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EVIDENCE BRIEF

COVID-19 Omicron Variant Sub-lineage BA.2: Evidence and Risk Assessment (up to date as of March 8, 2022)

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Key Messages

- The proportion of whole genome sequencing samples identified as BA.2 in Ontario have an increasing trend over the past several weeks: 6.3% the week of January 23 to 29, increasing to 12.3% the week of February 13 to 19.
- As of March 7, 2022, more than 227,695 BA.2 sequences have been reported globally from at least 92 countries. Denmark continues to report the majority of BA.2 cases, with cases increasing in several other countries, including the United Kingdom and the United States.
- Studies and real world epidemiological data continue to suggest BA.2 is more transmissible than the Omicron sub-lineages that dominated recent and current Omicron epidemic waves (B.1.1.529, BA.1, BA.1.1), but the relative contributions of increased transmissibility inherent in BA.2 and immune evasion (due to mutations and waning immunity), is unclear.
- The current risk of BA.2 sub-lineage transmission in Ontario is high with a moderate degree of uncertainty. The risk of severe disease in Ontario is moderate, with a moderate degree of uncertainty. The risk of reinfection is high with a moderate degree of uncertainty in Ontario. The risk of breakthrough infection in Ontario is high with a moderate degree of uncertainty. The risk of impact of the BA.2 sub-lineage on testing in Ontario is moderate, with a moderate degree of uncertainty. The risk of impact on surveillance in Ontario is moderate with a low degree of uncertainty. Variant surveillance supported by whole genome sequencing can be used to distinguish the BA.2 sub-lineage from other variants.

Issue and Research Question

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) Omicron Variant of Concern (VOC) consists of several sub-lineages (i.e., B.1.1.529, BA.1, BA.1.1, BA.2, and BA.3).[1] The Omicron variant BA.2 sub-lineage has been identified in at least 92 countries, with the highest case counts reported in Denmark.[2] Considering the increased transmissibility of the Omicron BA.1 sub-lineage, it is important to monitor the potential impact the BA.2 sub-lineage might have in Ontario. Since the last report published on March 1, 2022,[3] more evidence has emerged regarding BA.2, including its transmissibility, immune evasion, and disease severity. This evidence brief updates the Public Health Ontario (PHO) report published March 1, 2022, and summarizes available information and evidence on the BA.1 sub-lineage relevant to the risk in Ontario up to March 8, 2022. Data from Ontario was available up to March 9, 2022.

Methods

PHO Library Services conducted daily searches of primary and preprint literature using the MEDLINE database (search strategies available upon request). In addition, PHO performed grey literature searches daily using various news feeds and custom search engines. English-language peer-reviewed and non-peer-reviewed (preprint) records that described Coronavirus Disease 2019 (COVID-19) variants were included. In some of the literature, the term Omicron is used to refer to BA.1 and/or BA.1.1, which have been the dominant sub-lineages in most jurisdictions.

Genomic Features

The Omicron variant lineage consists of five sub-lineages: B.1.1.529, BA.1, BA.1.1, BA.2, BA.3.2.[4] The Omicron sub-variants share 39 mutations (mostly in the spike protein); however, BA.2 has an additional 27 mutations, including 10 unique mutations.[5] BA.1 differs from BA.2 by 28 mutations and 50 amino acids, which is approximately twice as many amino acid differences as the number of differences between four other VOC (Alpha, Beta, Gamma, Delta) and wild-type SARS-CoV-2. In a February 22, 2022 statement, the World Health Organization (WHO) stated that BA.2 should remain classified as an Omicron sub-lineage,[6] despite growing evidence of BA.2 possessing unique traits.

S-gene target failure (SGTF) has been used as a proxy for the Omicron BA.1 and BA.1.1 variants due to the amino acid deletion at position 69 and 70 of the S protein, and S-gene target positive (SGTP) has been used as a proxy for BA.2 because it is usually missing this deletion. Recently, however, a small number of BA.2 sequences containing the deletion at 69 and 70 have been identified.[7] As of February 16, 2022, there were 20 BA.2 sequences in the United Kingdom (UK) genomic data with the deletion detected, out of 27,179 BA.2 sequences.

- Since the last PHO BA.2 Risk Assessment,[3] a study using sera from infected hamsters completed antigenic cartography to quantify and visualize the antigenic differences between SARS-CoV-2 VOCs .[8] Antigenic cartography is used to measure antigenic drift and inform seasonal influenza virus vaccine antigen selection. The study found that although early variants clustered together based on antigens, Omicron BA.1 and BA.2 sub-lineages are distinct antigenic outliers. Omicron BA.2 with BA.1 were positioned distantly from each other in the map, with BA.2 slightly closer to the main cluster than BA.1, which the authors say is suggestive of BA.1 inducing qualitatively unique antibody responses, and BA.1 and BA.2 are antigenically distinct variants.

Diagnostics

Since the last PHO BA.2 Risk Assessment, no additional publications about diagnostics were identified.[3]

Epidemiology

- As of March 4, 2022, whole genome sequencing (WGS) from surveillance testing across Canada reported that of SARS-CoV-2 samples collected the week of February 13, 2022, 99.8% were Omicron (29.2% BA.1, 59.6% BA.1.1, 11.0% BA.2), but data were still accumulating.[9] This is an increase compared to the proportion of BA.2 for samples collected the week of January 30, 2022 (99.5% Omicron: 33.5% BA.1, 56.7% BA.1.1, 9.3% BA.2). On March 8, 2022, Canada reported 5,654 new cases, 53 new deaths, 113,187 active cases, and the daily percent positivity (over the previous 7 days) was 11.9%, all of which are a decrease compared to the previous two weeks. The Public Health Agency of Canada notes that due to changes in COVID-19 testing policies in many jurisdictions starting in late December 2021, case counts will underestimate the total burden of disease.

- Based on 3,683 cases sequenced by the Ontario COVID-19 Genomics Network for representative surveillance from January 23 to February 19, 2022:[10]

    - The proportion of cases identified as BA.2 have had an increasing trend over the past several weeks: 6.3% week of January 23 to 29, 9.0% week of January 30 to February 5, 11% week of February 6 to 12, and o 12.3% week of February 13 to 19.

    - From November 28, 2021 to February 19, 2022, the weekly growth rate of BA.2 was 1.61 (95% confidence interval [CI] 1.54 - 1.68) times that of BA.1.1.

    - A total of 525 BA.2 cases have been identified since January 1, 2021.

    - Among Delta and Omicron cases from January 23, 2022 to February 19, 2022 linked to Public Health Case and Contact Management Solution (n=3,419), the majority of BA.2 cases occurred in individuals who had completed their vaccination series, i.e. post-series completion unvaccinated individuals (34.2%), followed by individuals who were post-booster dose (31.2%), followed by unvaccinated individuals (30.6%).

Notable epidemiological trends from select jurisdictions are:

- **Global:** As of March 7, 2022, GISAID reported 227,695 sequences of the BA.2 sub-lineage, with reports from at least 92 countries.[2] According to GISAID, the 7-day rolling average of BA.2-positive sequences globally on February 24, 2022 was 53% (95% CI 52-54). Of countries reporting to GISAID, cumulative prevalence between December 5, 2021 and February 27, 2022 (posted on March 8, 2022) was highest in Denmark, at 56%.[2,11] The WHO March 8, 2022 weekly COVID-19 report (with data up to March 6, 2022) stated that of Omicron lineages reported within the last 30 days, BA.1.1 was the predominant sub-variant (187,058 sequences, 41%), followed by BA.2 (156,014 sequences, 34.2%) and BA.1 (112,655 sequences, 24.7%) and BA.3 (101 sequences, <1%).[12] The WHO notes that due to surveillance limitations, their global VOC distribution data should be interpreted cautiously.

- **Denmark:** Total COVID-19 case numbers have decreased by 36% between weeks 7 and 8 of 2022.[13] In week 8, of 2151 samples with WGS, 68.8% were BA.2, 28.0% BA.2_H78Y, 1.7% BA.1.1, 1.4% BA.1, and 0.0% BA.3.

- **India:** According to the OutbreakInfo website, using data from the GISAID initiative database, the BA.2 sub-lineage was found in 12% of sequenced samples.[2]

- **Norway:** According to the OutbreakInfo website, using data from the GISAID initiative database, the BA.2 sub-lineage was found in 3% of sequenced samples.[2]

- **UK:**[14] In the week ending February 26, 2022, the estimated percentage of BA.2 infections increased in England, Wales, and Scotland and decreased in Northern Ireland. During the same time period, the percentage of cases compatible with the Omicron BA.1 variant decreased in England, Wales, and Northern Ireland and increased in Scotland.[15] The UK Health Security Agency's (UKHSA) most recent VOC and variants under investigation report for England [7] found that of all WGS cases between February 13 and 20, 2022, 69.2% were Omicron BA.1 (VOC21NOV-01), 30.5% were Omicron lineage BA.2 (VUI-22JAN-01), and 0.3% were other variants. The proportion of S-gene target positive (SGTP) cases increased to 52.3% on February 20, 2022 from 18.7% on February 6, 2022. Further, 97.2% of SGTP are BA.2, making SGTP a reasonable proxy for BA.2 in England. Based on data from December 1, 2021 to February 16, 2022, the median growth rate of BA.2 is +82.7% per week relative to other Omicron sub-lineages.

- **United States (US):** According to sequences tested the week ending February 26, 2022 by the US Centers for Disease Control and Prevention (CDC), BA.2 makes up approximately 8.3% (95%CI 6.3, 10.7) of new infections.[16] According to NOWCAST modelling projections, the US CDC estimated that for the week ending March 5, 2022, 100% of SARS-CoV-2 cases were Omicron (73.7% BA.1.1, 14.7% B.1.1.529, 11.6% BA.2). As of March 2, 2022, the 7-day moving average of daily new SARS-CoV-2 cases (53,017) decreased -28.5% compared to the previous week's 7-day moving average (74,143).[4]

Transmissibility

Since the last PHO BA.2 Risk Assessment, additional studies have shown that BA.2 has a growth advantage over BA.1.[3,17] It is unclear to what extent any increased transmission of BA.2 compared to BA.1 or BA1.1 is due to inherent characteristics of this sub-lineage (i.e., enhanced ability to infect cells, tissue tropism) or due to immune evasion.

- An updated analysis of GISAID data reported by the WHO estimated a pooled mean transmission advantage for BA.2 of 56% (95% CI: 42%-72%) compared to BA.1, under the assumption of an unchanged generation time.[12]

- According to the most recent UKHSA variants of concern and variants under investigation report for England, the growth rate of BA.2 estimated with data up to February 21, 2022 was 0.83 per week, which is lower than the estimate of 1.03 using data up to February 7, 2022.[7] Based on case test dates January 1 to 31, 2022 and contact tracing data up to February 21, 2022, the adjusted BA.2 secondary attack rate was 14.3% (13.6%-14.9%) for households and 6.1% (5.0%-7.2%) for non-households (adjusted for age and sex of the exposer and the contact, the week of positive test of the exposer and whether the contact completed contact tracing). For reference, the BA.1 SARs were 11.4% (11.2%-11.5%) and 4.6% (4.5%-4.8%), for household and non-household, respectively.

- A study in Qatar investigated the effects of previous vaccination and prior infection on Omicron BA.1 (n=32,153) and BA.2 (n=124,049) infectiousness (based on cycle threshold (Ct) value).[18] Relative to BA.1, BA.2 had 3.53 fewer cycles (95% CI: 3.46-3.60), indicating more virus and which the authors state indicates higher infectiousness. The Ct value decreased with time since second and third vaccinations, which the authors suggest indicates waning vaccine effectiveness. Individuals who received their boosters in the month preceding had the four highest Ct values. Individuals with a prior infection had Ct values 1.30 (95% CI: 1.20-1.39) cycles higher than those without prior infection, which the authors say suggesting previous infection may lead to a lower level of infectiousness. Ct values declined gradually with age. Ct values were lowest for individuals tested because of symptoms of COVID-19.Stratified analyses for BA.1 and BA.2 showed similar findings.

- An algebraic topology-based model was used to evaluate Omicron sub-lineage infectivity by examining binding free energy (BFE) changes of the receptor binding domain (RBD)-angiotensin converting enzyme 2 (ACE2) complex (larger change means higher infectivity).[19] This study found that BA.2 had the highest BFE change when compared to BA.1 and BA.3, and estimated BA.2 as approximately 20, 4.2, and 1.5 times as infectious as ancestral SARS-CoV-2, Delta variant, and BA.1, respectively. This study analyzed the impact of antibody and S protein complex mutations on potential for vaccine breakthrough infection. BA.2 had an estimated vaccine breakthrough rate of 0.91, whereas breakthrough rates for BA.1, BA.3, and Delta were 0.88, 0.89 and 0.37, respectively. Using analyses of neutralization capability, the study estimated BA.2 to be 30% and 17-fold more capable than BA.1 and Delta, respectively, to escape current vaccines.

- To compare the relative fitness and infectivity of BA.1 and BA.2, a study inoculated five hamsters with a mixture (1:1) of BA.1 and BA.2.[20] At 4 days post infection (dpi), WGS showed that BA.1 became dominant in the nasal turbinates of all the animals, which the authors say is suggestive that BA.1 outcompetes BA.2 during upper airway tract replication in hamsters. The study compared the histopathology caused by BA.1 and BA.2 infections. In BALB/c mice, inflammatory cell infiltration around the bronchi/bronchioles and in the alveolar spaces was minimal at 2 and 5 dpi in both BA.1- and BA.2-infected mice, and viral RNA and antigen were found in the bronchiolar and alveolar epithelium of both BA.1- and BA.2-infected mice, decreasing over time. Compared to earlier studies of BALB/c infection with the Beta variant, BA.1 and BA.2 revealed substantially less infectivity in the lung.

Symptoms

In a media interview, a health officer in the US stated that dizziness and fatigue seem to be new COVID-19 symptoms associated with BA.2 infections,[21] but little new evidence regarding symptoms and clinical presentation have emerged since the last PHO BA.2 Risk Assessment.[3]

Disease Severity

Evidence of disease severity caused by BA.2 as compared to COVID-19 caused by ancestral SARS-CoV-2 and other variants is slowly emerging, but remains unclear.[3] Publications since the last PHO BA.2 Risk Assessment are described below.

- According to the most recent UKHSA variant technical report, the risk of hospitalization following a BA.2 infection appears similar to that of a BA.1 infection (hazard ratio 0.87, 95% CI: 0.75-1.00).[7]

- In week 8 of 2022, Denmark reported 68.8% of samples from WGS were BA.2, which is the highest proportion of BA.2 reported in the GISAID. In week 8 in Denmark (68.8% of WGS samples were BA.2),[13] the number of new hospital admissions increased by 11% whereas admissions to the ICU and the proportion receiving COVID-specific treatment in the ICU were relatively stable. The number of COVID-related deaths increased in week 8 compared to week 7.

- A study inoculated BALB/c mice with 10^5 plaque-forming units of BA.1 or BA.2 or a control, and reported that intranasal inoculation with BA.1 or BA.2 did not cause body weight changes.[20] Using surrogate markers for bronchoconstriction and airway obstruction, no changes were observed in the BA.1- or BA.2-infected groups at any timepoint post-infection compared to the mock-infected group, whereas previous studies with B.1.351 infected mice resulted significant changes in bronchoconstriction and airway obstruction at 2 dpi. BA.2-infected mice had significantly higher levels of several pro-inflammatory cytokines and chemokines (e.g., IL-1β, IFN-γ, and MIP-1β) at 2 or 3 dpi compared to BA.1 infected mice; but, compared to Beta-infected mice, BA.2 mice had relatively low cytokine and chemokine levels, suggesting a limited inflammatory response overall, but higher than during BA.1 infection. The authors conclude that BA.2 pathogenicity in mice and hamsters is similar to that of BA.1, and attenuated relative to ancestral or other variant strains.

Vaccine Effectiveness (VE)

- After one dose of Pfizer-BioNTech vaccine, neutralizing titers were 8-fold lower against BA.2 compared with ancestral SARS-CoV-2 virus.[8] After two vaccine doses, BA.2 neutralizing titers were 13-fold lower compared with ancestral virus (as compared to BA.1, which had 61-fold less neutralization after two doses). After three doses of vaccine there was 11 and 7-fold loss of neutralization for BA.1 and BA.2 compared to ancestral virus.

- To analyze neutralizing activity against BA.2 after infection and/or vaccination, sera from individuals who were 1 month post-third dose of Pfizer-BioNTech (n=10); individuals who received two doses of Pfizer-BioNTech after an infection during the first wave (1 [n=13] or 3 [n =11] month post-second dose); individuals who received two doses of Pfizer-BioNTech prior to a Delta breakthrough infection (n=5); and individuals who received two doses of Pfizer-BioNTech or the mRNA-1273 (Moderna) vaccine prior to Omicron breakthrough infection (n = 5), were compared.[20] Relative to ancestral and Delta strains, the reduction in neutralizing titers in individuals who received three doses of Pfizer-BioNTech was similar between the BA.1, BA1.1, and BA.2 Omicron viruses. In individuals who received two doses of vaccine after an infection, geometric mean titers against BA.1, BA1.1, and BA.2 were lower than those against the ancestral and Delta strains, and the reduction in neutralizing titers was larger for BA.1 and BA.1.1 than for BA.2 at 1- and 3-months post-vaccination, the authors state this may suggest antibodies elicited by the Pfizer-BioNTech vaccine and/or SARS-COV-2 infection have reduced neutralizing activity against BA.2 compared to other Omicron strains.

- A novel algebraic topology-based deep learning model was used to evaluate BA.2 vaccine breakthrough capability and antibody resistance (described in the Transmissibility section).[19] The study reported BA.2 to be 30% and 17-fold more capable than BA.1 and Delta, respectively, to escape current vaccines.

Re-infection

Since the last PHO BA.2 Risk Assessment, no additional publications about re-infections were identified.[3]

Public Health Measures

Throughout February 2022, most of the international jurisdictions scanned lifted nearly all of their public health measures. Germany and Italy are two jurisdictions that are maintaining more stringent measures. The most common measure still in place across the jurisdictions (either recommended or mandated) is indoor mask requirements. However, most of the jurisdictions have eased this measure so that it is specific to high-risk settings (e.g., public transportation). Some jurisdictions that still have a mask mandate in place have mentioned reassessing this measure and possibly lifting it in the near future. In addition, some jurisdictions are beginning to announce the next phase of their COVID-19 response, which includes “living with COVID” (e.g., England) or being prepared to respond quickly for the next wave or VOC (e.g., California).[22]

Due to high levels of immunity, some jurisdictions are now discussing phasing out their vaccination program (e.g., Denmark; no details provided yet) or reducing their vaccine program by decreasing the size of vaccination clinics and decreasing the total number of vaccine clinics offered (e.g., Portugal). At the same time, some jurisdictions are increasing eligibility for booster doses (e.g., England, Germany, Netherlands, and Ireland).[22,23]

Ontario Risk Assessment

The current risk of BA.2 sub-lineage transmissibility in Ontario is high, with a moderate degree of uncertainty. The risk of severe disease in Ontario is moderate, with a moderate degree of uncertainty. The risk of reinfection is high with a moderate degree of uncertainty in Ontario. The risk of breakthrough infection is high with a moderate degree of uncertainty in Ontario. Early evidence suggests the risk of reinfection and degree of vaccine effectiveness is similar for BA.1 and BA.2. The risk of impact of the BA.2 sub-lineage on testing is moderate, with a moderate degree of uncertainty. The risk of impact on surveillance is moderate with a low degree of uncertainty.

The overall risk assessment may change as new evidence emerges (see Table 1).

Table 1. Risk Assessment for Omicron variant sub-lineage BA.2

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

Implications for Practice

- Given the prevalence of BA.2 globally and early evidence of increased transmissibility relative to other dominant Omicron sub-lineages, a cautious approach to assessing its risk in Ontario is warranted.
- Current epidemiological trends for SARS-CoV-2 in Ontario were decreasing, although the decreasing trends may now have slowed and several public health units are reporting a higher case rate this week compared to the previous week.[24-26] Although case counts are an underestimate due to changes to PCR testing eligibility, case rates are higher than at most other points since the pandemic began.[27] Ontario will lift many existing public health measures on March 21, 2022[28] (e.g., removing mandatory masking requirements in most settings) which will require close surveillance of BA.2.[29,30] Close monitoring of epidemiologic trends in other jurisdictions with BA.2 pre-dominance or increasing prevalence will be useful, in particular the epidemiological trends following changes to public health measures.

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