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EVIDENCE BRIEF

Risk Assessment for Omicron Sublineages BQ.1 and BQ.1.1 (as of Oct 5, 2022)

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Key Messages

- The earliest documented sequences of the BA.5 sublineages BQ.1 and BQ.1.1 date from mid-July 2022 and have been reported in multiple countries including Nigeria, United Kingdom (UK), Japan, United States (US), France, Belgium, Denmark, and Italy.[1] As of October 3, 2022, there has been 12 documented cases of BQ.1.1 in Canada.[2] As of October 7th, 2022, globally there are 326 sequences uploaded to GISAID.[3]

- While BQ.1 and BQ.1.1 currently comprise a small proportion of all COVID-19 cases globally, in some settings the proportion of cases is increasing at a rate suggestive of increased transmissibility relative to other circulating variants.

- The convergence of spike protein mutations found in BQ.1 and BQ.1.1 are a concern and merit ongoing monitoring due to their potential to cause significant immune escape.

- There is little evidence to inform the risks of BQ.1 and BQ.1.1 with respect to transmissibility, immune evasion, and disease severity. The risk to Ontario is currently highly uncertain.

Issue and Research Question

There are multiple PANGO sublineages 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 sublineages have their own sublineages (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 efficacy (VE) of these sublineages compared to other VOCs, it is important to monitor the potential impact they might have in Ontario's context.

This evidence brief summarizes available information and evidence on the Omicron sublineages 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) relevant to Ontario.[4] Based on its mutation profile, BA.5 sublineages (including BQ.1. and BQ.1.1) have been designated Omicron sublineages under monitoring by the World Health Organization (WHO).[5]

Methods

Public Health Ontario (PHO) Library Services has been conducting daily searches of primary and preprint literature on Omicron variants and sublineages 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 October 3rd, 2022 and concluding October 6th, 2022. English-language peer-reviewed and preprint records that described the Omicron variants BQ.1 and BQ.1.1 were included if identified.

Ontario Risk Assessment

The current risk of BQ.1 and BQ.1.1 with respect to transmissibility, reinfection, and breakthrough infection in Ontario is high with a high degree of uncertainty. The risk of severe disease is unknown. 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 Sublineages BQ.1 and BQ.1.1

Issues	Risk Level	Degree of Uncertainty
Increased Transmissibility	High	High
Potential for Increased Disease Severity	Unknown	High
Potential for Reduced Effectiveness of COVID-19 Therapeutics	Unknown	High
COVID-19 Reinfection	High	High
Reduced Vaccine Effectiveness Against Infection	High	High
Impact on Testing	Unknown	High

Genomic Features

- BQ.1 and BQ.1.1 are sublineages of the BA.5 variant, including the mutations seen in BA.5.3.1 with additional mutations on its receptor-binding domain (RBD) that suggest possible immune evasion.[6]

- 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.[6] It is thought that some of these S protein mutational sites are prone to antibody evasion based on previous broad mutational scanning analyzes.[7,8] In addition to the spike (S) protein, BQ.1 and BQ.1.1 share the NSP12 protein (RNA-dependent RNA polymerase) mutation Y273H (also annotated as ORF1b:Y264H), and BQ.1.1 also contains the NSP13 protein (helicase) mutation N268S (also annotated as ORF1b:N1191S).[4,9]

- The first BQ.1 and BQ.1.1 sublineage sequences reported in GISAID date from mid-July 2022 in Nigeria, and have since been reported in multiple countries including Nigeria, United Kingdom (UK), Japan, United States (US), France, Belgium, Denmark, and Italy.[9]

Epidemiology

- As of October 7th, 2022, in Ontario, the total number of sequenced cases for BQ.1 is 13, and for BQ.1.1 is four according to the GISAID website.[10,11]

- The University of Regina reported that BQ.1 and BQ1.1 were identified in Regina's wastewater in September 2022.[12]

- As of September 23, 2022, some have estimated that BQ.1 cases in the United Kingdom (UK) accounted for less than 0.5% of variant cases.[13] As of October 7th, 2022, there are 60 samples within the UK.[3]

- As of September 22, 2022 three cases of BQ.1 have been noted in New Zealand.[14]

Transmissibility and Infectivity

- Although there is limited information on BQ.1.1, informal analyses note that it appears to be highly transmissible as its relative share of COVID-19 infections has been at least doubling every week based on limited data from social media reports in North America and Europe, taking only 19 days to grow 8-fold from 5 sequences to 200 sequences.[15]

- BQ.1 is estimated to have a growth rate of 0.8 (0.06 – 0.10) and BQ.1.1 is estimated to have a 0.10 (0.05 – 0.16) growth rate per day according to the CovSpectrum website.[10,11] Informal analyses posted by media and on social media estimate BQ.1 to have a growth rate advantage of almost 15% per day as compared to BA.5.2, and a 14% per day growth rate advantage compared to BA.2.[16]

- In a preprint, Cao et al., investigated the relative human angiotensin converting enzyme 2 (hACE2) receptor binding affinity of several variants by evaluating hACE2 neutralizing potency against VSV pseudoviruses harboring the variant's mutated spike protein, based on the theory that higher neutralizing efficacy of soluble hACE2 indicates a higher ACE2-binding affinity (binding affinity refers to the strength of the binding interaction between the spike protein and hACE2 receptor, where high binding affinity may or may not lead to higher infectivity).[6] The authors report that the spike mutations seen in BQ.1 and BQ.2 do not lead to significant impairment of ACE2 binding affinity.

Disease Severity

- We did not come across any epidemiological reports on the severity of disease caused by BQ.1 and BQ.1.1. Current literature on these variants is limited to one preprint, discussed below.

COVID-19 Therapeutics

- Therapeutic neutralizing antibodies (NAbs) are one tool for reducing the severity of SARS-CoV-2 infection. Using VSV pseudoviruses harboring mutated spike proteins of various sublineages, it was reported that cilgavimab/tixagevimab (Evusheld) neutralizing activity is significantly impaired by the BQ.1 and BQ.1.1 S protein mutations R346T, K444T, and F486V.[2,6] Similarly, the neutralizing activity of casirivimab/imdevimab (REGEN-COV) and other investigational NAbs was also reduced compared to some BA.2 sublineages. Although noteworthy, detailed assessment of potential impacts on NAbs is beyond the scope of this risk assessment. This information comes from a pre-print and is not yet peer-reviewed.

- Nirmatrelvir/ritonavir (Paxlovid) is an antiviral drug used to treat mild-to-moderate COVID-19 in individuals at high risk for progression to severe disease. Nirmatrelvir is a novel protease inhibitor that binds to the main viral protease (M^{pro}) of SARS-CoV-2 to inhibit virus replication.[17] No literature reporting reduced activity of nirmatrelvir/ritonavir against BQ.1 and BQ.1.1 were identified.

Immune Evasion

- Cao et al., investigated how sublineages may escape the neutralization of plasma samples obtained from persons with various immune histories, specifically cohorts of individuals who received whole inactivated COVID-19 vaccine (CoronaVac), with or without history of breakthrough infection by BA.1, BA.2, or BA.5.[6] Convalescent samples were collected around four weeks after hospital discharge, and plasma samples from vaccine recipients were collected two weeks after their third dose. Authors found:

    - BQ.1.1 caused a reduction in the 50% neutralization titer (NT50) of the plasma from vaccine recipients (including one booster), BA.1 breakthrough infection, BA.2 breakthrough infection, and BA.5 breakthrough infection by 3.0-, 3.9-, 4.4- and 6.4-fold compared to BA.5, respectively. Lower NT50 values imply higher likelihood to evade immunity (neutralizing antibodies).

    - The authors suggest that that immunity induced by previous Omicron sublineages and vaccination by CoronaVac (not distributed in Canada) may not achieve as broad a protection against BQ.1.1 infection compared to protection against BA.5 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 not known, 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.

Table 2: Preliminary Public Health Ontario Genomics Data on Omicron BQ.1 Sublineages as of October 7th, 2022

BQ.1	BQ.1.1	BQ.1.2	BQ.1.3	BQ.1.4
52	12	7	2	1

* Numbers are based on mutation profiles; these subvariants are not being designated as official lineages in Pango version.
*Numbers are of October 7th, 2022 and may change as databases are updated

Implications for Public Health Practice

- The emergence of BQ.1 and BQ.1.1 in Canada and other parts of the world warrant a cautious approach and ongoing monitoring of their risk in Ontario.
- Based on experience with previous Omicron sublineages with increased transmissibility (e.g., BA.2 and BA.5), if BQ.1 and BQ.1.1 have increased transmissibility compared to the most frequently detected sublineages at present, this could lead to a risk of increased COVID-19 cases during the fall, test positivity, and province-wide wastewater signals. Studies on the vaccine escape potential of BQ.1 and BQ.1.1 with the new bivalent COVID-19 vaccines, immune escape from previous infection, and treatment resistance to COVID-19 therapeutics are needed to inform future risk assessments for Ontario.
- Based on evidence from previous SARS-CoV-2 variants, while current COVID-19 vaccines and previous SARS-CoV-2 infection provide protection against severe disease, they do not provide 100% sterilizing immunity (i.e., full protection from infection or reinfection) or prevent onward transmission.[18]

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