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EVIDENCE BRIEF

SARS-CoV-2 Omicron Variant Sub-Lineages BA.4 and BA.5: Evidence and Risk Assessment (up to date as of June 23, 2022)

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Key Messages

- The proportion of SARS-CoV-2 whole genome sequencing (WGS) samples identified as BA.4 and BA.5 is increasing in many jurisdictions, including Ontario, while the proportion of BA.2 and most BA.2 sub-lineages is declining. BA.5 and BA.4 are expected to soon become the dominant variants in Europe and the United States (US) and lead to increasing COVID-19 cases due to increased transmissibility and immune evasion.
    - In South Africa and Portugal, BA.5 and BA.4 waves peaked at 128.0 cases per million population (7-day moving average daily new confirmed COVID-19 cases) within three to four weeks of detection, with a test positivity rate of 25.47%.[1] However, their epidemiology may not be generalizable to the Ontario context.
- The weekly growth rates of BA.4 and BA.5 in Ontario are approximately 2.72 and 3.11 that of BA.2, respectively. In Ontario, BA.5 is projected to reach 52.9% of cases by June 29, 2022 and will likely increase the number of cases. The prevalence of BA.4 is projected to remain below 15%. Hospitalization and mortality are likely to increase due to the volume of cases, but there is uncertainty about the extent of the increase since the severity of BA.4 and BA.5 cases is unclear.
- Among those eligible for molecular testing in Ontario, the number of positive cases continues to decline, however there are early signs of increasing positivity from wastewater surveillance programs and early evidence of plateauing test positivity.
- Current COVID-19 vaccines and previous SARS-CoV-2 infection do not provide sterilizing immunity (i.e., full protection from infection or reinfection). Emerging evidence that SARS-CoV-2 reinfection adds risk of all-cause mortality, hospitalization and adverse health outcomes during acute and post-acute SARS-CoV-2 reinfection, and that the risk and burden may increase in a graded manner according to the number of infections, suggests preventing reinfection could reduce overall SARS-CoV-2 burden of death and disease in Ontario.
    - To minimize morbidity and mortality, as well as societal disruption, current public health responses could be augmented based on the epidemiological context, using interventions that reduce the risk SARS-CoV-2 transmission. Public health measures may include staying home when sick or with symptoms of COVID-19, ventilation, use of outdoor spaces and modes of transportation, and wearing a well-fitted mask whenever feasible when indoors in closed spaces, crowded places, and close contact settings (e.g., public transit).

Issue and Research Question

There are multiple PANGO sub-lineages associated with the B.1.1.529 (Omicron) variant of concern (VOC). The main BA.1, BA.2, BA.3, BA.4, and BA.5 sub-lineages may also 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). 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. This evidence brief updates the Public Health Ontario (PHO) BA.4 and BA.5 report published on SARS-CoV-2 Omicron variant sub-lineages BA.4 and BA.5.

Methods

PHO Library Services conducted daily searches of primary and preprint literature 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. Formal critical appraisal of published and preprint COVID-19 literature is out of scope for this PHO risk assessment. PHO performed grey literature searches daily using various news feeds and custom search engines. English-language peer-reviewed and preprint records that described COVID-19 variants were included. Sections from prior risk assessments for which there is no new literature of note are removed from the current update.

Ontario Risk Assessment

The current risk of BA.4 and BA.5 transmissibility in Ontario is high with a low degree of uncertainty. The risk of severe disease is low with a high degree of uncertainty. The risks of reinfection and of breakthrough infection are high with a moderate degree of uncertainty, given the evidence that BA.4 and BA.5 may evade neutralizing antibodies acquired by vaccination or generated from previous BA.1.1 infection, and to a lesser extent BA.2 infection. The risk of impact on testing is low with a moderate degree of uncertainty. The overall risk assessment may change as new evidence emerges (see Table 1).

Additional Considerations

- Post-COVID-19 sequelae (PACS or "long-COVID") are not included in the risk assessment table, but several reviews report that the sequelae and their incidence vary.[2-6] If considering PACS in a population or individual risk assessment, the risk could be moderate with a moderate degree of uncertainty. Preventing high levels of COVID-19 community transmission may mitigate the incidence of PACS and its long term impacts.

- Emerging evidence indicates that reinfection adds risk of all-cause mortality, hospitalization and adverse health outcomes during acute and post-acute SARS-CoV-2 reinfection. Additionally, the risk and burden may increase in a graded manner according to the number of infections, which suggests preventing reinfection could reduce overall SARS-CoV-2 burden of death and disease.[7] Current COVID-19 vaccines and previous SARS-CoV-2 infection do not provide sterilizing immunity (i.e., full protection from infection or reinfection).

- Even if BA.4 or BA.5 are found to be no more severe than BA.1 and BA.2, the increased transmissibility potential of BA.4 and BA.5 suggests that the total number of cases (and potentially the total number of severe cases) would be expected to rise. High vaccine uptake, partial immunity from previous infections, and having additional public health measures in place may attenuate an increase in cases from BA.4 and BA.5, and their impact in Ontario.

- The emergence of new Omicron sub-lineages in Ontario introduces uncertainty until more is known about their transmissibility, severity, immune evasion, and detection potential in the Ontario context.
    - Although South Africa's progress through its combined BA.4 and BA.5 wave is ahead of the rest of the world, the epidemic curve experienced in South Africa may not be generalizable to the Ontario context due to differences in history of previous SARS-CoV-2 infection, vaccination status, public health measures, as well as age distribution of the population.[8] Portugal's recent experience with BA.5 is more applicable to the Ontario context but still has limitations.
- COVID-19 hospitalizations have decreased after the decline of the BA.1 wave; however, health care worker absences, shortages, and impacts to scheduled care may remain challenging during this current period of prolonged community transmission. Transmission of other respiratory viruses (e.g., influenza) is another consideration for health care system recovery and capacity planning in Ontario.[9]
- Although summers have been lower transmission periods for COVID-19 in Ontario during the past two years, and people can gather outdoors which lowers the risk of transmission events, key considerations for increased risk in Ontario at this time include (in no particular order): first, SARS-CoV-2 VE against infection has been waning in individuals last vaccinated more than four months ago, and more so in individuals who received two doses compared to three doses (based on studies from earlier Omicron waves); second, BA.4 and BA.5 are more transmissible than earlier sub-lineages and their proportional representation in Ontario is increasing according to WGS surveillance activities; third, although strains may share a common ancestor and sub-lineage, there can be significant point mutations and antigenic changes between evolving strains of the same sub-lineage (e.g., BA.2.12 versus BA.2.12.1, BA.2 versus BA.4/5), resulting in variable antibody cross-neutralization after an infection. As a result, reinfections and breakthrough infections may result in a resurgence of COVID-19.

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

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

Genetic Features

- BA.5 and BA.4 have the same spike (S) gene mutation profile, but have different sets of mutations in the rest of their genome.[10]
- Signature mutations in the S protein of BA.4 and BA.5 compared to BA.2 include Δ69-70, L452R, F486V and R493Q.1.[10,11]
    - Additional mutations present in BA.4 but not in BA.5 include ORF1a:Δ141/143, ORF6: D61L, ORF7b:L11F, and N:P151S.
    - A mutation present in BA.5 but not BA.4 is M:D3N.
    - A sub-lineage of BA.5, BA.5.1, has been described with an additional mutation ORF10:L37F.

Epidemiology

Globally

- As of June 19, 2022, 11,376 BA.5 sequences have been reported in at least 59 countries, and 10,812 BA.4 sequences have been reported in at least 57 countries.[12,13] BA.5 represents 24.78% of all Omicron lineages submitted to GISAID as of June 197, 2022, with an increase of 8.67% from the week ending June 12 to the week ending June 19, 2022.[14] Meanwhile, BA.4 represents 8.62% of all Omicron lineages submitted to GISAID as of June 19, 2022, with an increase of 2.35% from the week ending June 12 to the week ending June 19, 2022.[14] An increase in COVID-19 cases, without concurrent increase in hospitalizations and intensive care unit (ICU) admissions, was seen in several WHO regions that reported an increase in BA.5 and BA.4 prevalence; however, hospitalization and ICU admission are lagging indicators.[14]
- In **South Africa**, BA.5 was first detected in January 2022.[15] BA.5 comprised 3% of all variants sequenced in March 2022. By April and May 2022, the proportion of BA.5 among all sequenced variants rose to 19% and 26%, respectively.[16] BA.4 was first detected in February 2022.[15] BA.4 comprised 13% of all variants sequenced in March 2022. By April and May 2022, the proportion of BA.4 among all sequenced variants rose to 54% and 68%, respectively.
    - BA.4 and BA.5 together became dominant (73%) in April, and comprised 94% of all sequenced samples in May.
    - From May 11, 2022, test positivity rates for COVID-19 have been declining from 25.3% to 4.1% on June 20, 2022,[17] compared to a peak test positivity rate of 35.1% on December 21, 2021 during the BA.1 wave.[1] Epidemiological trends suggest the BA.4 and BA.5 wave in South Africa has passed its peak.
        - The 7-day average test positivity on June 22, 2022 was 7.6%, which was lower than the day before (8.1%).[17]
        - Weekly incidence risk reported by all nine provinces have been declining by 45.2% for the week ending June 4, 2022,[18] and by 35.1% for the week ending June 11, 2022.[19]

    - Weekly hospitalization risk has been declining by 41% for the week ending June 4, 2022,[20] and by 33% for the week ending June 11, 2022.[21]

- **Portugal** was the first European Union/European Economic Area (EU/EEA) country to report a significant increase in BA.5 case counts, and BA.5 comprised 88% of cases based on random sample sequencing in the week of June 6-12, 2022.[22] The relative frequency of BA.2, BA.2.12.1, and BA.2.35 have been declining since BA.5 relative frequency began increasing. Portugal's most recent wave began the first week of June 2022. In recent weeks, case counts have stabilized and decreased, suggesting that the BA.5 peak was reached in the region.[23] Meanwhile, the European Centre for Disease Prevention and Control epidemiological update on June 13, 2022 reported that BA.4 and BA.5 are expected to soon become the dominant sub-lineages in the EU/EEA, likely resulting in increasing cases in these regions.[10]

- In the **United States**, the estimated proportions of BA.5 and BA.4 among circulating variants have been increasing, from <0.4% (95% CI: 0.2%–0.7%) for BA.5 and <0.6% (95% CI: 0.5%–0.8%) for BA.4 the week ending May 7, 2022, to 23.5% (95% PI: 20.3%–27.0%) for BA.5 and 11.4% (95% PI: 8.8%–14.5%) for BA.4 the week ending June 18, 2022.[24] During the same period, the estimated proportion of BA.2 dropped from 53.7% (95% CI: 50.7%–56.7%) to 9.1% (95% PI: 7.9%–10.5%), while that for BA.2.12.1 rose from 44.5% (95%PI: 41.5%–47.6%) to 64.2% (95% PI: 59.9%–68.3%) the week of June 11, 2022, then decreased to 56% (95% PI: 51.4%-60.5%).[24] The 7-day moving average cases has risen from 71,131 to 98,303 per 100,000 population.[25]

- The **UK** Health Security Agency (UKHSA)'s June 22, 2022 Risk Assessment categorized the overall growth advantage of BA.4 and BA.5 as the highest level (red) with high confidence.[26] On May 18, 2022, BA.4 and BA.5 were classified as variants of concern based on a growth advantage which may lead to increased transmission in the community. As of June 15, 2022, BA.4 and BA.5 were estimated to represent 22.3% (95% CI: 16.3%–28.8%) and 39.5% (95% CI: 32.2%–51.3%), respectively, of the sequenced samples in the UK (not weighted by the population size of the constituent regions).[27] The 7-day moving average cases has risen from 129.53 to 179.06 per 1,000,000 population from May 18, 2022 to June 15, 2022.[1] BA.5 was projected to be dominant in all UK regions by the week ending June 19, 2022.[27]

Canada and Ontario

- WGS surveillance across **Canada** indicated that BA.5 and BA.4 represented 6.5% and 3.9% respectively of the samples sequenced for the week of May 29–June 4, 2022, up from 3.0% and 3.1% respectively the week before (data still accumulating).[28]

- Ontario case counts are based on positive molecular tests from populations eligible for molecular testing and therefore remain an underestimate of total COVID-19 cases in the province. Representative WGS surveillance is also only performed on cases with positive molecular tests. Thus, triangulation across indicators can provide greater confidence in trends.

- For the week of June 5-11, 2022, BA.2.12.1 was the most prevalent lineage (42.0%), followed by BA.2 (21.3%), BA.5 (14.4%), BA.2.3 (5.9%) and BA.4 (5.8%).[29]

- The proportion of **BA.5** is increasing in Ontario, from 6.8% (May 29–June 4, 2022) to 14.4% (June 5–11, 2022) with a weekly growth rate 3.11 (95% confidence interval [CI]: 2.79–3.48) times that of BA.2 over the past 12 weeks.[29] Based on Nowcast modelling, the proportion of BA.5 is projected to reach 52.9% by June 29, 2022 (95% CI: 41.0%–64.4%).

- The proportion of **BA.4** is increasing in Ontario, from 3.3% (May 29–June 4, 2022) to 5.8% (June 5–11, 2022), with a weekly growth rate 2.72 (95% CI: 2.36–3.12) times that of BA.2 over the past 12 weeks.[29] Based on Nowcast modelling, the proportion of BA.4 is projected to reach 14.1% by June 29, 2022 (95% CI: 7.7%–23.9%).

    - The number of reported cases in Ontario declined for an eighth week in a row to 4,350 cases the week of June 11–18, 2022, down from 5,050 the previous week.[30] Percent test positivity began slowly declining in mid-April 2022.[31] There are early signs of a potential plateauing in recent weeks, but percent positivity remains relatively high compared to earlier periods of the pandemic (e.g., June 13, 2022, PHO reported 6.9% test positivity).[30]

    - Hospitalizations, intensive care unit (ICU) admissions and deaths are lagging indicators, often occurring days or weeks after cases are initially reported to public health units, and are subject to reporting lags (i.e., reporting to public health units or entry into the Public Health Case and Contact Management Solution [CCM]). Therefore, trends may change and may not be fully representative of the most up-to-date situation. Hospital admissions and deaths continue to decrease from their wave six peaks. Congregate care and congregate living settings reported more outbreaks the week of June 11–18, 2022 compared to the previous week.

    - On June 23, 2022, the Ontario Dashboard indicated that COVID-19 cases, percent positivity, hospital occupancy, and ICU occupancy were decreasing, but the province-wide wastewater signal showed an increasing trend suggesting community transmission may be increasing again.[32] Uncertainty remains about whether these trends will continue.

Transmissibility

There is epidemiological,[33,34] molecular,[35,36] and *in vitro*[37] evidence that suggest a growth advantage for BA.5 and BA.4 compared to BA.1 and BA.2.

- BA.4, and BA.5 share a signature S protein mutation, L452R, that is thought to confer increased transmissibility through both higher cell fusogenicity and immune escape characteristics.[35,36]

- Using a multinomial logistic regression model on SARS-CoV-2 data from the two most populous provinces in South Africa (Gauteng and KwaZulu-Natal), Tegally et al. estimated a daily growth advantage of 0.12 (95% CI: 0.09–0.15) for BA.5, and 0.08 (95% CI: 0.07–0.09) for BA.4, compared to BA.2 in South Africa in April 2022. The authors postulated that the transmission advantage may be due to waning immunity (particularly that acquired from BA.1 infection), given that the transmission advantage became apparent approximately four months from the start of the Omicron wave in South Africa.[33] Note that a daily selective advantage of 0.12 is equivalent to a weekly relative growth rate of 2.32 [$e^{0.12 * 7}$].

- After adjusting for geographic and temporal variation in case numbers, sequenced data in the UK sampled between April 8 and June 8, 2022 showed a median logistic growth rate of 0.758 for BA.4 compared to that for BA.2, and 0.656 per week for BA.5 compared to BA.2.[27]

- Cell culture experiments showed that pseudoviruses bearing the BA.4/5 S protein (the S protein is identical between both sub-lineages) replicate 34-fold ($P < 0.0001$) more efficiently in human alveolar epithelial cells than BA.2 pseudovirus.[37]

Disease Severity

It remains unclear if BA.4 or BA.5 cause more severe disease than BA.1.1 or BA.2.

- A large study using databases from the US Department of Veterans Affairs reported that individuals with SARS-CoV-2 reinfection(s) exhibited increased risks of all-cause mortality (Hazard Ratio [HR] 2.14; 95% CI: 1.97, 2.33), hospitalization (HR 2.98 (2.83, 3.12), and several prespecified sequelae (e.g., pulmonary disorders, HR 2.49 [2.34, 2.65]; extrapulmonary organ systems including cardiovascular disorders, HR 2.36 [2.23, 2.51]; coagulation and hematologic disorders, HR 2.22 [2.05, 2.41]), compared to individuals with a first infection.[38] Risks were most pronounced in the acute phase, but persisted post-acute reinfection, and risks for most sequelae remained evident at six months. Risk and burden increased in a graded fashion according to the number of infections. The study was not specific to BA.4 or BA.5 dominant periods, but the increased transmissibility and immune evasion of BA.4 and BA.5 may increase the number of cases in Ontario, including among those previously infected.

- A report from June 1, 2022, on Portugal's BA.5 wave indicated that the ratio between the number of hospitalized cases and notified infections was 0.09, suggesting a lower severity of infection as compared to previous COVID-19 waves (> 1.0 during the Alpha wave in the Spring of 2021, and between 0.3 and 0.7 during the Delta wave in the summer of 2021), but similar to that observed since the beginning of 2022 (during the BA.1 and BA.2 waves).[39] Mortality from all causes, however, is above the expected value for this time of the year, suggesting an excess of all-cause mortality.

- The UK is monitoring a small increase (0.3%) in hospital admission rate with COVID-19 across all age groups since April 2022; the reason for the rise has not been determined as yet.[27]

Immune Evasion

National surveillance data of health care workers in the UK have noted a slight increase in reinfections in June 2022 (even with prior Omicron infections). However, breakdowns on reinfection rates by the variants were not reported.[27]

Preliminary hospital-based and community-based data from April 18 to May 29, 2022 did not identify significant changes in vaccine effectiveness against infection. Among breakthrough infections after 2, 3 or 4 doses of COVID-19 vaccine:[26,27]

- Adjusted odds ratio of BA.4 vs. BA.2 = 1.13 (95% CI: 0.88–1.44)
- Adjusted odds ratio of BA.5 vs. BA.2 = 0.83 (95% CI: 0.64–1.08)

BA.4/5 pseudovirus substantially escape neutralizing antibodies induced by both vaccination and infection (in particular BA.1.1).[40-42] Booster vaccination may offer more protection against BA.4/5 pseudovirus than prior BA.1 infection.[43]

- Khan et al. reported that immunity by BA.1 infection may not protect against symptomatic BA.4/5 infections, in particular in unvaccinated individuals.[41]
    - 50% focus reduction neutralization test ($FRNT_{50}$, or the inverse of the dilution for 50% neutralization) by BA.1 convalescent sera of vaccine-naïve individuals (n = 24):
        - Reduced by 7.6-fold (95% CI 4.9–12.0; P < 0.001) against **BA.4** isolated from clinical samples compared to BA.1.
        - Reduced by 7.5-fold (95% CI 4.4–12.5; P < 0.001) against **BA.5** isolated from clinical samples compared to BA.1.
    - $FRNT_{50}$ by breakthrough BA.1 sera (n = 15):
        - Reduced by 3.2-fold (95% CI 2.3–4.4; 0.001 < P < 0.01) against BA.4 compared to BA.1.
        - Reduced by 2.6-fold (95% CI 1.8–3.7; 0.001 < P < 0.01) against BA.5 compared to BA.1.
    - Absolute neutralization levels in unvaccinated vs. vaccinated individuals against BA.4/5 was reduced approximately 5-fold.
- Hachmann NP et al. reported that **BA.4/5** pseudovirus substantially escape neutralizing antibodies induced by vaccination and infection.[40]
    - Median neutralizing antibody titres to BA.4/5 in 3-dose vaccinees (Comirnaty Pfizer-BioNTech COVID-19 vaccine; n = 27) at two-week post-booster:
        - Reduced by 21.0-fold compared with wild-type WA1/2020.
        - Reduced by 3.3-fold compared to BA.1.

- Median neutralizing antibody titres to BA.4/5 in sera of Omicron breakthrough convalescents (n = 27, including 1 vaccine-naïve convalescent; median days post diagnosis = 29):
    - Reduced by 18.7-fold compared to VA1/2020.
    - Reduced by 2.9-fold compared to BA.1.

- In vaccine-naïve BA.1 convalescent sera, Willett BJ et al. reported that vaccination improves neutralizing ability against BA.4/5.[42]
    - Neutralizing titres by vaccine-naïve BA.1 convalescent sera
        - Reduced by 23-fold against pseudoviruses **BA.4/5** compared to BA.1.
        - Reduced by 7.6-fold against pseudoviruses BA.2 compared to BA.1.
    - Neutralizing titres by breakthrough infection sera from hospitalized patients:
        - Reduced by 3.3-fold against BA.4/5 pseudovirus compared to BA.1 by sera from hospitalized BA.1 breakthrough infections (5/6 individuals had had 3 vaccine doses; samples collected 18–27 days post diagnosis or post symptom onset).
        - Reduced by 5.5-fold against BA.4/5 compared to BA.2 by sera from hospitalized BA.2 breakthrough infections (5/6 individuals had had 3 vaccine doses; samples collected 9–25 days post diagnosis or post symptom onset).

- Qu P et al. reported booster vaccination may offer more protection against BA.4/5 pseudovirus than prior BA.1 infection.[43]
    - Neutralization titres against **BA.4/5** vs. D614G strain:
        - Reduced by 21.9-fold (n = 15; P < 0.0001) by 2-dose mRNA vaccinee sera (4 with Moderna Spikevax™; 11 with Comirnaty).
        - Reduced by 4.0-fold (n = 15; P < 0.0001) using 3-dose mRNA vaccinee sera (4 with Moderna Spikevax™; 11 with Comirnaty).
    - Neutralization titres against BA.4/5 vs. D614G strain by Delta convalescent sera:
        - Reduced by 4.8-fold (n = 12; P < 0.01) in unvaccinated ICU patients.
        - Reduced by 5.2-fold (n = 6; P < 0.01) in vaccinated ICU patients.
    - Neutralization titres against BA.4/5 vs. D614G strain by BA.1 convalescent sera:
        - Reduced by 1.4-fold (n = 15; P < 0.01) in unvaccinated non-ICU patients.
        - Reduced by 4.7-fold (n = 7; P < 0.001) in 3-dose vaccinated non-ICU patients.

- Moderna announced that its bivalent vaccine (mRNA-1273.214) boosted neutralizing titers against BA.4/BA.5 by 5.4-fold (95% CI: 5.0, 5.9) above baseline (regardless of prior infection), and by 6.3-fold (95% CI: 5.7, 6.9) in seronegative participants.[44] Neutralizing titers against BA.4/BA.5, were however approximately 3-fold lower than neutralizing titers against BA.1 (previously reported).

Impact on Testing and WGS Surveillance

- Antigen testing: The performance of rapid antigen tests for BA.4 and BA.5 is currently unknown, but has been maintained to slightly reduced (depending on the study, specimen source, and assay) for Omicron in general compared to other variants. Furthermore, the BA.4 sub-lineage contains an additional mutation on the nucleocapsid (N) protein, P151S, and its impact on antigen tests detecting the N protein is not yet established.

- Molecular testing: No impact is expected on the capability of molecular tests to detect BA.4 or BA.5. Of note, BA.4 and BA.5 have the del69-70 mutation leading to the S gene target failure (SGTF) pattern which could help distinguish it from BA.2 sub-lineages (these don't have the SGTF pattern).

- WGS surveillance: No impact is expected on the capability of WGS to detect and differentiate BA.4 and BA.5.

Implications for Public Health Practice

- Although COVID-19 case counts are dropping in Ontario, the emergence of BA.4 and BA.5 requires close monitoring of the potential impact and characteristics of these sub-lineages. Similar to the BA.2 wave that emerged in the midst of Ontario's BA.1 and BA.1.1 wave, emergence of BA.4 and BA.5 could cause a resurgence in COVID-19 cases during the summer and potentially reverse current downward case trends. Waning vaccine effectiveness against infection, variable antibody cross-neutralization across SARS-CoV-2 sub-lineages after an infection, and the reduction in public health measure mandates, require that Ontario COVID-19 epidemiology be closely monitored.

- As we continue to learn about Omicron sub-lineages circulating in Ontario, to minimize morbidity and mortality (including post-acute COVID-19 syndrome or "long COVID") as well as societal disruption, current public health responses could be augmented with interventions aimed at reducing SARS-CoV-2 transmission. Consideration should be given to the least restrictive and most equitable measures to achieve pandemic response goals based on epidemiological trends. Layers of protection, including getting vaccinated, staying home when sick or with symptoms of COVID-19, practicing physical distancing and avoiding crowded spaces, spending time outdoors or in well-ventilated indoor spaces, wearing a well-fitted mask in indoor or enclosed public settings (e.g., public transit), and practicing respiratory etiquette and washing hands should continue to be promoted for all.[45]

- 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 (including under-vaccinated) communities, as well as boosters for eligible individuals. Groups at higher risk for severe outcomes should be prioritized.

    - While vaccination is a key public health tool for the pandemic, because COVID-19 vaccination and previous SARS-CoV-2 infection do not provide sterilizing immunity, a COVID-19 pandemic strategy that relies entirely on immunity from vaccination and past infection will not contain transmissions. In addition, vaccine protection against infection is time-limited. 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., BA.4, BA.5). Related, 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. Continuous WGS surveillance, monitoring of the impacts of implementation/removal of public health measures, and efforts to increase vaccine equity can all help prepare Ontario for the next stages of the COVID-19 pandemic.

- Evidence that a new SARS-CoV-2 VOC could emerge and alter the course of the pandemic remains a concern.[46-48] At a May 11, 2022 press conference, the WHO's technical lead for the COVID-19 response said "the more the virus circulates, the more opportunities it has to change."[49] The emergence of sub-lineages such as BA.2.12.1, BA.4, and BA.5 in Ontario,[50] South Africa, and Portugal[51] soon after they experienced the decline of their BA.1 or BA.2 waves, underscores the need for sustained WGS surveillance.

- Clear risk communication to the population regarding current levels of SARS-CoV-2 transmission and COVID-19 disease risk can be helpful, especially in the context of increasing wastewater signal, <50% third dose COVID-19 vaccine uptake, low uptake of primary COVID-19 vaccine series in some age groups (e.g., 40.3% for children 5–11 years of age), and the emergence of more transmissible sub-lineages, particularly BA.5, in Ontario.[52]

References

1. Ritchie H, Mathieu E, Rodés-Guirao L, Appel C, Giattino C, Ortiz-Ospina E, et al. Coronavirus pandemic (COVID-19) [Internet]. Oxford: Our World in Data; 2022 [cited 2022 Jun 24]. COVID-19 cases, tests, positive rate, and reproduction rate. Available from: https://ourworldindata.org/coronavirus#explore-the-global-situation

2. Nguyen LKN, Howick S, McLafferty D, Anderson GH, Pravinkumar SJ, Van Der Meer R, et al. Evaluating intervention strategies in controlling COVID-19 spread in care homes: an agent-based model. Infect Control Hosp Epidemiol. 2020 Dec 14 [Epub ahead of print]. Available from: https://doi.org/10.1017/ice.2020.1369

3. Raman B, Bluemke DA, Lüscher TF, Neubauer S. Long COVID: post-acute sequelae of COVID-19 with a cardiovascular focus. Eur Heart J. 2022;43(11):1157-72. Available from: https://doi.org/10.1093/eurheartj/ehac031

4. Stefanou M-I, Palaiodimou L, Bakola E, Smyrnis N, Papadopoulou M, Paraskevas GP, et al. Neurological manifestations of long-COVID syndrome: a narrative review. Ther Adv Chronic Dis. 2022;13:20406223221076890. Available from: https://doi.org/10.1177/20406223221076890

5. Ontario Agency for Health Protection and Promotion (Public Health Ontario). Impact of vaccination on post-acute COVID-19 syndrome (PACS) - what we know so far [Internet]. Toronto, ON: Queen's Printer for Ontario; 2022 [cited 2022 Jun 22]. Available from: https://www.publichealthontario.ca/-/media/Documents/nCoV/COVID-WWKSF/2022/04/impact-vaccination-post-acute-covid-19-syndrome.pdf?sc_lang=en

6. Ontario Agency for Health Protection and Promotion (Public Health Ontario). Post-acute COVID-19 syndrome (PACS) in adults [Internet]. Toronto, ON: Queen's Printer for Ontario; 2022 [cited 2022 Jun 22]. Available from: https://www.publichealthontario.ca/-/media/Documents/nCoV/ipac/2022/04/post-acute-covid-syndrome-pacs.pdf?sc_lang=en

7. United Kingdom. Office for National Statistics. Coronavirus (COVID-19) Infection Survey, characteristics of people testing positive for COVID-19, UK: 22 June 2022 [Internet]. London: Crown Copyright; 2022 [cited 2022 Jun 24]. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/coronaviruscovid19infectionsurveycharacteristicsofpeopletestingpositiveforcovid19uk/22june2022#risk-factors-associated-with-coronavirus-covid-19-re-infections-uk

8. Ontario Agency for Health Protection and Promotion (Public Health Ontario). Omicron in Ontario: risk analysis for approaching public health measures in winter 2022 [Internet]. Toronto, ON: Queen's Printer for Ontario; 2022 [cited 2022 Jun 24]. Available from: https://www.publichealthontario.ca/-/media/documents/ncov/phm/2022/01/covid-19-omicron-ontario-risk-analysis.pdf?sc_lang=en

9. Australian Government. Department of Health. Australian influenza surveillance report and activity updates [Internet]. Canberra: Australian Government; 2022 [modified 2022 Jun 10; cited 2022 Jun 22]. Available from: https://www1.health.gov.au/internet/main/publishing.nsf/Content/cda-surveil-ozflu-flucurr.htm#:~:text=Influenza%2Dlike%2Dillness%20(ILI,a%20diagnosis%20date%20this%20fortnight.

10. European Centre for Disease Prevention and Control. Implications of the emergence and spread of the SARS-CoV-2 variants of concern BA.4 and BA.5 for the EU/EEA: 14 June 2022 [Internet]. Stockholm: European Centre for Disease Prevention and Control; 2022 [cited 2022 Jun 20]. Available from: https://www.ecdc.europa.eu/sites/default/files/documents/epidemiological-update-BA4-BA5-13-june-2014.pdf

11. Gangavarapu K, Latif AA, Mullen J, Alkuzweny M, Hufbauer E, Tsueng G, et al; GISAID core and curation team; Center for Viral Systems Biology. Outbreak.info: SARS-CoV-2 (hCoV-19) mutation reports: lineage comparison [Internet]. Jupiter, FL: Scripps Research; 2022 [cited 2022 Jun 21]. Available from: https://outbreak.info/compare-lineages?pango=BA.5&pango=BA.4&pango=BA.5.1&gene=ORF1a&gene=ORF1b&gene=S&gene=ORF3a&gene=E&gene=M&gene=ORF6&gene=ORF7a&gene=ORF7b&gene=ORF8&gene=N&gene=ORF10&threshold=75&nthresh=1&sub=false&dark=false

12. Latif AA, Mullen JL, Alkuzweny M, Tsueng G, Cano M, Haag E, et al. outbreak.info: BA.5 lineage report [Internet]. Jupiter, FL: Scripps Research; 2022 [cited 2022 Jun 20]. Available from: https://outbreak.info/situation-reports?pango=BA.5

13. Latif AA, Mullen JL, Alkuzweny M, Tsueng G, Cano M, Haag E, et al. outbreak.info: BA.4 lineage report [Internet]. Jupiter, FL: Scripps Research; 2022 [cited 2022 Jun 20]. Available from: https://outbreak.info/situation-reports?pango=BA.4

14. World Health Organization. COVID-19 weekly epidemiological update: edition 97, 22 June 2022 [Internet]. Geneva: World Health Organization; 2022 [cited 2022 Jun 22]. Available from: https://www.who.int/docs/default-source/coronaviruse/situation-reports/20220622_weekly_epi_update_97.pdf?sfvrsn=71bb00cd_10&download=true

15. European Centre for Disease Prevention and Control. Implications of the emergence and spread of the SARS-CoV-2 B.1.1.529 variant of concern (Omicron) for the EU/EEA [Internet]. Stockholm: European Centre for Disease Prevention and Control; 2021 [cited 2021 Dec 2]. Available from: https://www.ecdc.europa.eu/sites/default/files/documents/Implications-emergence-spread-SARS-CoV-2%20B.1.1.529-variant-concern-Omicron-for-the-EU-EEA-Nov2021.pdf

16. Network for Genomic Surveillance in South Africa (NGS-SA). SARS-CoV-2 sequencing update: 10 June 2022 [Internet]. Johannesburg: National Institute for Communicable Diseases; 2022 [cited 2022 Jun 20]. Available from: https://www.nicd.ac.za/wp-content/uploads/2022/06/Update-of-SA-sequencing-data-from-GISAID-10-June-2022.pdf

17. South Africa. National Institute for Communicable Diseases. Latest confirmed cases of COVID-19 in South Africa (22 June 2022) [Internet]. Johannesburg: National Institute for Communicable Diseases; 2022 [cited 2022 Jun 24]. Available from: https://www.nicd.ac.za/latest-confirmed-cases-of-covid-19-in-south-africa-22-june-2022/

18. South Africa. National Institute for Communicable Diseases. COVID-19 weekly epidemiology brief: week ending 04 June 2022 (week 22 of 2022) [Internet]. Johannesburg: National Institute for Communicable Diseases; 2022 [cited 2022 Jun 20]. Available from: https://www.nicd.ac.za/wp-content/uploads/2022/06/COVID-19-Weekly-Epidemiology-Brief-week-22-2022.pdf

19. South Africa. National Institute for Communicable Diseases. COVID-19 weekly epidemiology brief: week ending 11 June 2022 (week 23 of 2022) [Internet]. Johannesburg: National Institute for Communicable Diseases; 2022 [cited 2022 Jun 20]. Available from: https://www.nicd.ac.za/wp-content/uploads/2022/06/COVID-19-Weekly-Epidemiology-Brief-week-23-2022.pdf

20. South Africa. National Institute for Communicable Diseases. COVID-19 hospital surveillance update: week 22, 2022 [Internet]. Johannesburg: National Institute for Communicable Diseases; 2022 [cited 2022 Jun 20]. Available from: https://www.nicd.ac.za/wp-content/uploads/2022/06/NICD-COVID-19-Weekly-Sentinel-Hospital-Surveillnace-update-Week-22-2022.pdf

21. South Africa. National Institute for Communicable Diseases. COVID-19 hospital surveillance update: week 23, 2022 [Internet]. Johannesburg: National Institute for Communicable Diseases; 2022 [cited 2022 Jun 20]. Available from: https://www.nicd.ac.za/wp-content/uploads/2022/06/NICD-COVID-19-Weekly-Sentinel-Hospital-Surveillnace-update-Week-23-2022.pdf

22. Portugal. Serviço Nacional de Salude. Situation report on genetic diversity of the new coronavirus SARS-CoV-2 in Portugal - 21-06-2022 [Internet]. Lisbon: Servico Nacional de Salude; 2022 [cited 2022 Jun 24]. Available from: https://www.insa.min-saude.pt/relatorio-de-situacao-sobre-diversidade-genetica-do-novo-coronavirus-sars-cov-2-em-portugal-21-06-2022/

23. Ritchie H, Mathieu E, Rodés-Guirao L, Appel C, Giattino C, Ortiz-Ospina E, et al. Spain: coronavirus pandemic country profile [Internet]. Oxford: Our World in Data; 2020 [modified 2020 Nov 17; cited 2020 Nov 17]. Available from: https://ourworldindata.org/coronavirus/country/spain?country=ESP~GBR~IRL

24. Centers for Disease Control and Prevention. COVID data tracker: variant proportions [Internet]. Atlanta, GA: Centers for Disease Control and Prevention; 2022 [modified 2022 Jun 23; cited 2022 Jun 23]. Available from: https://covid.cdc.gov/covid-data-tracker/#variant-proportions

25. Centers for Disease Control and Prevention. COVID data tracker: trends in number of COVID-19 cases and deaths in the US reported to CDC, by state/territory [Internet]. Atlanta, GA: Centers for Disease Control and Prevention; 2022 [modified 2022 Jun 24; cited 2022 Jun 24]. Available from: https://covid.cdc.gov/covid-data-tracker/#trends_dailycases

26. UK Health Security Agency. 22 June 2022 risk assessment for SARS-CoV-2 variants VOC-22APR-03 and VOC-22APR-04 [Internet]. London: Crown Copyright; 2022 [cited 2022 Jun 24]. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1085552/22-june-2022-risk-assessment-for-VOC-22APR-03-and-VOC-22APR-04.pdf

27. UK Health Security Agency. SARS-CoV-2 variants of concern and variants under investigation in England: technical briefing 43 [Internet]. London: Crown Copyright; 2022 [cited 2022 Jun 24]. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1085404/Technical-Briefing-43.pdf

28. Public Health Agency of Canada. COVID-19 epidemiology update [Internet]. Ottawa, ON: Government of Canada; 2022 [modified 2022 Jun 17; cited 2022 Jun 20]. COVID-19 variants in Canada. Available from: https://health-infobase.canada.ca/covid-19/#VOC

29. Ontario Agency for Health Protection and Promotion (Public Health Ontario). Epidemiologic summary: SARS-CoV-2 whole genome sequencing in Ontario, June 24, 2022. Toronto, ON: Queen's Printer for Ontario; 2022.

30. Ontario Agency for Health Protection and Promotion (Public Health Ontario). Weekly epidemiologic summary: COVID-19 in Ontario - June 12, 2022 to June 18, 2022. Toronto, ON: Queen's Printer for Ontario; 2022.

31. Ontario Agency for Health Protection and Promotion (Public Health Ontario). Ontario COVID-19 Data Tool: lab tests [Internet]. Toronto, ON: Queen's Printer for Ontario; 2022 [cited 2022 Jun 20]. Available from: https://www.publichealthontario.ca/en/Data-and-Analysis/Infectious-Disease/COVID-19-Data-Surveillance/COVID-19-Data-Tool?tab=labTests

32. Jüni P, Maltsev A, Katz GM, Perkhun A, Yan S, Bodmer NS. Ontario dashboard: tracking Omicron [Internet]. Toronto, ON: Ontario COVID-19 Science Advisory Table; 2021 [cited 2022 Jun 23]. Available from: https://doi.org/10.47326/ocsat.dashboard.2021.1.0

33. Tegally H, Moir M, Everatt J, Giovanetti M, Scheepers C, Wilkinson E, et al. Continued emergence and evolution of Omicron in South Africa: new BA.4 and BA.5 lineages. medRxiv 22274406 [Preprint]. 2022 May 2 [cited 2022 Jun 20]. Available from: https://doi.org/10.1101/2022.05.01.22274406

34. UK Health Security Agency. SARS-CoV-2 variants of concern and variants under investigation in England: technical briefing 42 [Internet]. London: Crown Copyright; 2022 [cited 2022 Jun 20]. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1077180/Technical-Briefing-42-20May2022.pdf

35. World Health Organization. COVID-19 weekly epidemiological update: edition 95, 8 June 2022 [Internet]. Geneva: World Health Organization; 2022 [cited 2022 Jun 20]. Available from: https://www.who.int/docs/default-source/coronaviruse/situation-reports/20220608_weekly_epi_update_95.pdf?sfvrsn=9c87f377_3&download=true

36. Qu P, Evans JP, Faraone JN, Zou X, Zheng Y-M, Carlin C, et al. Differential evasion of Delta and Omicron immunity and enhanced fusogenicity of SARS-CoV-2 Omicron BA.4/5 and BA.2.12.1 subvariants. bioRxiv 492158 [Preprint]. 2022 May 17 [cited 2022 Jun 16]. Available from: https://doi.org/10.1101/2022.05.16.492158

37. Kimura I, Yamasoba D, Tamura T, Nao N, Oda Y, Mitoma S, et al. Virological characteristics of the novel SARS-CoV-2 Omicron variants including BA.2.12.1, BA.4 and BA.5. bioRxiv 493539 [Preprint]. 2022 May 26 [cited 2022 Jun 20]. Available from: https://doi.org/10.1101/2022.05.26.493539

38. Al-Aly Z, Bowe B, Xie Y. Outcomes of SARS-CoV-2 reinfection. Res Sp 1749502 [Preprint]. 2022 Jun 17 [cited 2022 Jun 24]. Available from: https://doi.org/10.21203/rs.3.rs-1749502/v1

39. Portugal. Serviço Nacional de Salude. Monitoring of COVID-19 [Internet]. Report n. 12. Lisbon: Servico Nacional de Salude; 2022 [cited 2022 Jun 20]. Available from: https://www.insa.min-saude.pt/wp-content/uploads/2022/06/20220601_Monitorizacao_COVID-19.pdf

40. Hachmann N, Miller J, Collier A-r, Ventura J, Yu J, Rowe M, et al. Neutralization escape by the SARS-CoV-2 Omicron variants BA.2.12.1 and BA.4/BA.5. medRxiv 22275151 [Preprint]. 2022 May 19 [cited 2022 Jun 20]. Available from: https://doi.org/10.1101/2022.05.16.22275151

41. Khan K, Karim F, Ganga Y, Bernstein M, Jule Z, Reedoy K, et al. Omicron sub-lineages BA.4/BA.5 escape BA.1 infection elicited neutralizing immunity. medRxiv 22274477 [Preprint]. 2022 May 1 [cited 2022 Jun 20]. Available from: https://doi.org/10.1101/2022.04.29.22274477

42. Willett BJ, Kurshan A, Thakur N, Newman J, Manali M, Tyson G, et al. Distinct antigenic properties of the SARS-CoV-2 Omicron lineages BA.4 and BA.5. bioRxiv 493397 [Preprint]. 2022 May 25 [cited 2022 Jun 20]. Available from: https://doi.org/10.1101/2022.05.25.493397

43. Qu P, Faraone J, Evans JP, Zou X, Zheng Y-M, Carlin C, et al. Neutralization of the SARS-CoV-2 Omicron BA.4/5 and BA.2.12.1 subvariants. New Engl J Med. 2022 Jun 15 [Epub ahead of print]. Available from: https://doi.org/10.1056/NEJMc2206725

44. Moderna. Moderna announces bivalent booster mRNA-1273.214 demonstrates potent neutralizing antibody response agaiinst Omicron subvariants BA.4 and BA.5 [Internet]. Cambridge, MA: Moderna; 2022 [cited 2022 Jun 24]. Available from: https://s29.q4cdn.com/435878511/files/doc_news/Moderna-Announces-Bivalent-Booster-mRNA-1273.214-Demonstrates-Potent-Neutralizing-Antibody-Response-Against-Omicron-Subvariants-BA.4--DQBD7.pdf

45. Ontario. Ministry of Health. Management of cases and contacts of COVID-19 in Ontario [Internet]. Version 14.1. Toronto, ON: Queen's Printer for Ontario; 2022 [modified 2022 Apr 19; cited 2022 Jun 20]. Available from: https://www.health.gov.on.ca/en/pro/programs/publichealth/coronavirus/docs/contact_mngmt/management_cases_contacts.pdf

46. Bedford T. Continuing SARS-CoV-2 evolution under population immune pressure [Internet]. Presented at: Food and Drug Administration, Vaccines and Related Biological Products Advisory Committee Meeting. 2022 Apr 6 [cited 2022 Jun 20]; Silver Spring, MD. Available from: https://bedford.io/talks/sars-cov-2-continuing-evolution-vrbpac/#/

47. Colson P, Delerce J, Marion-Paris E, Lagier J-C, Levasseur A, Fournier P-E, et al. A 21L/BA.2-21K/BA.1 "MixOmicron" SARS-CoV-2 hybrid undetected by qPCR that screen for variant in routine diagnosis. medRxiv 22273010 [Preprint]. 2022 Mar 31 [cited 2022 Jun 20]. Available from: https://doi.org/10.1101/2022.03.28.22273010

48. Ou J, Lan W, Wu X, Zhao T, Duan B, Yang P, et al. Tracking SARS-CoV-2 Omicron diverse spike gene mutations identifies multiple inter-variant recombination events. bioRxiv 484129 [Preprint]. 2022 Mar 14 [cited 2022 Jun 20]. Available from: https://doi.org/10.1101/2022.03.13.484129

49. World Health Organization. Live Q&A on COVID-19 virtual press conference transcript - 11 May 2022 [Internet]. Geneva: World Health Organization; 2022 [cited 2022 Jun 20]. Available from: https://www.who.int/publications/m/item/live-q-a-on-covid-19-virtual-press-conference-transcript---11-may-2022

50. Doucleff M. 2 new omicron variants are spreading in N.Y. and elsewhere. Here's what we know. NPR News [Internet], 2022 Apr 14 [cited 2022 Jun 20]. Available from: https://www.npr.org/sections/goatsandsoda/2022/04/14/1092812456/two-new-omicron-variants-are-spreading-in-n-y-and-elsewhere-heres-what-we-know

51. Prater E. BA.4 and BA.5, two new Omicron variants sweeping South Africa, detected in U.S. Fortune [Internet], 2022 Apr 30 [cited 2022 Jun 20]; Health. Available from: https://fortune.com/2022/04/30/are-ba4-ba5-in-united-states-detected-omicron-covid-stealth-omicron-more-transmissible/

52. Ontario Agency for Health Protection and Promotion (Public Health Ontario). COVID-19 vaccine uptake in Ontario: December 14, 2020 to June 5, 2022 [Internet]. Toronto, ON: Queen's Printer for Ontario; 2022 [cited 2022 Jun 20]. Available from: https://www.publichealthontario.ca/-/media/documents/ncov/epi/covid-19-vaccine-uptake-ontario-epi-summary.pdf?sc_lang=en

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