19 cases that are BQ.1 increased from 12.5% (November 6 to 12, 2022) to 14.3% (November 13 to 19, 2022), while that of BQ.1.1 increased from 7.1% (November 6 to 12, 2022) to 12.2% (November 13 to 19, 2022). By December 7, 2022, BQ.1 is projected to increase to 24.5% (95% Confidence Interval [CI]: 21.1% 28.3%) and BQ.1.1 is projected to increase to 21.8% (95% CI: 15.9% 27.6%).
- Evidence continues to show that BQ.1 and BQ.1.1 are highly immune evasive, which may be responsible for increased transmission of BQ.1 and BQ.1.1 relative to co-circulating sub-lineages. The contributions of increased transmissibility inherent in BQ.1 and its sub-lineages (indicated as BQ.1\*) and waning immunity, are unclear.
- It is uncertain whether the severity of disease caused by BQ.1\* differs from previous SARS-CoV-2 variants. Increases in bivalent booster vaccine uptake and immunity from previous infections may attenuate the risk of severe BQ.1\* cases.
  - If there is an increase in the number of COVID-19 cases due to the ability of BQ.1\* to evade the immune system, this may result in an increase in the absolute number of severe cases. This would 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 subvariant under monitoring, and therefore, necessary to continue monitoring.<sup>1</sup> The Omicron sub-lineage BQ.1 (a sub-lineage of BA.5) was given United Kingdom Health Security Agency (UKHSA) variant designation on October 28, 2022.<sup>2</sup> This evidence brief summarizes available information and evidence on the Omicron sub-lineage BQ.1 (alias of BA.5.3.1.1.1.1.1) and its sub-lineages (BQ.1\* e.g., BQ.1.1 [alias of BA.5.3.1.1.1.1.1]) that emerged since the last Public Health Ontario (PHO) BQ.1 and BQ.1.1 risk assessments, relevant to Ontario.<sup>3-5</sup>

### 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 17, 2022 and concluding November 30, 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 three previous risk assessments on BQ.1 and BQ.1.1.<sup>3-5</sup>

### **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 <u>Table 1</u>).

Issues	Risk Level	Degree of Uncertainty
Increased Transmissibility	High	Moderate
Increased Disease Severity	Unknown	High
COVID-19 Reinfection	High	Moderate
Lowered Vaccine Effectiveness Against Infection	High	Moderate
Impact on Testing	Unknown	High

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

### **Genomic Features**

The genomic characteristics of BQ.1 and BQ.1.1 have been described previously.<sup>3-5</sup> 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.<sup>6</sup> It is thought that some of these S protein mutational sites are prone to antibody evasion based on previous broad mutational scanning analyses.<sup>7</sup>

Scarpa et al., analyzed phylodynamics and structural aspects of BQ.1 compared to BA.5 (BQ.1 parent lineage), in order to assess the risk of BQ.1 expansion globally.<sup>8</sup> The authors conclude that their genetic and structural analyses suggest that BQ.1 does not show evidence of having high expansion capability, but note the need for continued monitoring.

## Epidemiology

#### Global

Globally, from October 14 to November 14, 2022, BQ.1 rose from 13.3% to 16.2% of cases.<sup>9</sup> The proportion of BQ.1 and BA.5 sub-lineages (with additional mutations e.g., R346X, K444X, V445X, N450D and/or N460X) continues to rise. As of November 21, 2022, there have been BQ.1\* samples from 81 countries uploaded to GISAID.<sup>10</sup>

#### Canada

- Nationally, the proportion of cases sequenced as BQ.1 decreased to 3.5% (October 30 to November 6, 2022) from 5.4% (October 23 to 30, 2022) and increased for BQ.1.1 to 8.4% (October 30 to November 6, 2022) from 5.9% (October 23 to 30, 2022).<sup>9,11</sup>
- The proportion of cases sequenced as BQ.1 in Ontario continues to increase. The proportion of BQ.1 cases rose from 12.5% (November 6 to 12, 2022) to 14.3% (November 13 to 19, 2022). By December 7, 2022, BQ.1 is projected to rise to make up 24.5% (95% CI: 21.1% 28.3%) of all sequenced cases. The weekly relative growth rate of BQ.1 is 1.62 (95% CI: 1.58 1.67) times that of BA.5.2.1.<sup>12</sup>
- The proportion of cases sequenced as BQ.1.1 in Ontario is also increasing. The proportion of BQ.1.1 grew from 7.1% (November 6 to 12, 2022) to 12.2% (November 13 to 19, 2022). By December 7, 2022, BQ.1.1 is projected to increase to 21.8% (95% CI: 15.9% 27.6%). The weekly relative growth rate of BQ.1.1 is 1.73 (95% CI: 1.66 1.79) times that of BA.5.2.1.<sup>12</sup>
- It is uncertain whether an increasing proportion of cases sequenced as BQ.1\* will translate into additional cases.

#### France

Based on sequences uploaded to GISAID, in France, between October 30 and November 30, 2022, there were 96 sequences of BQ.1  $(4.4\%)^{13}$ , and 709 sequences of BQ.1.1 (33.1%).<sup>14</sup> This is an increase in proportion from the previous month (September 29 to October 29, 2022) when there were 389 sequences of BQ.1 (2.7%),<sup>15</sup> and 2449 sequences of BQ.1.1 (17.4%).<sup>16</sup>

#### United Kingdom (UK)

In the UK, as of November 25, 2022, BQ.1\* represents greater than 40% of all sequenced UK samples. From October 30 to November 5, 2022, 38.3% of sequenced cases were BQ.1\* in the UK. BQ.1 has a 49% weekly growth rate relative to BA.5.2.<sup>10</sup>

#### United States (US)

In the US, estimated proportions of BQ.1 and BQ.1.1 among circulating variants the week November 20 to 26, 2022, were 27.9% (95% Prediction Interval [PI]: 25.5- 20.5%) and 29.4% (95% PI: 27 – 31.9%), respectively.<sup>17</sup> This is an increase from the previous week (November 13 to 19, 2022), when BQ.1 and BQ.1.1 were estimated to be 24.4% (95% PI: 22.2-26.7%) and 23.6% (95% PI: 21.6-25%), respectively.<sup>18</sup> During the same periods, BA.5 (the variant previously comprising the largest proportion of cases) dropped to 19.4% (95% PI: 17.1 -21.9%), from 27.5% (95% PI: 24.8-30.3%) the previous week.<sup>17,18</sup>

### **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 have increased transmissibility potential as their relative share of COVID-19 infections has been rising since early October, 2022.<sup>12,19,20</sup>

Wang et al., created spike (S) trimer proteins of Omicron sub-lineages (including BQ.1, BQ.1.1), and tested their binding affinities to human ACE2 (hACE2) using surface plasmon resonance (SPR).<sup>21</sup> Analysis of hACE2 binding affinities showed that the viral receptor affinities of BQ.1 and BQ.1.1 S proteins were comparable to that of BA.4/5, suggesting the mutations in BQ.1 and BQ.1.1 did not impact the S protein binding affinity to hACE2.

### **Disease Severity**

No new reports on the severity of disease caused by BQ.1 or BQ.1.1 were identified since the previous  $BQ.1^*$  risk assessments.<sup>3-5</sup>

### **COVID-19** Therapeutics

Since the previous Risk Assessments for Omicron Sub-lineages BQ.1 and BQ.1.1,<sup>3-5</sup> three new studies describing COVID-19 therapeutics were identified and are described below.

- Arora et al. compared neutralization of Omicron sub-lineages by individual monoclonal antibodies (mAbs) (casirivimab, imdevimab, bamlanivimab, etesevimab, cilgavimab, tixagevimab, amubarvimab, romlusevimab, adintrevimab, regdanvimab, bebtelovimab, sotrovimab) and combinations of mAbs (casirivimab/imdevimab, bamlanivimab/etesevimab, cilgavimab/tixagevimab, amubarvimab/romlusevimab) and found that BQ.1.1 was resistant to all individual mAbs and mAbs combinations tested.<sup>22</sup>
- Planas et al. analyzed the sensitivity of Omicron sub-lineages to mAbs and found that BQ.1.1 is resistant or only weakly sensitive.<sup>23</sup> Imdevinab, bebtelovimab and casirivimab were inactive against BQ.1.1. Cilgavimab and tixagevimab, alone or in combination (Evusheld), were also inactive against BQ.1.1. Sotrovimab was weakly active against BQ.1.1.

 Wang et al. evaluated the susceptibility of BQ.1, BQ.1.1, XBB, and XBB.1 to a panel of 23 mAbs. BQ.1.1 was greatly or completely resistant to most mAbs tested, including cilgavimab/ tixagevimab (Evusheld), sotrovimab, and bebtelovimab.<sup>21</sup>

### **Immune Evasion**

Evidence for real-world VE of bivalent mRNA COVID-19 vaccines against BQ.1 and BQ.1.1 is limited at this time, in part due to incomplete bivalent booster uptake and BQ.1\* not yet dominant in many settings where it is circulating.<sup>24</sup> Recent studies of immune evasion are summarized below.

- Sullivan et al., systematically reviewed recent primary research studies that reported neutralization of BQ.1.1 by plasma from vaccinated individuals with or without COVID-19 or after a recent Omicron infection alone, within six months.<sup>25</sup> Please see previous BQ.1 and BQ.1.1 PHO risk assessments and below for summaries of the primary studies described by Sullivan et al.<sup>3-5</sup> Among their observations, Sullivan et al. found that while there was a 20-fold reduction in neutralization by sera from individuals with 2-4 vaccine doses plus a breakthrough infection (cohort referred to as VaxCCP) against BQ.1.1 compared to an ancestral strain (WA-1), more than 96% of the boosted VaxCCP samples neutralized BQ.1.1. Their summary showed that four studies characterized BQ.1.1 virus neutralizations with plasma after the new BA.4/5 bivalent mRNA vaccine booster, with 88% (103/117 samples) neutralization activity within four weeks of bivalent booster.
- Wang et al., evaluated the neutralization of BQ.1 and BQ.1.1 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.<sup>21</sup> Cohorts included individuals with three doses of the original COVID-19 mRNA vaccines (n=15) or four doses (n=19), both termed three shots wildtype (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/45 breakthrough. The authors found that compared to D614G, the geometric mean 50% inhibitory dose (ID<sub>50</sub>) titres against BQ.1 and BQ.1.1 were <37-fold and <55-fold lower, respectively, in the three shots WT cohort, <43-fold and <81-fold lower, respectively, in the four shots WT cohort, <24-fold and <41-fold lower in the three shots WT plus bivalent cohort, <20fold and <29-fold lower in the BA.2 breakthrough cohort, and <13-fold and <31-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. Using their serum neutralization results, the authors created an antigenic map that suggested that BQ.1.1 has drifted away from BA.4/5 antigenically as much as BA.4/5 has drifted from the ancestral D614G.

- Tauzin et al., analyzed the sera from vaccinated individuals without a history of previous infection (n=15), infected after vaccination (n=15), as well as infected during the first wave of COVID-19 in early 2020 (n=15). This study examined each cohort's ability to recognize and neutralize Omicron variants, including BQ.1.1.<sup>26</sup> Four months after a third COVID-19 vaccine dose, recognition for BQ.1.1 S protein remained stable in the previous infection group. The BQ.1.1 S protein was less recognized than the S protein of the ancestral strain (D614G) or other Omicron subvariants, at both four weeks and four months. Using pseudoviral particles bearing different Omicron S proteins, four months after the third dose there were no significant differences between previously infected and breakthrough infected individuals. Four months after the third dose, weak or no neutralizing activity against Omicron subvariants S was detected in most naïve individuals. The authors conclude that the BQ.1.1 S protein is markedly less recognized and neutralized compared to ancestral and other Omicron subvariant S proteins tested, and individuals who have been infected before or after vaccination present better humoral responses than SARS-COV-2 naïve vaccinated individuals, suggesting that hybrid immunity generates better humoral responses against the subvariants tested.
- Planas et al., used a highly permissive cell line (IGROV-1) to amplify BA.2.75.2, BA.4.6 and BQ.1.1 isolates and analyze their sensitivity to sera from BNT162b2 (Pfizer-BioNTech) vaccine recipients, and to individuals with BA.1/BA.2 or BA.5 breakthrough infections.<sup>23</sup> Sera from individuals one month post third vaccine dose (n=18) and individuals four months post third dose (n=10) showed a low Effective Dose 50% (ED50) within the range observed for BA.5. Sera from individuals with BA.1/BA.2 breakthrough infections showed neutralizing antibody (Nab) titers were reduced 18-fold against BQ.1.1 (7x10<sup>2</sup>) compared to BA.1. Eight months after infection, titers against some variants, including BQ.1.1, showed a strong decline (ED50 of 2x10<sup>2</sup>). Using sera from individuals about one month after BA.5 infection (n=15), showed that neutralization of BA.2 breakthrough infection favors neutralization of BA.1 and BA.2 derived strains, relative to the BA.5 lineage, whereas BA.5 breakthrough infection triggers a better neutralization of viral isolates of the BA.5 lineage than BA.1/BA.2-derived strains.
- Pfizer-BioNTech released data on the effectiveness of its bivalent COVID-19 vaccine against currently circulating variants, including BQ.1 and BQ.1.1, compared to a fourth dose with the original vaccine (following three doses of the original vaccine).<sup>27</sup> The results are reported in the study by Zou et al.<sup>28</sup> Pfizer-BioNTech concluded that their bivalent Omicron booster induces a stronger immune response against circulating Omicron sub-lineages BQ.1.1, BA.4.6, BA.2.75.2 and XBB, compared to a fourth dose of its original vaccine. Zou et al., collected human sera from individuals >55 years of age and further divided them based on evidence of SAR-CoV-2 infection using viral nucleocapsid antibodies and RT-PCR test.<sup>28</sup>
  - For all participants, the fourth dose of monovalent BNT162b2 vaccine (n=40) induced a 2.3-, 2.1-, 1.8- and 1.5-fold geometric mean neutralizing titer fold rise (GMFR) for BA.4.6, BA.2.75.2, BQ.1.1 and XBB.1, respectively, whereas the bivalent BA.4/5 vaccine (n=38) induced 11.1-, 6.7-, 8.7- and 4.8-fold GMFRs, respectively.
  - For participants without SAR-CoV-2 infection history, the authors found the monovalent BNT162b2 vaccine (n=19) induced 2.5-, 2.0-, 1.5-, and 1.3-fold GMFRs for BA.4.6, BA.2.75.2, BQ.1.1 and XBB.1, respectively, whereas the bivalent BA.4/5 vaccine (n=20) induced 22.2-, 8.4-, 12.6- and 4.7-fold GMFRs, respectively.

 The authors conclude that the bivalent BA.4/5 vaccine consistently elicited higher neutralizing responses against BQ.1.1 than the original BNT162b2 monovalent vaccine when administered as a fourth dose booster, regardless of SARS-CoV-2 infection history. They add that individuals with SARS-CoV-2 infection history developed higher neutralizing titers than those without infection history after the fourth dose; and that for each Omicron sub-lineage they tested, the difference between the monovalent original and bivalent GMFR was greater for the group of sera without previous infection than the group with previous infection.

# 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 sublineages 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 Practice**

The implications for practice remain largely unchanged from the previous BQ.1\* Risk Assessment.<sup>4</sup>

- Despite current trends of a decrease or stabilization in the total number COVID-19 cases and percent positivity,<sup>29</sup> very limited data on BQ.1\* disease severity suggest increased immune evasiveness and transmissibility potential. Community-based public health measures and accelerated vaccination efforts can help protect Ontarians, reduce the risk of further strain on the health system, and limit disruption to critical infrastructure and in-person learning.
- 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 COVID-19 vaccine primary series in under-vaccinated communities and age groups (e.g., children <5 years of age), as well as a fall booster for eligible individuals.<sup>30</sup>
  - 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 emerging. 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.
- BQ.1\* severity trends should be monitored closely, as an increase in severe cases may impact the Ontario health care system (i.e., surge in pediatric emergency department visits, admissions and ICU occupancy) due to high circulation of other respiratory viruses in Ontario (e.g., RSV and influenza).<sup>31</sup>
- 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 infectionacquired and vaccine-acquired immunity, emerging evidence for the risks associated with postacute COVID-19 syndrome,<sup>32-35</sup> 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.

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