

EVIDENCE BRIEF

SARS-CoV-2 Omicron Variant BA.2 and Sub-lineages of BA.2: Evidence and Risk Assessment (up to date as of June 14, 2022)

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Key Messages

- Based on representative surveillance sequencing, the most prevalent severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants in Ontario the week of May 22-28, 2022 were Omicron BA.2 (41.3%), BA.2.12.1 (25.8%), BA.2.12 (7.7%), BA.2.3 (7.5%), BA.2.20 (3.8%), BA.2.9 (3.6%), BA.5 (2.9%), BA.1.1 (1.3%), BA.4 (1.3%), and BA.2.3.4 (0.9%).
- The weekly growth rate of BA.2.12.1 is approximately 1.74 times that of BA.2 and BA.2.12.1 could become the dominant variant in the coming weeks. An increase in the prevalence of BA.4 and BA.5 in recent weeks suggests that these variants also have the potential to become dominant in Ontario.
- There is variable infection-induced antibody cross-neutralization between SARS-CoV-2 variants, making it difficult to gauge the level of protection against reinfection by other variants.
- Among those eligible for molecular testing in Ontario, the number of positive cases and test positivity rates continue to decline; however, there are early signs of increasing positivity from wastewater surveillance programs at this time. The potential impact of an increasing prevalence of BA.2.12.1, which is more transmissible than the current dominant BA.2 lineage that is declining in prevalence in Ontario, is unclear at this time.
- Despite decreasing epidemiological trends in Ontario, the daily number of COVID-19 cases and test positivity rates remain high when compared to earlier pandemic waves. Some public health measures such as provincial masking mandates have been lifted, leading to increased uncertainty around the progression of the pandemic. Population-level and individual-level measures to reduce disease transmission, particularly in essential indoor public settings (e.g., grocery stores), can help minimize inequitable impacts on those at highest risk of severe disease due to medical and/or social factors, those ineligible for vaccination (i.e., children less than 5 years) and those impacted by disruptions in educational and other essential settings (e.g., when individuals cannot attend due to being infected or symptomatic).

- Public health measures that reduce the risk of transmission can be layered onto a vaccination strategy to reduce the number of cases driven by a more transmissible dominant variant and the emergence of an even more transmissible sub-lineage (i.e., BA.2.12.1). Public health measures may include ventilation, use of outdoor spaces and modes of transportation, and masking whenever feasible when indoors in closed spaces, crowded places, and close contact settings. Preventing high levels of community transmission will also mitigate the incidence and impacts of post-acute COVID-19 syndrome (PACS, also known as “long COVID-19”) for which evidence is accumulating.

Issue and Research Question

There are multiple and increasing PANGO sub-lineages associated with the B.1.1.529 (Omicron) variant of concern (VOC).^{1,2} 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). 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.2 report published June 3, 2022.^{3,4} Evidence on BA.1 and BA.3 sub-lineages, as well as recombinant lineages (e.g., XD, XE, XF), are made available in other reports and may be included in this document for context.⁵⁻⁷ Omicron sub-lineages BA.4 and BA.5 will be covered in a subsequent report.

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 Omicron transmissibility in Ontario is high with a low degree of uncertainty due to BA.2 and currently emergent sub-lineages (e.g., BA.2.12). The risk of severe disease is low with a high degree of uncertainty. The risk of reinfection is high with a moderate degree of uncertainty. The risk of breakthrough infection is high with a high degree of uncertainty. The risk of impact on testing is low with a low 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.⁸⁻¹² 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.
- 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.
- The evidence shows that BA.2.12.1 has a growth advantage over BA.1 and BA.2 (see below and Transmissibility section). Even if BA.2.12.1 is found to be no more severe than BA.1 and BA.2, the increased transmissibility potential of BA.2.12.1 suggests that the total number of cases (and potentially the total number of severe cases) would be expected to rise. High vaccine uptake, immunity from previous infections, and having additional public health measures in place may attenuate an increase in cases from emergent sub-lineages.
 - Studies on BA.1/2 showed that a complete COVID-19 vaccine primary series, plus the recommended booster dose(s) for those eligible, provide increased protection against severe outcomes. Additional dose(s) also reduce the risk of symptomatic infection; however, VE against symptomatic infection is lower and wanes more quickly than VE against severe disease.¹³ As of June 6, 2022, 49.9% (7,355,601 individuals) of the Ontario population have completed their COVID-19 vaccine primary series and received at least one booster dose, and 30.8% (1,093,425 individuals) of the eligible Ontario population 60 years of age and older have completed their primary series and received two booster doses.¹⁴
- As whole genome sequencing (WGS) surveillance tools improve and new variants are assigned a PANGO lineage, additional Omicron sub-lineages and recombinants may be identified. As a result of the dynamic nature of SARS-CoV-2 variants and limitations of the available tools, “BA.2” may include emerging sub-lineages or variants that are yet to be given a PANGO designation.
- 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 challenges 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.¹⁵

- While Ontario is entering summer, which have been lower transmission periods for COVID-19 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 immunity 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; second, BA.2.12.1 is more transmissible than earlier sub-lineages and its 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), resulting in variable antibody cross-neutralization after an infection. As a result, reinfections and breakthrough infections may result in a resurgence of COVID-19.

Ontario Epidemiology

Since December 31, 2021, molecular testing has been limited to populations at higher risk of transmission and/or higher risk of impacts resulting from transmission (e.g., severe disease, health care systems). On April 11, 2022, provincial PCR testing guidance was updated related to eligibility for COVID-19 treatment (e.g., inclusion of all symptomatic people aged 70 and older).¹⁶ Case counts are primarily based on positive molecular tests from these targeted populations therefore remain an underestimate of total COVID-19 cases in the province (e.g., not including populations ineligible for molecular testing and/or using antigen tests). Representative WGS surveillance is also only performed on cases with positive molecular tests. Changes to testing, reporting, and how epidemiological variables are defined (e.g., COVID-19 hospitalizations and deaths) have necessitated recalibration of epidemiological models and deeper understanding of new data sources (e.g., wastewater testing). Triangulation across indicators can provide greater confidence in trends.¹⁷

- The Ontario COVID-19 Genomics Network moved from sequencing 10% of eligible samples to 25% on May 12, 2022 and 100% on June 10, 2022.¹⁸
 - The most prevalent SARS-CoV-2 variant during the week of May 22-28, 2022 was BA.2 (41.3%), followed by BA.2.12.1 (25.8%), BA.2.12 (7.7%), BA.2.3 (7.5%), BA.2.20 (3.8%), BA.2.9 (3.6%), BA.5 (2.9%), BA.1.1 and BA.4 (each 1.3%), and BA.2.3.4 (0.9%).¹⁹
 - The proportion of BA.2 decreased from 54.5% (May 15-21) to 41.3% (May 22-28). The proportion of BA.2.12.1 increased from 16.8% (May 15-21) to 25.8% (May 22-28). The proportion of BA.5 cases increased from 1.2% (May 15-21) to 2.9% (May 22-28). The proportion of BA.4 cases increased from 0.7% (May 15-21) to 1.3% (May 22-28).
 - From March 6 to May 28, 2022, the weekly growth rate relative to BA.2 was: 1.74 (95% confidence interval [CI] 1.69-1.80) for BA.2.12.1, and 1.23 (95% CI 1.19-1.27) for BA.2.12.
- The weekly rate of confirmed COVID-19 cases has had a decreasing trend since the week of April 17, 2022.²⁰ From May 29 to June 4, 2022, 5,319 cases were reported to public health units compared to 6,049 cases the previous week.²¹ By age group, however, case rates increased the week of May 29 to June 4, 2022, compared to the previous week among the 0 to 4 (7.0%), 5 to 11 (1.9%) and 12 to 19 (7.9%) age groups; this is the first increase in these age groups since the week of April 3-9, 2022. In general, the number of cases should be interpreted with caution due to changes in testing eligibility.

- From early April 2022 onward, percent test positivity reported by PHO was relatively stable near 18-19%, before starting a downward trend.²² On June 10, 2022, PHO reported 7.1% test positivity.²² Although percent positivity is slowly declining since the end of April, it remains relatively high compared to earlier periods of the pandemic.
- The number of cases in long-term care home (LTCH) residents was lower in the weeks May 22 to June 4, 2022 (700 cases), compared to the prior two weeks (1,190 cases from May 8-21, 2022).²³ The number of outbreaks (25 vs 63), hospitalizations (13 vs 31) and deaths (2 vs 33) among residents also decreased the weeks of May 22 to June 4, compared to the previous two weeks.
- 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. Based on information included in CCM as of June 4, 2022, from the week of May 1, 2022 to the week of May 22, 2022, weekly hospitalizations decreased from 521 to 245, weekly ICU admissions decreased from 59 to 32, and weekly deaths decreased from 124 to 52.²⁴
- On June 14, 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. Uncertainty remains about whether these trends will continue.²⁵

Table 1. Risk Assessment for SARS-CoV-2 Omicron sub-lineage BA.2 and BA.2 sub-lineages

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

Epidemiology in Other Jurisdictions

Canada

WGS surveillance across Canada indicated that, of SARS-CoV-2 samples collected the week of May 22, 2022 (data still accumulating), 100% were Omicron, including: 1.6% BA.1.1, 90.8% BA.2 and its sub-lineages [38.8% BA.2, 27.8% BA.2.12.1, 16.9% BA.2.3, 7.3% other BA.2], 4.6% BA.4, and 3.0% BA.5.²⁶ On June 10, 2022, the government of Canada switched from daily to weekly reporting of COVID-19 epidemiological indicators. The Public Health Agency of Canada (PHAC) reported that, for the period of May 29 to June 4, 2022, the average daily number of cases decreased by 6% (1,464 to 1,376), the average positivity rate decreased by 0.4% (8.8% to 8.4%), and the average daily number of deaths decreased by 28% (18 to 13).²⁷

Select Other Jurisdictions

Global: The World Health Organization (WHO) reported that, as of the week May 15-20, BA.2.12.1, BA.5, and BA.4 sub-lineages are rising in prevalence globally and represented 28%, 4% and 2% of circulating sub-lineages, respectively.²⁸ From May 30 to June 5, 2022, the number of cases and new weekly deaths decreased globally by 12% and 22%, respectively, as compared to the previous week. Omicron lineages BA.1, BA.1.1, BA.1.X (BA.1 and pooled descendent sub-lineages) and BA.3 sub-lineages have declined to <1%. The WHO reported that the number of SARS-CoV-2 recombinant sequences submitted to the GISAID database continues to decline weekly, now representing <0.1% of sequences submitted during week.²⁰ The WHO notes that trends should be interpreted with caution due to several countries having changed their COVID-19 testing strategies. The WHO recommends maintaining enhanced SARS-CoV-2 testing and sequencing surveillance through the acute phase of the pandemic.

England: The UK Health Security Agency's (UKHSA) most recent VOC and variants under investigation (VUI) briefing reported that for England, of sequenced cases between April 24 to May 8, 2022, 97.0% were Omicron lineage BA.2 (VOC-22JAN-01), 0.4% were BA.1 (VOC-21NOV-01), 2.6% were comprised of BA.4 (VOC-22APR-03), Omicron lineage BA.5 (VOC-22APR-04) and Omicron recombinant XE (V-22APR-02).^{4,29} As of April 1, 2022, free universal symptomatic and asymptomatic testing is no longer provided to the general public in England ("Pillar 2" testing indications).³⁰ COVID-19 case rates and test positivity from "Pillar 1" testing indications (i.e. testing for those with a clinical need and for health/social care workers) remained similar in the week of June 6-12, 2022, compared to the previous week.³¹ Around the same time, UK general practitioner sentinel swabbing schemes reported one positive test. Between June 3-9, 2022, 58,590 people had a confirmed positive test result, which is an increase of 64.5% compared to the previous seven days.³² The Office for National Statistics (ONS) reported early signs of a possible increase in COVID-19 cases.³³ Between June 5-12, 2022, 4,305 individuals went into hospital with COVID-19, which is an increase of 33.0% compared to the previous seven days.³² During June 3-9, 2022, there were 273 deaths within 28 days of a positive SARS-CoV-2 test, which is a decrease of 17.0% compared to the previous seven days.

US: According to NOWCAST modelling projections, the US Centers for Disease Control and Prevention (CDC) estimated that for the week ending June 11, 2022, approximately 100% of SARS-CoV-2 cases were Omicron (64.2% [95% PI 59.9-68.3%] BA.2.12.1, 14.2% [95% PI 12.7-15.9%] BA.2, 13.3% [95% PI 10.0-17.4%] BA.5, and 8.3% [95% PI 6.3-10.7%] BA.4).³⁴ According to the COVID Data Tracker Weekly Review for June 10, 2022, as of June 8, 2022, the 7-day moving average of daily new SARS-CoV-2 cases (109,032) increased 8.0% compared to the previous week's 7-day moving average (100,916), and is a continuation of a rising trend in cases.³⁵ The 7-day average percent positivity is increasing and is 13.7%. The 7-day daily average hospitalizations for June 1-7, 2022, was 4,127, which is an 8.0% increase from May 25-31, 2022 (3,820). The 7-day moving average of new deaths increased 18.6%, from 258 down to 306 in the CDC June 10, 2022 Interpretive Summary.

Genomic Features and Evolution

High transmission events, combined with other co-circulating lineages, suboptimal vaccination coverage, and waning immunity, may result in further lineage evolution and recombination events.^{36,37} A few studies are highlighted below:

- Using cell lines expressing angiotensin converting enzyme-2 (ACE2) orthologs from different animal species and engineered pseudoviruses bearing various S protein mutations, Neerukonda et al. investigated the ability of BA.1, BA.1.1, BA.2, and BA.3 to use ACE2 orthologs from African green monkey, Chinese rufous horseshoe bat, ferret, mouse, Chinese hamster, Syrian golden hamster, white-tailed deer, swine, bovine, and Malayan pangolin.³⁸ Pseudoviruses bearing Omicron S proteins exhibited significantly higher levels of infection compared to wild-type with pseudoviruses bearing wild-type S proteins in cells expressing African green monkey, Chinese rufous horseshoe bat, ferret, mouse, Chinese hamster, Syrian golden hamster, white-tailed deer (except BA.1), swine, and bovine ACE2 receptors. The authors conclude that the S protein substitutions in the BA.1, BA.1.1, BA.2, and BA.3 sub-lineages allow for use of diverse ACE2 orthologues for entry and therefore have the potential to broaden the risk of Omicron variants to infect animal species and spill back to humans.
- Kannan et al., analyzed available gene sequences and confirmatory structures of combined S protein-ACE2 receptor or S protein-antibody complexes, and conducted molecular dynamics simulations to gain insight into the BA.2 mutation profile and the impact of mutations on interactions with receptor and/or monoclonal antibodies.³⁹ Sequence analyses revealed a total of 50 signature mutations in BA.2 (with ~100% prevalence), as compared to 48 mutations present in BA.1. In addition, 17 mutations of BA.1 were not found in BA.2 and BA.2 had 19 mutations that were not found in BA.1. Out of the 50 signature BA.2 mutations, 28 (56%) were in the S protein. In addition, 8 of 28 BA.2 S protein mutations were not present in BA.1, and 12 of 32 BA.1 S protein mutations were not present in BA.2. There were 20 common mutation sites shared by BA.1 and BA.2. Of the 28 mutations in the BA.2 S protein, 24 of were in the S1 subunit which is involved in the initial receptor binding. The authors note that the presence of the G142D mutation in BA.2, which was a signature mutation of the highly infectious and pathogenic Delta variant, suggests BA.2 could evade monoclonal antibody recognition through a similar mechanism as the Delta variant. In summary, the authors conclude that it appears that BA.2 retained most of the BA.1 mutational profile but had additional mutations, including G142D of Delta variant improving evasion of antibody binding, while preserving some wild-type SARS-CoV-2 residues to maintain receptor binding.

Testing

Antigen testing: Most of the antigen tests used in Ontario detect the nucleocapsid (N) protein. In theory, the limited number of N protein mutation differences between BA.1 and BA.2 (BA.2 having an extra S413R mutation)⁴⁰ suggests that antigen test performance between all three sub-lineages should be similar, although additional conformational changes distant from the N protein may impact detection as well.⁴¹ Recently, Mak et al., evaluated the *in vitro* analytical sensitivity of 12 antigen assays to detect BA.2.⁴² The authors reported similar sensitivity among all 12 assays, with five assays having slightly increased sensitivity (up to 10-fold difference). As expected, polymerase chain reaction (PCR) was at least 100-fold more sensitive than the antigen tests. The authors conclude that the antigen assays evaluated in their study can be used for first-line screening of BA.2. Similar results were found at the PHAC's National Microbiology Laboratory (NML), where the limit of detection of Wuhan, Alpha, BA.1, and BA.2 strains was relatively comparable among seven antigen tests approved by Health Canada (internal communication; unpublished). Further studies are required to evaluate the clinical impact of sub-lineage variations on antigen test performance in real-world settings. For example, BA.2.20 has an additional N protein mutation (D348H) which is not found in other Omicron sub-lineages at present, and its impact is not yet known. In addition to mutations, other differences between Omicron sub-lineages such as viral load dynamics and tissue tropism may impact the accuracy of antigen tests at different time points and collection sites during a COVID-19 infection.

Molecular testing: So far, the detection capacity of Omicron sub-lineages (including BA.1 and BA.2) has been maintained on molecular testing platforms. Due to the higher intrinsic sensitivity of molecular tests compared to antigen tests, a reduction in accuracy due to sub-lineage mutations has not yet been reported. The BA.2 sub-lineages also do not harbour the *del69-70* mutation and are therefore not expected to have an S gene target failure/dropout pattern on some molecular assays. However, similarly to antigen testing, differences between Omicron sub-lineages such as viral load dynamics and tissue tropism may impact the accuracy of molecular tests at different time points and collection sites during a COVID-19 infection.

Whole genome sequencing surveillance: Current BA.2 sub-lineages can be detected and differentiated with the pangolin bioinformatics pipeline used by the Ontario COVID-19 Genomic Network for WGS surveillance.⁴³

Transmissibility

It remains unclear to what extent the increased transmission of BA.2 compared to BA.1 or BA.1.1, and BA.2.12.1 compared to BA.2, is due to inherent characteristics of these sub-lineages (i.e., viral load, enhanced ability to infect cells, tissue tropism) or due to immune evasion or antibody waning. Evidence suggests higher viral load might play a role in the BA.2 advantage over BA.1 and BA.1.1.⁴⁴⁻⁴⁶ For context, when BA.1 and BA.1.1 emerged, these sub-lineages were the most transmissible sub-lineages up to that time. When BA.2 emerged, it dominated transmission over BA.1 and BA.1.1. At the moment, BA.2.12.1 has emerged in Ontario and is comprising a growing proportion of cases by WGS surveillance.⁴⁷ BA.2.12.1 harbours an S protein mutation at the L452 residue that is thought to confer increased transmissibility through both higher cell fusogenicity and immune escape characteristics.²⁸

- Sofonea et al., analyzed the epidemiology of BA.1 and BA.2 in France.⁴⁸ Using sequencing data, they estimated BA.2 to have a growth advantage of 48.9% (95% CI 44.2-53.6%) over BA.1. They also observed that cases likely caused by Omicron had a significantly higher cycle threshold (Ct) value than cases likely caused by Delta. BA.2 cases had a lower Ct than BA.1 cases, indicating higher viral load.
- Hirose et al., evaluated the environmental stability and disinfection efficacy of the wild-type Wuhan strain as well as Alpha, Beta, Gamma, Delta, BA.1, and BA.2 on plastic and human skin surfaces.⁴⁹ On plastic surfaces, the median survival times of the Wuhan strain, Alpha, Beta, Gamma, Delta, BA.1, and BA.2 were 56.0 hours (95% CI, 39.0-76.7 hours), 191.3 hours (95% CI, 152.5-232.1 hours), 156.6 hours (95% CI, 122.7-192.9 hours), 59.3 hours (95% CI, 43.9-77.7 hours), 114.0 hours (95% CI, 91.3-139.1 hours), 193.5 hours (95% CI, 153.1-236.2 hours), and 199.7 hours (95% CI, 163.9-237.1 hours), respectively, and on human skin, the median survival times were 8.6 hours (95% CI, 6.5-10.9 hours), 19.6 hours (95% CI, 14.8-25.3 h), 19.1 hours (95% CI, 13.9-25.3 hours), 11.0 hours (95% CI, 8.1-14.7 hours), 16.8 hours (95% CI, 13.1-21.1 hours), 21.1 hours (95%CI, 15.8-27.6 hours), and 22.5 hours (95% CI, 16.3-29.7 hours), respectively. Thus, BA.1 and BA.2 had similar stability and the longest survival times among tested strains. Analyses of half-life showed similar trends. *In vitro* disinfectant analyses showed that the Wuhan strain and Gamma were completely inactivated within 15 seconds by 32.5% EA (Effectiveness of Ethanol, log reduction > 4), and BA.1 and BA.2 were completely inactivated within 15 seconds by 40% EA. The ethanol concentration that was required to achieve a logarithmic decrease of 3.5 in virus titer concentration in a 15-second disinfection reaction for the Wuhan strain, Alpha, Beta, Gamma, Delta, BA.1, and BA.2 were 27.5%, 29.3%, 29.7%, 27.3%, 30.2%, 31.1%, and 32.7%, respectively. On human skin, all viruses were completely inactivated after exposure to 35% EA for 15 seconds. The authors state that the high environmental stability of BA.1 and BA.2 could increase the risk of contact transmission and contribute to the spread of these variants.
- Zhang et al., monitored the aerosol emission characteristics of patients infected with BA.2 (n=51) or BA.1 (n=34) as well as virus growth rates in human cells, and analyzed the relationship between viral load in upper respiratory tract and the amount of exhaled viral aerosols.⁵⁰ The total positive rate of exhaled breath condensate (EBC) samples from BA.1 patients was 17.65%, whereas it was 29.41% for BA.2 patients. The Ct value of throat swabs targeting the ORF1ab and N genes at admission was higher among BA.2 patients as compared to BA.1 patients (for N gene, *P = 0.027; for ORF1ab gene, **P = 0.009). The average virus breath emission rate (BER) for BA.1 patients was from 1.48×10^4 to 4.04×10^5 copies/hour, whereas the overall BER from BA.2 patients was from 2.06×10^4 to 2.93×10^6 copies/hour. Both BA.1 and BA.2 patients had a similar average BER early in infection. The authors observed that the viral load in the upper respiratory tract had a similar trend as to the BER. The authors conclude that the viral load in the upper respiratory tract and the amount of exhaled viral aerosols have the same variation trends, which may provide evidence for the increasing transmissibility of SARS-CoV-2 variants when the viral loads in upper respiratory tract also increased.

Disease Severity

- Loconsole et al., described the first 284 BA.2 patients in southern Italy and assessed the differences in the clinical characteristics of patients infected with BA.1 (n=175) compared to BA.2.⁵¹ Of the 284 BA.2 patients, 163 (57.4%) were asymptomatic compared to 138 (78.9%) of BA.1 cases. 74 BA.2 infections (26.1%) were mild compared to 31 (17.7%) for BA.1 (p=0.039), 35 BA.2 infections (13.3%) were moderate compared to 6 (3.4%) for BA.1 cases (p=0.0005). 66 BA.2 cases (23.2%) required hospitalization compared to 29 (16.6%) for BA.1 (p=0.086), and five BA.2 cases (1.7%) died compared to zero deaths among the BA.1 cases. Mild infection was defined as the absence of fever (< 38°C) with cough, malaise, or gastrointestinal symptoms, and moderate infection was defined as fever (≥ 38 °C), upper respiratory symptoms, anosmia/ageusia, and/or gastrointestinal symptoms. The number of reinfections increased from 0.06% during week 6 of 2022 to 2.2% during week 10. Although none of these patients had severe disease (presence of fever ≥ 38 °C with dyspnea and lower respiratory tract infection), six required hospitalization.
- Sievers et al., used WGS and the German national surveillance database to estimate the odds ratio for severe disease progression associated with BA.1 and BA.2 infections compared with Delta infection in a retrospective cohort study.⁵² A higher percentage of Delta cases (8.3%) resulted in hospitalizations compared to cases with BA.1 and BA.2 (both 3.0% hospitalization); however, for children < 15 years old there was no difference between Delta (1.5%; 77/5,230) and BA.1 (1.5%; 40/2,738) or BA.2 (1.4%; 14/977) infections in terms of frequency of hospitalization. After adjusting for age group, vaccination status, sex, federal state of notifying health authority and calendar week of notification, the adjusted odds ratio (adjOR) of hospitalization for BA.1 and BA.2 infections compared with a Delta variant infection were similar (adjOR BA.1: 0.35; 95% CI: 0.29–0.43 and adjOR BA.2: 0.30; 95% CI: 0.22–0.40). Analysis by age showed that 0–14 year old individuals had no significant difference in hospitalization depending on the variant, but a strong effect was observed in age groups 35 years and above (odds of hospitalization reduced up to 80% for BA.1 and BA.2). Using the same covariates as for hospitalization, the odds of a COVID-19 case being admitted to ICU was reduced by more than 80% for BA.1 and BA.2 as compared to Delta (adjOR BA.1: 0.20 (95% CI: 0.12–0.32); adjOR BA.2: 0.17 (95% CI: 0.07–0.39)). Using the same covariates as for hospitalisation, the odds for dying after an infection with BA.1 or BA.2 were reduced as compared with Delta (adjOR BA.1: 0.38 [95% CI: 0.25–0.58]; adjOR BA.2: 0.16 [95% CI: 0.08–0.3]).
- Fowle et al., described a university-affiliated cohort of 44 BA.2 cases in Arizona, USA.⁵³ The median age of case-patients was 21 (interquartile range 19–24) years. At least 26 (59%) cases experienced > 1 symptom, most of which were consistent with an upper respiratory tract viral infection (e.g., sore throat, rhinorrhea and cold-like symptoms, cough, and/or fever). Only 8 (18%) of cases sought medical attention from the university clinic <7 days before or after their BA.2 positive specimen collection date. None of the cases were hospitalized and none died. The authors note that because their study involved a university-affiliated cohort, the findings might not be generalizable to more diverse populations.

VE and Reinfections

Monitoring of VE and reinfection risk for BA.2.12.1, and other emerging BA.2 sub-lineages is important for assessing the impact associated with these sub-lineages in Ontario. Evidence on VE and reinfections will continue to be confounded by differences in public health measures and vaccination programs, history of infections, and recentness and coverage of booster programs across jurisdictions. Several new studies that emerged since the last PHO Risk Assessment are described below:

- Chemaitelly et al., used a matched test-negative case-control study to estimate duration of protection of second and third doses of mRNA COVID-19 vaccines against BA.1 and BA.2 symptomatic infections in Qatar.⁵⁴ BNT162b2 (Pfizer-BioNTech) VE against BA.2 infection was highest at 51.7% (95% CI: 43.2–58.9%) in the first 3 months after the second dose, then declined to roughly 10% or less, and then increased to 43.7% (95% CI: 36.5–50.0%) in the first month after a third dose, dropping slightly to 40.2% (95% CI: 34.2–45.7%) in the second month and onwards. The authors report a similar pattern was observed for mRNA1273 (Moderna) effectiveness. The VE against severe, critical, or fatal COVID-19 due to an Omicron infection (e.g., BA.1 or BA.2), was within 70–80% any time after the second dose of either Pfizer-BioNTech or Moderna; though, Pfizer-BioNTech VE was >90%, and the 95% CIs for the Moderna VE lacked adequate statistical precision due to small number of cases hospitalized. An analysis of differential waning for BA.1 versus BA.2 showed no difference in the pattern of waning over time between the two sub-lineages. The authors conclude that mRNA VE against severe outcomes due to Omicron infections is strong after the second dose (>70%), and even stronger after a third dose (>90%) and suggest the need to consider rapid implementation of an additional vaccine dose coincident with the emergence of a new wave or variant, at least to those most vulnerable to severe outcomes.
- Neerukonda et al. investigated the neutralizing activity in sera from individuals who received three doses of the Pfizer-BioNTech vaccine.³⁸ Neutralization titers against pseudoviruses expressing BA.1 (geometric mean titer [GMT]:1087), BA.2 (GMT:961), BA.3 (GMT:916), and BA.1.1 (GMT:916) S proteins were reduced by 6.6-fold ($p \leq 0.05$), 7.8-fold ($p \leq 0.0005$), 8.2-fold ($p \leq 0.0001$), and 7.7-fold ($p \leq 0.0005$), respectively, compared to pseudoviruses expressing wild-type S proteins (GMT:7527). Based on sera from five vaccinated individuals who experienced a breakthrough infection after a third vaccine dose, when BA.1 or BA.1.1 were predominant, the highest neutralization activity was against pseudoviruses expressing wild-type S proteins (GMT: 16270) followed by BA.1 (GMT: 6204), BA.1.1 (GMT: 5873), BA.3 (GMT: 5407) and BA.2 (GMT: 3906), which is 7-8-fold lower compared to wild-type.
- Qasmieh et al., conducted a cross-sectional survey in New York City during the BA.2/BA.2.12.1 surge, when the official SARS-CoV-2 case count was 49,253 and BA.2.12.2 comprised 20% of reported cases.⁵⁵ Confidence intervals were quite wide in their analyses. They observed that fully vaccinated, boosted individuals had higher SARS-CoV-2 prevalence (25.2%, 95% CI 19.8%-30.5%) compared to vaccinated but not boosted individuals (11.8%, 95% CI 3.5%-20.1%) and unvaccinated individuals (18.9%, 95% CI 10.2%-27.5%). The authors state that these differences are likely due to differences in SARS-CoV-2 exposure and behaviors between the two groups. Individuals who claimed to have tested positive for SARS-CoV-2 once within 14 days of the study survey (40.4%, 95% CI 27.2%, 95% CI 27.2%-53.6%) or more than once (39.2%, 95% CI 28.2%-50.2%) had higher prevalence than individuals who said they never tested positive (10.7%, 95% CI 4.7%-16.6%). Among individuals who were either fully vaccinated or vaccinated, boosted

those who had a past SARS-CoV-2 infection (hybrid protection) had a prevalence of 28.9% (95% CI 22.6%-35.1%), compared with 12.9% (95% CI 5.6%-20.1%) among those who did not have a previous SARS-CoV-2 infection (vaccine-induced protection only). Among individuals who were not vaccinated and/or boosted, those who had infection-induced protection only, had a prevalence of 29.8% (95% CI 16.6%-43.1%), compared with 0.9% (95% CI 0.0%-2.7%) among those with no protection from vaccine or infection. The authors state that this suggests prior infection is a strong marker for exposure during surges and could be a marker for risk compensation. The authors suggest that increasing first, second and subsequent vaccine doses in this group is a key strategy to reduce the population risk of severe COVID and death.

- The aforementioned study by Sievers et al., also analyzed BA.2 severity compared by Delta, based on vaccination status.⁵² When stratifying by vaccination status, the proportions of hospitalisations for (booster-) vaccinated cases compared with unvaccinated cases was reduced (for BA.1: 2.3% hospitalizations (244/10,440) among (booster-) vaccinated cases vs 4.3% among unvaccinated; for BA.2: 2.3% (113/4,963) hospitalizations among (booster-) vaccinated cases vs 4.7% among unvaccinated; for Delta: 7.3% (768/10,482) hospitalizations among (booster-) vaccinated cases vs 9.1% among unvaccinated cases). Regardless of vaccination status, the odds of being hospitalized after BA.1 or BA.2 infection was significantly reduced compared with Delta.
- Hachmann et al., reported that BA.2.12.1 substantially escapes neutralizing antibodies (NAb) induced by both vaccination and infection.⁵⁶ Two weeks following a third Pfizer-BioNTech COVID-19 vaccine dose, median neutralizing antibody titers increased but were 6.4-, 7.0-, 14.1-fold reduced to BA.1, BA.2, and BA.2.12.1, compared with a wild-type strain (WA1/2020), respectively. Median BA.2.12.1 titers were 2.2-fold lower compared to BA.1 titers. In the infected cohort, only one individual was unvaccinated (therefore almost entirely breakthrough cases), with sera collected a median of 29 days after diagnosis. These sera showed a 6.4-, 5.8-, 9.6-fold reduction in neutralizing titers to BA.1, BA.2, and BA.2.12.1, compared to WA1/2020, respectively. Median BA.2.12.1 neutralizing titers were 1.5-fold lower than median BA.1 titers. The authors conclude that their observations indicate that BA.2.12.1 substantially escapes neutralizing antibodies induced by both vaccination and infection. BA.2.12.1 titers were lower than BA.1 and BA.2 titers, suggesting continued SARS-CoV-2 evolution with increasing ability to escape neutralization.

Implications for Practice

- Although epidemiological indicators show that the BA.2 wave is declining in Ontario, the emergence of sub-lineages of BA.2 (e.g., BA.2.12.1, BA.2.3, BA.2.20), as well as 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, other Omicron sub-lineages with increased transmissibility such as BA.2.12.1, could cause an increase in COVID-19 cases during the summer and potentially reverse current downward case trends. Waning vaccine immunity, variable antibody cross-neutralization across SARS-CoV-2 sub-lineages after an infection, and the progressive reduction in public health measures, require that Ontario COVID-19 epidemiology be closely monitored.

- As we continue to learn about Omicron sub-lineages circulating in Ontario, to achieve the overarching pandemic response goals of minimizing morbidity and mortality (including PACS), as well as minimizing 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.⁵⁷
- 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 have limited ability to reduce transmissions. In addition, VE against infection wanes over time i.e., 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 lower VE. 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.⁵⁸⁻⁶⁰ 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."⁶¹ The emergence of the BA.2 sub-lineage when jurisdictions were experiencing a decline of the BA.1 and BA.1.1 waves, and the identification of other sub-lineages such as BA.2.12, BA.4, and BA.5 in Ontario,⁶² South Africa, and Portugal,⁶³ underscore the need for sustained WGS surveillance.
- Ongoing risk communication to the population regarding high levels of SARS-CoV-2 transmission and COVID-19 disease risk can be helpful, especially in the context of decreasing case counts but high test positivity rates among those eligible for testing, <50% third dose uptake, and the emergence of more transmissible sub-lineages in Ontario.¹⁴

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