EVIDENCE BRIEF

COVID-19 Variant of Concern Omicron (B.1.1.529): Risk Assessment, December 7, 2021

12/7/2021

Key Messages

- The number of countries reporting Omicron cases continues to increase globally. As of December 7, 2021 Omicron cases have been reported in 57 countries (3 requiring verification) from all six World Health Organization (WHO) regions, accounting for 0.1% of the 899,935 sequences collected from October 3 to December 2, 2021 and uploaded to GISAID.⁰ In Canada, a total of 49 cases of Omicron had been detected in five provinces.²⁻⁶

- Computational and biomechanical modelling suggests higher binding affinity between Omicron and human angiotensin converting enzyme 2 (ACE2), compared to the Delta variant, suggesting potential increased infectivity.

- Mutations in the receptor-binding domain suggest possible reduced efficacy of existing neutralizing antibodies, but modelling predicts no large enough conformational changes to cause complete evasion of neutralizing antibodies.

- At this point in time, the risk of Omicron importation in Ontario is high and the risks of further transmission, severe disease, reinfection, and breakthrough infection in Ontario is moderate with a high degree of uncertainty. The overall risk assessment may change as new evidence emerges.

Issue and Research Question

- The first known confirmed Omicron positive specimen globally was collected on November 8, 2021 in South Africa,⁷ although the precise timing and location of Omicron emergence are not yet known.⁸

- The B.1.1.529 lineage was designated a Variant of Concern (VOC) by:
  - The WHO on November 26, 2021, based on a possible increased risk of reinfection and increased ease of transmission.⁹
  - The European Centres for Disease Prevention and Control on November 26, 2021 due to concerns over potential immune escape and increased transmissibility compared to the Delta VOC.¹⁰
The United Kingdom (UK) Health Security Agency on November 27, 2021.11

The United States Centers for Disease Control and Prevention on November 30, 2021 based on: the emergence of Omicron cases (with and without travel history) in multiple countries; the replacement of Delta as the predominant variant in South Africa; the extensive mutations in its spike protein and potential impact on immunity from vaccine and natural infection.12

Since the last report on December 1, epidemiological, in-vitro, and modelling evidence has been emerging around the transmissibility and protection against infection from vaccination and prior COVID-19 infections. This evidence brief updates the Public Health Ontario (PHO) report from December 1, 2021 and summarizes available information and evidence on the Omicron VOC relevant to the risk of importation and transmission in Ontario up to December 7, 2021.13

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 COVID-19 variants were included.

Genomic Features

• Omicron has over 50 mutations including 32 mutations on the spike protein.14 Some of the mutations identified in Omicron are also found in other VOCs,15 and may be associated in theory or through functional studies of previous variants with immune escape, enhanced transmissibility via inducing cell fusion, and susceptibility to monoclonal antibody treatment.14,16-18 See PHO’s COVID-19 Variant of Concern Omicron (B.1.1.529): Risk Assessment for detail.13

Epidemiology

• Preliminary phylogenetic analysis of global sequences suggests that Omicron potentially emerged in early October. However, this estimate carries significant uncertainties given the limited data and potential sequencing errors.19

• Since its first detection from a specimen collected on November 8, 2021, Omicron has replaced Delta as the dominant variant at 74% (183/249) of genomes sequenced in South Africa.7 Substantial increases in weekly incidence of COVID-19 were also seen in some southern African countries in late November to early December 2021, e.g., Eswatini (1,990%), Zimbabwe (1,361%), Mozambique (1,207%), Namibia (681%), Lesotho (219%). While drivers of these increases remain unknown, it is possible that the observed spread of Omicron variant in combination with other factors such as low vaccination rate against COVID-19, relaxation of public health measures, and enhanced testing since the designation of Omicron as a VOC may be contributing to these observed rise in cases.1

• In Canada, Omicron cases have been reported in British Columbia (5), Alberta (11), Manitoba (1), Ontario (31) and Quebec (1) as of December 7, 2021.2-6

• Community and/or household transmission has been reported by some countries.19-21
• In England, community transmission is deemed highly likely across multiple regions.\textsuperscript{21}

• In Ontario, a cluster of at least 40 persons under investigation linked to an Omicron case involving schools, childcare centres and a church with links to a confirmed Omicron case has been reported.\textsuperscript{22}

• As most countries in Africa (except Botswana, South Africa, Ghana) were not sequencing sufficient COVID-19 samples to allow for detection of community transmission, Omicron may be more prevalent in some countries than current data show.\textsuperscript{19}

Transmissibility

Preliminary epidemiological data from South Africa, the UK and Hong Kong,\textsuperscript{23-25} as well as modelling data,\textsuperscript{26-28} suggest that Omicron may be more transmissible than the Delta variant. The UK Health Security Agency assessed that Omicron is at least as transmissible as Delta.\textsuperscript{29}

Epidemiological Evidence

• In South Africa, the estimated effective reproductive number (Re) for COVID-19 on November 18, 2021 ranged from 1.38-1.65 for all provinces, with the exception of Gauteng which had a high number of Omicron cases and an estimated Re of 2.33\textsuperscript{30} (Omicron was not distinguished from other variants when calculating Re’s). Although the number Omicron cases have rapidly increased in South Africa, it is plausible that sampling bias may be occurring (over-sampling in areas most affected by the variant), so the true prevalence of the variant in this region remains uncertain.\textsuperscript{23}

• In the UK, logistic growth model using community-based data estimated a growth rate of 141\% per week for S-gene target failures in late November 2021.\textsuperscript{11} While not a direct indication of increased transmissibility or rise in the absolute number of Omicron cases, the sharp increase can be considered a strong early signal of a growth advantage of Omicron.\textsuperscript{11} A shorter duration from infection to infectiousness was also reported by the UK Health Security Agency.\textsuperscript{21} In addition, a media report states that the number of Omicron cases may be doubling every three to four days.\textsuperscript{24}

• Ease of transmission of Omicron was also proposed in a transmission event between two unrelated travellers quarantined in facing rooms along the corridor of a hotel in Hong Kong. Both had been vaccinated with two doses of Pfizer-BioNTech Comirnaty vaccine against COVID-19, and had tested negative for COVID-19 by RT-PCR within three days prior to arrival on November 11 (index case, who was vaccinated in June 2021) and November 10 (secondary case, who was vaccinated in May 2021). The index case tested positive for COVID-19 on November 13 with a high viral load while asymptomatic and was isolated the following day. The secondary case developed mild symptoms on November 17 and tested positive for COVID-19 on November 18 also with a high viral load. Genome sequencing revealed difference by only 1 nucleotide. Investigation (including review of closed-circuit camera footage) confirmed no sharing of items between these individuals, and the only times they opened their room door were to pick up food delivered to outside their rooms. The individuals also opened their room doors for RT-PCR testing in 3-day intervals but given their arrival one day apart, it is unlikely that they were tested on the same day. Repeated testing of the other 12 individuals quarantined on the same floor during the study period and related staff did not find any additional case of COVID-19.\textsuperscript{25} While
transmission via the airborne route was proposed by the authors, information on airflow direction and ventilation within the hotel hallway was not available.

**In-Vitro and Modelling Evidence**

- Three modelling studies reported higher binding affinity to human ACE2 (hACE2) receptors by Omicron compared to Delta or the Wuhan wild-type.\(^{26-28}\) However, free energy of perturbation data suggest that the total effect of the cluster of mutations at the interaction surface of hACE2 may be similar to that observed with the Alpha variant.\(^{31}\) Therefore, multiple mechanisms may be involved in the high Omicron spread observed in South Africa.

- In quantum mechanical modelling of the binding between Omicron and hACE2, Genovese et al. suggested that binding affinity with hACE2, compared to Delta, is considerably increased, which might contribute to increased infectivity.\(^{26}\)

- Computational modelling by Kumar et al. examined the Delta and Omicron variants relative binding to hACE. They reported that Omicron has a higher affinity for hACE2 than the Delta variant, which as predicted by others, could lead to higher potential for transmission. Based on docking studies, the Q493R, N501Y, S371L, S373P, S375F, Q498R, and T478K mutations contribute significantly to high binding affinity with human ACE2. Compared to the Delta variant, both the entire spike protein and the receptor binding domain (RBD) in Omicron include a higher proportion of hydrophobic amino acids within the protein’s core, as well as a higher percentage of alpha-helix structures, which indicate a more stable structure for Omicron.\(^{27}\)

- Using molecular modelling, Woo et al. found that the Omicron mutations T478K, Q493K and Q498R significantly enhanced binding to ACE2 receptors and doubled the electrostatic potential of the receptor binding domain-ACE2 complex, compared to the wild-type Wuhan strain, with the potential of increasing the transmissibility of Omicron.\(^{28}\)

- In a free energy of perturbation study, Fratev explored the impact on hACE2 binding by nine mutations identified in the receptor-binding domain of Omicron, compared to binding by the Alpha variant. Substantial increases in binding were observed for mutations Q498R, Y505H and G446S (98-, 14- and 13-folds, respectively). However, binding affinity was dramatically reduced by >100-folds with mutations Q493R/K in combination with K417N and T478K, meanwhile the impact of the N440K, G446S and T478K mutations contributed little to the interaction. Based on the opposite effects by different groups of mutations, the author suggests the total effect of these mutations located on the interaction surface of RBD-hACE2 is similar to that of the Alpha variant.\(^{31}\)

**Disease Severity**

- Where information on disease severity is available, most cases were either asymptomatic at the time of testing or reported only mild symptoms.\(^{11,32-38}\) However, hospitalized cases of Omicron have been reported in South Africa\(^{39}\) but the WHO has yet to link any deaths described to this variant.\(^1\) Longer follow-up duration is required to more accurately assess the severity of Omicron infection.
• Among the cases in the European Union/European Economic Area with information on disease severity, half were asymptomatic and the other half reported only mild symptoms. One case of hospitalization has been reported in Iceland. However, most of these cases were fully vaccinated and not of older age, so the impact of Omicron on disease severity in vulnerable groups is still unknown.

• Early December data from a hospital complex in the Tshwane District of Gauteng Province in South Africa reported 3 cases of COVID-19 pneumonia among 42 patients in COVID-19 wards and only 1/42 patients was in intensive care unit at the time of the report. Omicron was assumed to be the strain infecting these patients as the National Institute for Communicable Diseases had confirmed that almost all cases in the Tshwane District were due to Omicron.

Vaccine Effectiveness

Epidemiological Evidence
• Breakthrough infections of Omicron have been reported in many countries, including Botswana, Hong Kong, Israel, Japan, South Korea, UK, Canada, and the United States. Current data are insufficient to assess to what extent Omicron can evade protection from vaccination.

In-Vitro and Modelling Evidence
• Findings from a live virus neutralization assay by Cele et al. showed a 41-fold reduction in geometric mean titer FRNT50 (1,321 vs. 32; P = 0.018) against Omicron compared to D614G by sera of twelve individuals (6 of whom were previously infected in the first wave of the COVID-19 pandemic in South Africa when the D614G strain was dominant) vaccinated with the Pfizer-BioNTech Comirnaty vaccine. Nonetheless, the authors noted that the sera from 5/6 previously infected individuals show relatively high neutralization titers with Omicron, and postulated that a history of COVID-19 followed by vaccination or booster will likely confer protection from severe disease with Omicron.

• Two modelling studies also suggested the possibility of reduced interaction with neutralizing antibodies.

Reinfection
• In a modelling study, Pulliam et al. estimated the risk of reinfection from routine surveillance data of the National Notifiable Medical Conditions Surveillance System, which comprised all confirmed COVID-19 in South Africa. Reinfection was suspected when there was ≥ 90 days between two specimen receipt dates. Between March 4, 2020 and November 27, 2021, there were 35,338 individuals with one reinfection and 332 individuals with two reinfections among 2,796,982 individuals with a laboratory-confirmed COVID-19 positive results ≥ 90 days before November 27, 2021. Comparing the epidemiological data with a null model which assumed that an individual’s risk of reinfection was proportional to the incidence rate, the authors found no evidence of immune escape at the population level during the COVID-19 waves driven by the Beta and Delta variants: the relative hazard ratio of reinfection to primary infection (95% confidence interval [CI] = 0.75 (0.59–0.97) for Beta and 0.71 (0.56–0.92) for Delta. However, in November 2021, the daily incidence of reinfection has risen above the 95% projection interval of...
the null model with substantial increase in the relative hazard ratio: 2.39 (1.88–3.11). This coincided with the emergence of the Omicron variant in South Africa, and the authors suggested that Omicron is associated with substantial ability to evade immunity from prior infection.

Diagnostic Assays

- Current molecular and antigen tests for SARS-CoV-2 are expected to be able to detect Omicron. See PHO’s COVID-19 Variant of Concern Omicron (B.1.1.529): Risk Assessment for detail.13

Measures in Response to Omicron

This section was informed by keyword searches in the Google search engine and government websites for literature related to Omicron, public health measures, and vaccination programming. A formal database search was not conducted due to time constraints; thus, some relevant articles may not be included. The following jurisdictions were searched: Denmark, England, Finland, France, Germany, Ireland, Israel, Italy, Netherlands, Norway, and Portugal. Although the focus was public health responses to Omicron, some the changes reported may also be in response to ongoing Delta resurgence in Europe.

Changes to Public Health Measures

Some of the jurisdictions reviewed here were increasing public health measures due to surging cases of the Delta variant, even before the discovery of Omicron. As a result, it is not always clear whether changes to public health measures or vaccine programming are specific to Omicron, or Omicron and Delta waves. It is also worth noting that the European Medicines Agency (EMA) approved the use of Pfizer-BioNTech’s COVID-19 vaccine for children between the ages of 5 and 11 on November 25, 2021, which is authorization several jurisdictions were awaiting before adding children to their vaccine programs.

- Since WHO announced the designation of Omicron as a VOC on November 26, 2021, the jurisdictions reviewed have updated public health measures in different ways.48
- Some have implemented mask mandates in indoor settings (e.g., Denmark, England, France, Ireland, Norway, Portugal), on public transportation (e.g., Denmark, England, Ireland, Italy, Norway), or at outdoor events (e.g., Germany, Italy).49-60
- In some jurisdictions, immunity certificates are now required in more settings than previously (e.g., Denmark, Germany, Ireland, Italy, Portugal), and eligibility for immunity certificates is more restrictive (e.g., how long a negative test result is valid or the duration of validity of the most recent vaccine dose) in some jurisdictions (e.g., Denmark, France, Italy).50,52-54,58-62
- Capacity limits were introduced to support social distancing at events, hospitality and cultural venues (e.g., Denmark, Germany, Ireland, the Netherlands), or venues were temporarily closed (e.g., nightclubs in Ireland), and large events cancelled (e.g., New Year’s Eve events in Germany). In some jurisdictions, there is national guidance limiting private gatherings as well (e.g. Germany, Ireland, Norway).50,54,57,60-62 Portugal, which has the highest vaccination coverage in Europe at around 87% fully vaccinated, is requiring a negative COVID-19 test to access large events and long-term care homes, likely as an additional effort to minimize the risk of large outbreaks.58,59
• As a containment strategy, Portugal has announced closure of schools, nightclubs, and mandatory telework orders the week of January 2 to 9, 2022 as a containment strategy after the New Year and December holidays. Lastly, remote work was recently recommended in some jurisdictions (e.g., Finland, Norway).

Changes to Vaccination Programming

Since the identification of Omicron, some of the jurisdictions reviewed here have updated their COVID-19 vaccination programs.

• Several jurisdictions have expanded eligibility for booster doses (e.g., Denmark, England, Finland, France, Germany, Ireland), and/or shortened the minimum interval between completion of a vaccination series and a booster dose (e.g., three months in England, five to six months in Finland, five months in France). Israel is starting to discuss fourth doses of vaccine for some populations.

• Following the European Medicines Agency’s authorization of the Pfizer-BioNTech COVID-19 vaccine for children 5 to 11 years old, some jurisdictions have announced plans for vaccinating vulnerable children and children residing with vulnerable individuals (e.g., Finland, France), or children 5 to 11 years old in general (e.g., Denmark).

Ontario Risk Assessment

• The current risk of Omicron importation in Ontario is high and the risks of further transmission, increased disease severity, reinfection, or breakthrough infection in Ontario is moderate with a high degree of uncertainty.

• As of December 7, 2021, 31 cases of confirmed Omicron had been detected in Ontario. See PHO’s COVID-19 Variant of Concern Omicron (B.1.1.529): Risk Assessment and SARS-CoV-2 (COVID-19 Virus) Variant of Concern (VoC) S Screening and Genomic Sequencing for Surveillance for Ontario’s Omicron surveillance strategy.

• In terms of the risk of importation, federal travel-related restrictions were implemented after Omicron was known to have been circulating in southern Africa, and the list of affected countries has expanded quickly. The overall risk assessment may change as new evidence emerges (see Table 1).

• In-vitro, modelling, and limited epidemiological evidence suggest that Omicron may be more transmissible with less protection offered by immunity from vaccination and natural infection. Further epidemiological and laboratory studies are in progress to ascertain any additional phenotypic impacts.

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<tr>
<th>Issue</th>
<th>Risk Level</th>
<th>Degree of Uncertainty</th>
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<tbody>
<tr>
<td>Importation in Ontario</td>
<td>High</td>
<td>Low</td>
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<tr>
<td>Increased Transmissibility</td>
<td>Moderate</td>
<td>High</td>
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Table 1. Risk Assessment for Omicron B.1.1.529
Implications for Practice

- Driven by the Delta variant, COVID-19 incidence has increased in Ontario since November, with an effective reproduction number estimated at 1.14 on December 2, 2021.\textsuperscript{79,80} Emerging evidence suggests that Omicron may be more transmissible than Delta with reduced protection from vaccination and prior infection. Local transmission of Omicron will likely push the incidence of COVID-19 above current projections and put the health care system under strain.\textsuperscript{79} While Omicron accounts for only 0.3% of all VOCs detected in Ontario from October 31 to December 7, 2021,\textsuperscript{6} it is prudent that Ontario adopts a precautionary approach to limit the importation and delay the spread of Omicron. Of note, this summary reflects publicly available information current to December 7, 2021.

- Limiting importation of the Omicron at the “early” stage of Omicron outbreak is important given the rapid spread seen in some countries and evolving understanding of Omicron infection severity, which increases the challenges in recognizing cases promptly for case isolation and contact quarantine. As the number of countries in which Omicron is detected increases, the practicality of travel-related restrictions and requirements for returning travellers as a containment strategy may lessen.

- As the Ontario incidence of Omicron rises, and as people spend more time indoors during winter, population-level and individual-level public health measures are important to limit the spread of COVID-19 in Ontario. These measures follow a multi-layered approach, including vaccination, masking, physical distancing, crowd avoidance, ventilation, hand washing, cough etiquette, staying home when sick or with any symptoms of COVID-19, as well as ensuring systems for prompt detection of cases and communication of trends are in place for timely adjustment of public health measures.\textsuperscript{81}

- Vaccination remains one of the most effective layers of protection against SARS-CoV-2, including for Delta strains currently representing 99.9% of the COVID-19 disease burden in Ontario.\textsuperscript{79,82}

- Wearing a well-constructed, well-fitting mask at public enclosed/indoor settings can help contain the respiratory particles one releases, as well as help reduce the amount of infectious respiratory particles one may breathe in. This applies to anyone regardless of vaccination status, as no vaccine is 100% effective and the level of protection may drop over time, so even fully-vaccinated individuals can become infected and transmit the virus to others.\textsuperscript{83}
Outbreaks have been liked to suboptimal ventilation and accumulation of infectious aerosols released by infected individuals. Good ventilation, which used together with other public health measures, helps reduce the risk of COVID-19 transmission over distance as it lowers the level of infectious particles indoors by replacing indoor air with outdoor air. As Ontarians spend more time indoor over the winter, it is important that ventilation be optimized in spaces that are closed and/or crowded.84

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COVID-19 Variant of Concern Omicron (B.1.1.529): Risk Assessment, December 7, 2021


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