Public Health Ontario | Santé publique Ontario

EVIDENCE BRIEF

# SARS-CoV-2 Omicron Variant Sub-Lineages BA.4 and BA.5: Evidence and Risk Assessment

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## Introduction

This evidence brief includes evidence that has emerged since the previous Public Health Ontario (PHO) BA.4 and BA.5 Evidence and Risk Assessment.[1]

## Key Messages

- The proportion of whole genome sequencing (WGS) samples identified as **BA.5** continues to increase in Ontario, from 14.8% (June 5-11, 2022) to 25.7% (June 12-18, 2022), with a weekly growth rate 3.11 (95% confidence interval [CI]: 2.89-3.34) times that of BA.2. The proportion of **BA.4** had a slight increase in Ontario, from 6.2% (June 5-11, 2022) to 6.9% (June 12-18, 2022), with a weekly growth rate 2.48 (2.27-2.71) times that of BA.2.
- Using Nowcast modelling, the proportions of BA.5 and BA.4 in Ontario are projected to reach 66.3% (95% CI: 58.3%-73.5%) and 9.7% (95% CI: 6.5%-14.0%), respectively, by July 6, 2022. Hospitalizations and mortality are likely to increase due to the rise in volume of cases, but there is uncertainty about the extent of the increase since evidence on severity of BA4 and BA.5 is uncertain.
- Based on those eligible for molecular testing in Ontario, Coronavirus Disease 2019 (COVID-19) cases and percent positivity are increasing after a period of gradual decline. Hospital occupancy shows early signs of potential plateau or increase, and the province-wide wastewater signal continues to increase. Together, these epidemiological trends indicate increasing community transmission.
- Evidence continues to show that BA.4 and BA.5 are highly transmissible, at least in part due to neutralizing antibody titers against BA.4 and BA.5 being reduced as compared to other variants. BA.4/5 could lead to high levels of community transmission in the absence of public health measures.
    - For previous sub-lineages of Omicron, a complete primary series and for those eligible, the recommended booster dose(s), provide optimal protection against severe outcomes.

- Evidence shows 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. The evidence that SARS-CoV-2 can cause immune dysregulation is increasing. Reducing the risk of SARS-CoV-2 infection and reinfection could reduce overall burden of death and disease in Ontario during the pandemic and longer-term.

- To minimize morbidity and mortality in Ontario, as well as societal disruption, current public health efforts could be augmented in response to the increasing epidemiological trends. Based on evidence of significant immune evasion by BA.4/5 and waning immunity following vaccination, use of public health measures will be the most effective way to reduce the risk of SARS-CoV-2 transmission, and includes: wearing a well-fitted high quality mask whenever feasible in indoor spaces, crowded places (including outdoors) and close contact settings (e.g., public transit), staying home when sick or with symptoms of COVID-19, optimizing ventilation, and use of outdoor spaces.

# 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.

# 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 risk of reinfection is high with a low degree of uncertainty. The risks of lowered VE and breakthrough infection are high with a moderate degree of uncertainty. 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-acute COVID-19 syndrome (PACS or "long-COVID") is not included in the risk assessment table, but several reviews report that the sequelae and their incidence vary.[2-12] Preventing high levels of COVID-19 community transmission may mitigate the incidence of post-COVID-19 sequelae and its long term impacts at the individual and population levels.

    - 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.[13] 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.[12] Current COVID-19 vaccines and previous SARS-CoV-2 infection do not provide sterilizing immunity (i.e., full protection from infection or reinfection), therefore public health measures have a considerable role to play in the current pandemic response.

- There is increasing evidence that SARS-CoV-2 infection can cause immune dysregulation.[2-9] Although all outcomes and the scale of immune dysregulation remain unclear, a potential increase in acquired impaired immunity in the Ontario population could have significant impact on the incidence and associated burden of infectious diseases (e.g., high viral loads, increased antibiotic use and resistance) and other conditions in the longer-term.

- Even if BA.4 or BA.5 are found to be no more severe than BA.1 and BA.2, the increased transmissibility of BA.4 and BA.5 suggests that the total number of cases (and therefore the total number of severe cases) would be expected to rise. Early evidence suggests several monoclonal antibodies approved for clinical use, exhibit substantial loss of activity *in vitro* against BA.4/5.[14] 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.

- COVID-19 hospitalizations are no longer declining in Ontario (see below). Health care worker absences, shortages, and impacts to scheduled care, could be yet more challenging in the context of BA.4 and/or BA.5 community transmission. Transmission of other communicable diseases (e.g., influenza, monkeypox) is another consideration for health care system recovery and capacity planning in Ontario.

- 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; 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 can result in a resurgence of COVID-19, which the current Ontario context may reflect.

**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 | Low |
| Lowered Vaccine Effectiveness or Breakthrough Infection | High | Moderate |
| Impact on Testing | Low | Moderate |

# Epidemiology

## Globally

- Based on sequences submitted to GSAID from May 27 to June 27, 2022, the Omicron VOC was the dominant variant circulating **globally**, accounting for 94% of reported sequences.[15] Among Omicron sequences, from the week of June 6-12 to the week of June 13-19, BA.2 declined from 30% to 25%, BA.2.12.1 declined from 18% to 11%, while BA.4 increased from 9% to 12%, and BA.5 increased from 28% to 43%. During the week of June 20-26, 2022, there was an 18% increase in weekly cases as compared to the previous week. The number of new weekly deaths remained similar to that of the previous week; however, hospitalization and intensive care unit (ICU) admissions are lagging indicators. The World Health Organization (WHO) advises that trends should be interpreted with caution due to limitations of surveillance systems.

- The European Centre for Disease Prevention and Control (ECDC) reported that BA.4/BA.5 are the dominant variants in 7 out of the 10 countries reporting adequate sequencing volumes.[16] Among the 10 countries with adequate sequencing volume for June 6-19, 2022, the estimated distribution of variants was 58.2% (36.3-99.9% from 10 countries) for BA.4/BA.5, 35.5% (0.1-59.7% from 10 countries) for BA.2, 11.1% (3.1-23.0% from 5 countries) for BA.2+L452X, 0.1% (0.0-0.5%, 118 detections from 7 countries) for BA.1 and 0.0% (0.0-0.0%, 3 detections from 2 countries) for B.1.617.2. The ECDC reported the start of a widespread wave driven by the BA.4 and BA.5, with a 27% increase in case rates among people aged 65 years and above in the week ending June 26, 2022 (compared to the previous week) in 21 out of the 26 countries reporting these data. Of 28 countries with data on hospital or ICU admissions/occupancy, 15 reported an increasing trend in at least one of these indicators in the week ending June 26, 2022, compared with the previous week. The European COVID-19 Forecast Hub predicts increasing trends in cases, stable trends in hospital admissions, and increasing trends in deaths for the **European Union (EU)/ European Economic Area (EEA)** overall by the end of the week ending July 10, 2022. Predictions should be interpreted with caution due to changes to testing and reporting criteria.

- In **South Africa**, BA.5 was first detected in January 2022, and BA.4 was first detected in February 2022.[17] Together, BA.4 and BA.5 became dominant (73%) in April, and comprised 94% of all sequenced samples in May. Epidemiological trends suggest the BA.4 and BA.5 wave in South Africa has passed its peak. The BA.4 and BA.5 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.[18]

    - From mid-May 2022, test positivity rates for COVID-19 have been declining, with a daily test positivity of 3.3% reported on July 4, 2022.[19] In the week ending June 25, 2022, there was a 30.4% decrease in the number of new cases (3,618) compared to the previous week (5,197).[20]

    - There was a 41% decrease in the number of new hospital admissions in the week ending June 25, 2022 (558) compared to the number of admissions the previous week (948).[21] Delays in reporting of hospital admissions may affect the numbers reported in the most recent week.

- **Portugal** was the first EU/EEA country to report a significant increase in BA.5 case counts, and BA.5 comprised 95% of cases based on random sample sequencing in the week of June 13-16, 2022.[22,23] 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 in most parts of the country, suggesting that the BA.5 peak was reached in the region.[23] The effective reproduction number is <1.

- In the **United States (US)**, the estimated proportions of BA.5 and BA.4 among circulating variants have been increasing, from 40.5% (95% CI: 37.5%-43.6%) for BA.5 and 14.8% (95% CI: 12.9%-16.9%) for BA.4 the week ending June 25, 2022, to 53.6% (95% CI: 49.5%-57.6%) for BA.5 and 16.5% (95% CI: 13.9%-19.4%) for BA.4 the week ending July 2, 2022.[24] During the same period, the estimated proportion of BA.2 dropped from 5.4% (95% PI: 4.8%-6.1%) to 2.8% (95% PI: 2.4%-3.3%), while that for BA.2.12.1 dropped from 39.2% (95% PI: 36.5%-42.1%) to 27.2% (95% PI: 24.2%–30.3%). As of June 22, 2022, the 7-day moving average of daily new cases (97,430) decreased 5.6% compared with the previous 7-day moving average (103,175);[25] however, the June 24, 2022 COVID Data Tracker Weekly Review also reported that the 7-day average of percent positivity from NAATs was 13.6%, which is an increase from the previous 7-day average of 12.1%. The 7-day daily average for new hospital admissions for June 15-21, 2022, was 4,375, which is a 1.0% increase from the prior 7-day average (4,329) from June 8-14, 2022.

- The **United Kingdom (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] The 7-day moving average cases has risen from 59.59 to 316.04 per 1,000,000 population from June 15, 2022 to July 1, 2022, with Scotland and Wales reaching record numbers of cases.[27] The UK's ZOE Health Study, which uses a phone app to crowd source data on COVID-19, has stated that the UK is in a new COVID-19 wave and they estimate daily cases could soon exceed 300,000, which is on par with case numbers at the height of the pandemic in the UK.[28]

- Based on data up to June 21, 2022, the UKHSA estimated that 22.28% (CI: 16.25-28.77) and 39.46% (CI: 32.19 to 51.31) of cases in **England** were currently BA.4 and BA.5, respectively.[29] In England, from June 20-26, 116,312 people had a confirmed positive SARS-CoV-2 test result, which is an increase of 33.3% compared to the previous 7 days.[30] As of June 24, 2022, the R range for England was 1.1 to 1.4 and the growth rate range was +2% to +5% per day.[31] The ICU or high dependency unit (HDU) rate for COVID-19 was at 0.27 per 100,000 in the week June 20-26, 2022, compared to 0.20 per 100,000 in the previous week. Between June 23-29, 2022, 9,033 individuals went into hospital with coronavirus, which is an increase of 34.2% compared to the previous 7 days.[30] Between June 20-26, 2022, there were 407 deaths within 28 days of a positive coronavirus test, which is an increase of 22.2% compared to the previous 7 days.

## Canada and Ontario

- WGS surveillance across **Canada** indicated that BA.5 and BA.4 represented 20.4% and 7.4%, respectively, of the samples sequenced for the week ending June 12, 2022, up from 13.3% for BA.5 and down from 7.5% for BA.4, the week before (data still accumulating).[32] On July 4, 2022, the reported 7-day average percent positivity was 11.8%, which is an increase compared to 9.3% reported on June 24, 2022.[33]

- 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 12-18, 2022, BA.2.12.1 was the most prevalent lineage (39.0%), followed by BA.5 (25.7%), BA.2 (14.3%), and BA.4 (6.9%).[34]

- The proportion of BA.5 is increasing in Ontario, from 14.8% (June 5-11, 2022) to 25.7% (June 12-18, 2022), with a weekly growth rate 3.11 (95% CI: 2.89 - 3.34) times that of BA.2 over the past 12 weeks. Based on Nowcast modelling, the proportion of BA.5 is projected to reach 66.3% (95% CI: 58.3%-73.5%) by July 6, 2022.[34]

- The proportion of BA.4 had a slight increase in Ontario, from 6.2% (June 5-11, 2022) to 6.9% (June 12-18, 2022), with a weekly growth rate 2.48 (2.27 - 2.71) times that of BA.2 over the past 12 weeks. Based on Nowcast modelling, the proportion of BA.4 is projected to reach 9.7% (6.5 - 14.0) by July 6, 2022.

- In the week of June 19-25, 2022, the number of reported cases in Ontario increased for the first time since April to 5,385 cases, up from 4,372 the previous week.[35] Case rates increased in all age groups. While recent testing volumes are stable, percent positivity was 8.4% the week of June 19-25, 2022, which is higher than 6.8% during the previous week.

- Hospitalizations, 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 appear to have stopped declining. At this time, Ontarians 80 years and older have higher rates of hospitalizations and deaths, compared to other age groups.[35]

- On July 5, 2022, the Ontario Dashboard indicated that COVID-19 cases, percent positivity, hospital occupancy, and the province-wide wastewater signal were increasing, indicating increasing community transmission.[36] This is a reverse of the trends since the last PHO risk assessment.

# Transmissibility

There is epidemiological, molecular, and *in vitro* evidence that suggest a growth advantage for BA.5 and BA.4, compared to BA.1 and BA.2.[1] Two recent reports are briefly described below.

- Data from the UK Genotype2Phenotype Consortium shows some changes in BA.4 and BA.5 interaction with the human host cell as compared with earlier Omicron variants, which could be associated with increased fitness.[29] The UKHSA stated that small changes in antigenicity and potentially small increases in fitness may both contribute to the observed growth advantage of BA.4 and BA.5. The UKHSA estimates that BA.5 has the largest relative fitness advantage, followed by BA.4, then BA.2.12.1, when comparing these three variants. It is anticipated that BA.5 will be the dominant variant in all UK regions. In the week ending June 19, 2022, the relative doubling time of BA.2.12.1, BA.4 and BA.5 were -24.38 days (CI: -10.91 to 104.03), -173.52 days (CI: -21.95 to 29.38), and 25.24 days (CI: -306.54 to 12.12), respectively. Based on data from England, the UKHSA estimates BA.4 and BA.5 to have median growth rates of 75.8% and 65.6% per week, respectively, relative to BA.2.

- Wang et al., used surface plasmon resonance (SPR) to measure the binding affinity of SARS-CoV-2 variant S proteins to hACE2 and reported that S proteins of the Omicron subvariants had similar affinities to hACE2, and slightly higher affinity than an ancestral SARS-CoV-2, D614G.[14] Dimeric hACE2 neutralization assays showed that the 50% inhibitory concentration (IC50) was lower for BA.4/5 compared to that of BA.2, suggesting BA.4/5 have not lost hACE2 affinity. Although F486V mutation compromised receptor affinity, R493Q can compensate to regain fitness in receptor binding.

- Tuekprakhon et al., conducted an antigenic characterization of BA.4/5 compared with the other Omicron sub-lineages, using neutralization assays and biophysical binding studies, amongst other methods.[37] They measure the affinity of the BA.4/5 receptor binding domain (RBD) for angiotensin converting enzyme-2 (ACE2) and report that it is higher than earlier Omicron strains BA.1 and BA.2.

# Disease Severity

It remains unclear if BA.4 or BA.5 cause more severe disease than BA.1 or BA.2. The lack of clarity is due to a lack of evidence as well as the fact that the severity of Omicron waves has varied across jurisdictions and in the literature.[38-43] The epidemiology, including disease severity, is not easily generalizable between jurisdictions.[44] Reports of increasing hospitalizations and ICU admission across age groups during BA.4/5-driven waves report that increases seem greatest in older populations, although it remains unclear if the increase in hospitalizations is due to intrinsic severity of BA.4 or BA.5, or the overall increase in case number.[15,16,45]

- Wolter et al., assessed risk factors for hospitalization and severity, comparing Delta, BA.2, BA.4 and BA.5 infections to BA.1, and also comparing Omicron lineage infections to Delta infections in South Africa.[38] Among Delta infections, 13.5% were admitted to hospital, compared to 4.0% of BA.1, 3.3% of BA.2 and 4.8% of BA.4/BA.5. In multivariate analyses they controlled for factors associated with hospitalization (including prior SARS-CoV-2 infection) and factors associated with severity (including known prior SARS-CoV-2 infection and SARS-CoV-2 vaccination status, but not time since last vaccination). Compared to BA.1, the odds of hospital admission were similar for BA.4/BA.5-infected individuals (adjusted odds ratio [aOR] 1.24, 95% CI 0.98–1.55). Compared to Delta variant infections, all Omicron lineages had a reduced odds of hospitalization (BA.1, aOR 0.29, 95% CI 0.25-0.35; BA.2, aOR 0.26, 95% CI 0.22-0.32; BA.4/BA.5, aOR 0.36, 95% CI 0.27-0.48). In a sensitivity analysis, individuals infected with BA.4/BA.5 had similar odds of hospital admission compared to individuals infected with BA.2 (aOR 1.00, 95% CI 0.65-1.53). Compared to BA.1 infections, odds of severe disease after hospitalization did not differ for BA.4/BA.5 infection (aOR 0.71, 95%CI 0.41-1.25). Compared to BA.2 infections, individuals infected with BA.4/BA.5 had similar odds of severe disease (aOR 0.78, 95% CI 0.37-1.62).

- 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, which was similar to that observed since the beginning of 2022 (during the BA.1 and BA.2 waves).[22] A June 29, 2022 report on Portugal's BA.5 wave indicated that the ratio between the number of hospitalized cases and notified infections had increased to 0.17.[23] While still indicating a similar severity to that observed since the beginning of 2022, this is an increasing trend. Mortality from all causes; however, is above the expected value for this time of the year, suggesting an excess of all-cause mortality.

- Davies et al., compared severity of BA.4/BA.5 infection with BA.1 and earlier variant infections among SARS-CoV-2 cases in those ≥20 years in the Western Cape, South Africa, using timing of infection to infer the lineage or variant causing infection.[46] The adjusted hazard ratio (aHR) of severe hospitalization (admission to intensive care or mechanical ventilation or oral/intravenous steroid prescription or death in the BA.4/BA.5 wave was similar to the BA.1 wave (aHR 1.12; 95% CI: 0.93; 1.34), and lower than previous non-Omicron waves. Prior infection was protective against severe hospitalization or death (aHR 0.29; 95% CI 0.24; 0.36) as was vaccination with three doses (Pfizer-BioNTech or Janssen) (aHR 0.17; 95% CI: 0.07; 0.40), two vaccine doses (0.37; 95% CI: 0.33; 0.42) and one vaccine dose (0.26; 95% CI: 0.21; 0.32). In the analysis restricted to the BA.4/BA.5 period, prior infection remained strongly protective against severe hospitalization or death (aHR 0.23; 95% CI 0.10; 0.52), as did vaccination with three doses (aHR 0.20; 95% CI: 0.08; 0.49), two doses (aHR 0.39; 95% CI: 0.25; 0.59) and one dose (0.51; 95% CI: 0.27; 0.99), with similar results for the outcome of death.

# Immunogenicity

The RBD mutations L452R and F486V found in BA.4 and BA.5 have the potential to effect antibody recognition of these sub-lineages.[37,47]

- On June 25, 2022, Pfizer-BioNTech reported positive data evaluating the safety, tolerability, and immunogenicity of two Omicron-adapted COVID-19 vaccine candidates: one monovalent and the other bivalent.[48] They reported that both Omicron-adapted candidates neutralize BA.4 and BA.5, though to a lesser extent than they do for BA.1. The company stated that in a SARS-CoV-2 live virus neutralization assay using sera from participants 56 years of age and older, sera efficiently neutralized BA.4/BA.5 with titers approximately 3-fold lower than BA.1 (unclear if sera were from monovalent or bivalent booster, or both). Additional BA.4/5 data is expected in the coming weeks.

- On June 28, 2022, a large majority of the US Vaccines and Related Biological Products Advisory Committee voted in favour of including a SARS-CoV-2 Omicron component in COVID-19 vaccines to be used for boosters in fall 2022.[49] The US Food and Drug Administration (FDA) have advised manufacturers planning to update their COVID-19 vaccines to develop modified vaccines that add a BA.4/5 spike protein component in order to create a two component (bivalent) booster vaccine.

- Wang et al., conducted a systematic antigenic analysis of Omicron subvariants to investigate their potential immune evasion.[14] To understand antigenic differences between BA.2.12.1 and BA.4/5 from BA.1, BA.1.1, BA.2, and the wild-type SARS-CoV-2 (D614G), they made each pseudovirus and assessed its sensitivity to neutralization by a panel of 21 monoclonal antibodies (mAbs) directed to known neutralizing epitopes on the viral S protein. Of 21 mAbs, 19 completely or partially lost their neutralizing ability against BA.4/5. Compared to BA.2 and BA.2.12.1, BA.4/5 exhibited substantially greater neutralization resistance to two class 2 RBD mAbs, and modest resistance to two class 3 RBD mAbs. Based on all their analyses, the authors suggest that mutations in BA.4/5 may impart greater evasion from antibodies to class 2 and class 3 regions, whereas mutations in BA.2.12.1 confer greater evasion from antibodies to class 3 region of RBD. Using sera from individuals who received three doses of mRNA vaccine, titers for BA.4/5 were 19.2-fold lower relative to D614G, and 4.2-fold lower relative to BA.2. Sera from individuals who received mRNA vaccines before or after a non-Omicron infection, and individuals with either BA.1 or BA.2 breakthrough infection after vaccination showed a similar trend. Relative to BA.2, BA.4/5 showed 1.6-fold to 4.3-fold greater resistance to neutralization by sera from individuals who had both mRNA vaccination and SARS-CoV-2 infection. Using authentic virus, sera from vaccinated and boosted individuals had neutralization titers for BA.4 that were 2.7-fold lower compared to titers for BA.2. Wang et al., also mapped the antigenic distances among D614G, various Omicron subvariants, and individual point mutants. Antigenic cartography showed that BA.4/5 is 4.3 antigenic units further than D614G, and 2 antigenic units further than BA.2. Based on these and additional analyses not described here, they authors state that BA.4/5 is substantially more neutralization-resistant to sera obtained from boosted individuals, with several mutations contributing to the antibody evasion.

- Tuekprakhon et al., used serum obtained 28 days following a third dose of the Oxford-AstraZeneca vaccine AZD1222 (n = 41) or Pfizer-BioNTech vaccine BNT162b2 (n = 19), and reported that for AstraZeneca, neutralization titers for BA.4/5 were reduced 2.1-fold compared with BA.1 ($p < 0.0001$) and 1.8-fold compared with BA.2 ($p < 0.0001$).[37] For three dose Pfizer-BioNTech recipients, BA.4/5 neutralization titers were reduced 3.1-fold ($p < 0.0001$) and 3.1-fold ($p < 0.0001$) compared with BA.1 and BA.2, respectively. Using sera from breakthrough infections,

they reported that at an early time point, BA.4/5 titers were reduced 1.9- ($p = 0.0005$) and 1.5-fold ($p = 0.0015$) compared with BA.1 and BA.2, respectively. At a later point, BA.4/5 titers were reduced 3.4- ($p = 0.0001$) and 2-fold ($p = 0.0017$) compared with BA.1 and BA.2, respectively. The authors conclude that the reductions in titers may reduce VE against infection, in particular at longer time points due to waning, but they expect VE against severe disease would remain intact. The authors corroborated the neutralization results with a biophysical analysis of binding of selected antibodies to BA.4/5 and BA.2 RBDs by surface plasmon resonance (SPR).

- The UKHSA reported preliminary analyses that the vaccination status of cases infected with BA.4 and BA.5 was not significantly different compared to that of cases infected with BA.2 (aOR 1.13; 95% CI 0.88-1.44 and aOR 0.83; 95% CI 0.88-1.44, respectively), suggesting that protection from the vaccines likely remains comparable to that observed previously.[29] A formal vaccine effectiveness analysis will follow when data are available.

- Wolter et al's., analyses of Delta, BA.1, BA.2 and BA.4/BA.5-infected individuals in South Africa reported that Omicron-infected individuals had a higher proportion of infections identified as re-infections (9.7% BA.1, 9.3% BA.2 and 11.7% BA.4/BA.5) compared to Delta-infected individuals (2.9%).[38]

# 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 be 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

- COVID-19 cases, percent positivity, hospital occupancy, and the province-wide wastewater signal are increasing in Ontario, indicating increasing community transmission, likely driven by BA.4 and BA.5. The current epidemiological trends suggest BA.4 and BA.5 could cause a resurgence in COVID-19 cases during the summer. Waning VE 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.[50]

- As we continue to learn about BA.4 and BA.5 severity, to minimize risk of 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 that reduce 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) or crowded outdoor settings (e.g., festivals), and practicing respiratory etiquette and washing hands should continue to be promoted for all.[51]

- Population-level measures, particularly in essential indoor public settings (e.g., grocery stores, pharmacies) and those where highest risk populations are served, can minimize inequitable impacts on those at highest risk of severe disease (e.g., immunocompromised, older adults, racialized, and low income populations), and those ineligible for COVID-19 vaccination (i.e., children less than 5 years).

    - Taking a cautious approach to isolation and quarantine, based on current evidence, is another component of a layered approach, which, together with other measures, can help break chains of SARS-CoV-2 transmission.[51,52] Staying home when experiencing symptoms of COVID-19 is important too, regardless of day of illness.

- 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, and because of strong evidence of BA.4 and BA.5 ability to evade neutralizing antibody immunity, a COVID-19 pandemic strategy that relies entirely on immunity from current vaccines and past infection will not contain transmission. 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. Ongoing 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.[53-55] The emergence of sub-lineages such as BA.2.12.1, BA.4, and BA.5 in Ontario, South Africa, and Portugal soon after they experienced the decline of their BA.1 or BA.2 waves,[56,57] 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., 40.5% for children 5–11 years of age), and the emergence of more transmissible sub-lineages, particularly BA.5, in Ontario.[58]

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