

EVIDENCE BRIEF

SARS-CoV-2 Omicron Variant Sub-Lineages BA.4 and BA.5

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Key Messages

- At this time, BA.4 and BA.5 are two of 75 sub-lineages of the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) B.1.1.529 (Omicron) variant of concern,¹ with just over 200 sequences reported globally.^{2,3}
- Early data from the National Institute for Communicable Diseases (South Africa) noted that the portion of BA.4 and BA.5 had risen to 44% of genomes sequenced in April 2022 compared to approximately 16% in March in South Africa.⁴
- The current risk of importation of BA.4 and BA.5 in Ontario is low given the low global prevalence and that no BA.4 or BA.5 sequences have been detected in Canada so far. However, the risk of sustained transmission in Ontario is yet to be defined considering the limited available evidence on these two sub-lineages to inform the risk assessment. The overall risk assessment may change as new evidence emerges.

Issue and Research Question

- Seventy-five sub-lineages under the parent SARS-CoV-2 B.1.1.529 (Omicron) variant of concern have been identified globally to date, with the most prevalent sub-lineages currently being B.1.1.529.1.1 (BA.1.1), B.1.1.529.1 (BA.1), B.1.1.529.2 (BA.2), and B.1.1.529.2.9 (BA.2.9).¹ More sub-lineages are likely to develop over time as the SARS-CoV-2 virus continues to evolve.
- In the week of March 27 to April 2, 2022:
 - BA.2 was the most prevalent sub-lineage (80.5%) in Ontario, followed by BA.1.1 (17.9%), out of the 3,298 COVID-19 isolates sequenced.⁵
 - BA.2 was the most prevalent (32.8%) sub-lineage in Canada, followed by BA.1.1 (18.6%), out of the 3,573 COVID-19 isolates sequenced.⁶
- The emergence of SARS-CoV-2 variants is generally a result of mutations that occur over time as the virus replicates in host cells. As with many RNA viruses, SARS-CoV-2 is prone to frequent mutations. The ongoing high rates of SARS-CoV-2 community transmission in the context of Omicron's emergence have led to concerns for novel variants emerging with different transmissibility, virulence, and/or immune evasion potential from prior infection and/or vaccination.⁷
- This evidence brief summarizes available information and evidence on the Omicron variant sub-lineages BA.4 and BA.5 relevant to the risk of transmission in Ontario.

Methods

From January 17, 2021, to April 26, 2022, Public Health Ontario (PHO) Library Services conducted daily searches of primary and preprint literature using the MEDLINE database (search strategies available upon request). In addition, PHO performed grey literature searches daily using news feeds in the Shared Library Services Partnership. English-language peer-reviewed and non-peer-reviewed (preprint) records that described COVID-19 variants were included.

Genomic Features

- The potential immune escape associated with mutations (L452R and F486V) in the spike protein of BA.4 and BA.5 prompted the World Health Organization to monitor these two recently added sub-lineages.⁸ The majority of BA.4 and BA.5 sequences have the 69-70 deletion response for S gene target failure (SGTF) in some molecular assays, and ultimately may be useful for surveillance purposes in regions where BA.2 is dominant, as BA.2 does not contain this deletion.⁸

BA.4

- Classified as a variant (V-22APR-03) in the United Kingdom (UK) on April 6, 2022 on the basis of possible biologically significant mutations in the spike protein, BA.4 shares all mutations and deletions with BA.2 and also contains the following:⁹
 - Spike protein: 69/70 deletion, L452R, F486V, Q493 (wild type)
 - Beyond the spike protein:
 - NSP4: L438F reverted to wild type
 - ORF 6: D61 (wild type)
 - ORF 7b: L11F
 - N: P151S

BA.5

- Classified as a variant (V-22APR-04) in the UK on April 6, 2022, BA.5 shares the same mutations and deletions as BA.4 and also has the following mutations outside the spike protein:⁹
 - M: D3N
 - ORF 7b: L11 (wild type)
 - N: P151 (wild type)
 - synonymous SNPs: A27038G, C27889T

Epidemiology

BA.4

- As of April 26, 2022, 222 BA.4 sequences have been reported in at least 10 countries: South Africa, Denmark, United Kingdom, Belgium, United States, Austria, Australia, Botswana, France, Switzerland.² In addition, media have reported 3 cases in Israel as of April 25, 2022.¹⁰
- The prevalence of BA.4 in South Africa increased from 0.34% (4/1,194) of all sequenced SARS-CoV-2 lineages in February 2022 to 28% (59/213) in April 2022.⁴

BA.5

- As of April 26, 2022, 99 BA.5 sequences have been reported in at least nine countries/jurisdictions: South Africa; Germany; Portugal, United Kingdom, United States, France, Denmark, Hong Kong and Spain.³ In addition, media have reported 2 cases in Israel as of April 25, 2022.¹¹
- The prevalence of BA.5 in South Africa increased from 0.08% (1/1,194) of all sequenced SARS-CoV-2 lineages in February 2022 to 16% (35/213) in April 2022.⁴

Transmissibility

- The United Kingdom Health Security Agency noted that the geographic spread of BA.4 around the world suggests its potential for successful transmission.⁹

Severity, Immune Evasion

- There is insufficient evidence to inform how infections with BA.4 or BA.5 may differ from those with the BA.2 sub-lineage in clinical severity and ability to evade immunity from natural infection and/or vaccination.
- Limited data to date have not detected any changes in disease severity in BA.4 and BA.5 despite an observed increase from 16% of the 1,154 genomes sequenced in March 2022 to 44% of the 213 genomes sequenced in April 2022 in South Africa.^{4,12,13}

Ontario Risk Assessment

- The current risk of transmission of the BA.4 and BA.5 sub-lineages in Ontario is low with a high degree of uncertainty. The prevalence of BA.4 and BA.5 can rise with conditions that lead to the spread of the SARS-CoV-2 virus in the population including suboptimal vaccine (and booster) coverage, waning immunity, and the ability of the Omicron variant of concern to escape immunity from natural infection and/or vaccination. In addition, SARS-CoV-2 intrinsic factors (e.g., increased transmissibility, reduced transmission competition from other circulating strains) as well as a lack of preventive measures and layers of protection to reduce transmission may contribute to risk of transmission. The overall risk assessment may change as evidence emerges (see [Table 1](#)).

Table 1. Risk Assessment for Omicron Sub-Lineages BA.4 and BA.5

Issue	Risk Level	Degree of Uncertainty
Importation in Ontario	Moderate	High
Increased Transmissibility	Insufficient information	High
Increased Disease Severity	Insufficient information	High
Re-infection	No information	High
Reduced Vaccine Effectiveness/Breakthrough Infections	No information	High
Impacts on Testing/Surveillance	Insufficient information	High

Implications for Public Health Practice

- The risk of mutation occurrence in the SARS-CoV-2 virus increases with ongoing transmission, and the risk of new sub-lineages emerging remains very high given the high transmissibility and immune evasion of the currently dominant Omicron variant, the current high levels of Omicron transmission in the province and globally, and the lifting of public health measures across Canada and globally.
- A comprehensive surveillance strategy including genomic sequencing for prompt identification of new variants that facilitates timely public health interventions to reduce their local introduction and spread is important to mitigate the emergence and spread of new variants.
- Due to limitations of individual public health measures (i.e., vaccination, masking, measures to reduce contacts), an approach that layers various measures can be used to mitigate community spread, including:
 - Achieving high, equitable vaccination (including primary series and booster doses) coverage globally as quickly as possible. Since COVID-19 vaccination and previous SARS-CoV-2 infection do not provide sterilizing immunity, a COVID-19 strategy that relies entirely on vaccination and previous infection will not eliminate transmission in the community.
 - Staying home when sick and when potentially infectious to others; wearing a well-fitting mask in indoor public settings; maintaining good ventilation in indoor spaces; practicing physical distancing, reducing contacts and avoiding crowded, closed indoor spaces; and practicing respiratory etiquette and washing hands should continue to be promoted for all.

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