EVIDENCE BRIEF

COVID-19 Variant of Concern Omicron (B.1.1.529): Risk Assessment, February 9, 2022

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Key Messages

- Current reporting of confirmed SARS-CoV-2 cases in some jurisdictions, including Ontario, is an underestimate of the true epidemiology of infections due to changes to polymerase chain reaction (PCR) testing eligibility. Rapid antigen tests (RATs) can be used in the community for diagnostic testing purposes, but there is growing evidence regarding the limitations of RATs.

- Evidence continues to demonstrate that three doses of a COVID-19 vaccine provides greater protection from severe outcomes of Omicron variant infection compared to two doses. The duration of protection from a third dose or recent infection remains unclear, but early reports suggest third dose effectiveness against symptomatic infection shows waning at 10, 16 and 24 weeks.

- Most of the evidence indicates that infection with the Omicron variant causes less severe disease compared to the Delta variant; however, there is increasing evidence that Omicron infections can still be severe in older age groups. Due to increased transmissibility of Omicron, the absolute number of severe cases has strained health system capacity and critical infrastructure in many jurisdictions, including Ontario. At this time, there is insufficient data to comment on hospitalization outcomes, mortality, or long-term COVID outcomes.

- The current risk of Omicron transmission in Ontario is high, with a low degree of uncertainty. The risk of reinfection and breakthrough infection (after two doses of Pfizer, Moderna, AstraZeneca, or a heterologous combination) in Ontario is high with a low degree of uncertainty. The risk of severe disease, particularly amongst unvaccinated individuals, is moderate with a low degree of uncertainty. The overall risk assessment may change as new evidence emerges.

Issue and Research Question

Since its identification on November 8, 2021 in South Africa, 1 Omicron has become the dominant severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variant in many countries. Since the last report on January 26, 2022 more evidence has emerged of Omicron’s transmissibility, potential immune evasion, and disease severity. This brief updates the evidence since the previous Public Health Ontario (PHO) risk assessments, 3-10 and summarizes available evidence on the Omicron variant of concern (VOC) relevant to the risk of transmission in Ontario up to February 7, 2022, and reported epidemiology up to February 9, 2022. The SARS-CoV-2 B1.1.529 sub lineage BA.2 is out of scope for this Risk Assessment, and will only be addressed when relevant to BA.1 (Omicron) literature.
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.

Main Findings

Genomics

Since the last PHO Risk Assessment, additional studies have explored the origin of the SARS-CoV-2 Omicron lineage, and analyzed its viral genome. Although it remains unclear how Omicron evolved, three hypotheses currently exist surrounding its origin. First, it has been suggested that the emergence of Omicron occurred through the gradual evolution of SARS-CoV-2 as it transmits from person-to-person. These mutations may have gone unnoticed for a period of time in regions of the world that have limited genomic sequencing and among individuals that do not typically get tested. A second hypothesis stems from the possibility of a fast-paced evolution observed in individuals with chronic infections. For example, one case report describing a 45-year old man with persistent infection, found SARS-CoV-2 to accumulate over a dozen mutations during a 5 month period. The third hypothesis suggests that Omicron may not have emerged from humans, but rather may have evolved in an animal host. The types of single-nucleotide mutations observed in Omicron’s genome reflect those typically observed when coronaviruses evolve in mice. Interestingly, the sub-lineages of Omicron are distinct enough that, according to this theory, each would represent a separate jump from animal to human. However, even a single viral jump from an animal to a human is a rare event.

The high volume of cases caused by the Omicron variant has presented challenges to testing in Ontario and therefore surveillance. Omicron has also highlighted the need for alternative surveillance strategies that can detect new variants circulating. Wastewater sampling is one such supplementary surveillance practice. A recent study reported on a method for rapid, real-time data acquisition on the Omicron VOC prevalence and transmission dynamics using wastewater sampling. The authors conclude that such surveillance constitutes a valuable supplementary practice because it does not require extensive sampling, and provides information on the prevalence of the disease in a timely and cost-effective manner.

Epidemiology

In Ontario, Canada:

- As of February 8, 2022, whole genome sequencing (WGS) from surveillance testing across Canada reported that of SARS-CoV-2 samples collected the week of January 16, 2022, 98.2% were Omicron, but data were still accumulating. On February 9, 2022, Canada reported 8,853 new cases, 122 new deaths, 159,002 active cases, and the daily percent positivity (over the previous 7 days) was 16.4%. The Public Health Agency of Canada (PHAC) notes that due to changes in COVID-19 testing policies in many jurisdictions starting in late December 2021, case counts will under estimate the total burden of disease.

- In Ontario, on December 28, 2021, 80.4% of samples tested at the PHO laboratory exhibited s-gene target failure (SGTF), indicating that Omicron was the dominant circulating variant. The PHO laboratory discontinued SGTF testing on December 30, 2021.
• Due to changes in the eligibility criteria for PCR testing in Ontario effective December 31, 2021, reported confirmed case counts are an underestimate of the true number of individuals with SARS-CoV-2 infection.

• The Ontario 7-day confirmed case average was 838 on December 1, 2021, 4,592 on December 23, 2021, 12,070 on December 31, 2021, 10,197 on January 15, 2022 and 4,356 on January 30, 2022. On December 31, 2021 (i.e., the day on which changes to the eligibility criteria for PCR testing took effect), the percent positivity was 34.3%. On January 15, 2022, the percent positivity was 22.7%, and on February 2 it was 13.2%.

• As of February 7, 2022, there were 277 ongoing outbreaks in long-term care homes, 165 in retirement homes, 202 in congregate living settings, 139 in hospitals, and 17 workplace outbreaks.

Notable epidemiological trends from select jurisdictions are:

• Based on 22 European Union/European Economic Area (EU/EEA) countries with an adequate sequencing volume and a valid denominator for week 52, 2021 and week 1, 2022, the median (range) VOCs reported were 69.4% (5.7–99.9%) for Omicron (as compared to 48.5% in the weeks 51 of 2021 to 52 of 2021), 23.3% (0.0–93.9%) for Delta, 0.0% (0.0–0.4%) for Gamma and 0.0% (0.0–0.0%) for Beta.

• According to modelling projections, the United States (US) Centers for Disease Control and Prevention (CDC) estimated that for the week ending January 29, 2022, 99.9% (95% Confidence Interval [CI]: 99.9-100 99.9) of SARS-CoV-2 cases were Omicron. As of February 2, 2022, the 7-day moving average of daily new cases (378,015) decreased -37.6% compared with the previous 7-day moving average (605,735). The 7-day daily average hospitalizations for January 26 to February 1, 2022, was 16,068, which is an -18.0% decrease from the prior 7-day average (19,593) from January 19 to 25, 2022.

• United Kingdom sequencing data up to January 16, 2022, indicated 96.1% of SARS-CoV-2 sequences were BA.1, 3.4% were BA.2 and 0.5% were other lineages.

• Between February 1 and 7, 2022, there were 555,729 confirmed COVID-19 cases, which is a decrease of -10.4% compared to the previous 7 days. Between January 26, 2022 and February 1, 2022, 11,069 individuals went into hospital with COVID-19, which is a decrease of -9.0% compared to the previous 7 days. The hospitalization rate for COVID-19 was at 15.41 per 100,000 in week 4 compared to 16.67 per 100,000 in the previous week. In week 4, the weekly intensive care unit (ICU) or high dependency unit (HDU) admission rates for COVID-19 decreased, from 0.51 per 100,000 in week 3 to 0.48 per 100,000 in week 4. Between February 1 and 7, 2022, there were 1,707 deaths within 28 days of a positive coronavirus test, which is a decrease of -7.1% compared to the previous 7 days.

• As of February 4, 2022, the reproduction number (R) for England ranged from 0.8 to 1.1 and the growth rate range for England was -3% to +1% per day.
Data from the GSAID website collected on February 9, 2022 indicated 99.6% of cases in Denmark were Omicron sub lineage BA.2 in the previous 4 weeks. The 7-day rolling average of new cases per million people increased from 722 on November 30, 2021 to a peak of 7,778 on January 28, 2022, and was 7,107.86 on February 5, 2022.

On February 8, 2022, South Africa reported 2,824 new COVID-19 cases and an 8.2% positivity rate, which are a decreased from two weeks before.

Transmissibility

Modelling, in vitro and in-silico analyses support epidemiological findings that Omicron is more transmissible, and suggest potential mechanisms. It remains unclear to what extent the increased transmission of Omicron is due to inherent characteristics of the virus (i.e., enhanced ability to infect cells, tissue tropism) or due to immune evasion.

- The human angiotensin-converting enzyme 2 (hACE2) receptor is used by SARS-CoV-2 to enter host cells; therefore, mutations that alter binding affinity or stability or tissue tropism (e.g., faster replication in human bronchi as opposed to lungs) could impact infectivity and transmission. Since the last PHO Risk Assessment, more studies have reported Omicron to have enhanced ACE binding, compared to wildtype or other VOCs.

- Additional studies have investigated the viral load of an Omicron infection compared to other SARS-CoV-2 infections. A total of 37,877 nasal swab PCR tests were conducted to investigate if Omicron is more likely than Delta to cause infections in vaccinated persons (sample: Delta = 1463/2987, 49.0%; Omicron=1524/2987, 51.0%). The analysis found that the cycle threshold (Ct) values were mostly consistent across vaccine doses, but Omicron infections had higher Ct values (i.e., lower viral load) than those infected with Delta (after adjusting for covariates). Using remnant clinical specimens, a US evaluation of viral load between Delta and Omicron infections was conducted during the period when both variants were co-circulating revealed no significant difference in Ct values, regardless of the vaccination status. Recovery of infectious virus in cell culture was reduced in boosted patients (additional mRNA dose after completing a primary series of mRNA or adenoviral vector vaccine) compared to fully vaccinated without a booster and unvaccinated when infected with the Delta lineage. However, in patients with Omicron infections, recovery of infectious virus was not affected by vaccination. Another study reported that Omicron infections exhibit a higher viral load at a later time point than Delta cases. In the study, most infected individuals had cleared the viral infection by day 12, but virus could be detected for longer in a higher number of individuals infected with Omicron as compared to Delta.
More studies have reported attack rates for Omicron. For example, analysis of Danish household register data, vaccination data and COVID-19 testing data compared transmission of Omicron sub-lineages BA.1 (6,419 households) and BA.2 (2,122 households). For BA.1, there were 13,358 potential secondary cases, of which 3,910 tested positive, resulting in a secondary attack rate (SAR) of 29%. In BA.1 households, the SAR was 6% and 29% on day 1 and day 7, respectively. The authors reported that for both Omicron BA.1 and BA.2 households, the susceptibility of potential secondary cases was highest among the unvaccinated and lowest among the boosted, but the effect of vaccination was lower for Omicron BA.2 than for BA.1. Transmissibility was lower in both BA.1 and BA.2 households when the primary case was booster vaccinated rather than fully vaccinated. A Korean study used contact tracing information from 76 case-patients with Omicron infection that originated from 2 imported cases (75 confirmed cases and 1 suspected case) and their contacts, to report infector-infectee relationships and household transmission (25 households, comprising 55 household member). Of 55 household members, 36 were Omicron-positive, with a SAR of 65% (95% CI 0.48–0.81); however, after excluding 18 household members who had other possible exposures, the remaining 18 Omicron cases resulted in an SAR of 50% (95% CI 0.35–0.72). Based on 12 transmission pairs, the mean incubation period was 2.5–4.3 days, and the median incubation period was 3–4 days. The mean (± standard deviation) serial interval for the pairs was 2.9 (± 1.6) days; the median serial interval was 3.0 days. The secondary attack rate among fully vaccinated persons was high (62.5%, 10/16), suggestive of immune evasion, in agreement with other studies.

Using available viral load data, Monte Carlo modelling estimated viral emissions in the fine aerosol size range for wildtype, Delta and Omicron infections, including simulation of indoor airborne transmission of SARS-CoV-2 by including a CO2 calculator and recirculating air cleaning devices. The authors found that a much larger proportion of individuals infected with Delta or Omicron are high, very high or super-emitters of airborne viruses: for wildtype, one in 1,000 infected was a super-emitter; for Delta one in 30; and for Omicron one in 20 or one in 10, depending on the viral load estimate used. Based on their model, the authors conclude that for Omicron, one half to two thirds of infected individuals emit enough virus into the air to pose a realistic infection risk to others by airborne transmission and therefore surgical masks are insufficient in most public settings, but correctly fitted FFP2 (N95 or KN95 style respirators) respirators provide sufficient protection, except in high aerosol producing situations such as singing or shouting.

Using contact tracing data collected in Belgium, a study estimated the serial interval for Omicron and Delta variants and compared the observed serial intervals for different combinations of vaccination status in transmission pairs. The empirical serial interval distribution for Omicron had a mean of 2.75 days (SD 2.53 days), compared to 3.00 days (SD 2.48 days) for Delta (p = 0.019). The authors reported a significant difference between the mean empirical serial interval of both variants within households, but not between households (p = 0.034 for within-household, and p = 0.686 for between-household transmission pairs). There was no difference in empirical serial intervals for pairs in which both cases were unvaccinated or partially vaccinated (2.69 vs 2.54 days, p = 0.931), but for transmission pairs in which both cases were vaccinated (without booster), the empirical serial interval for Omicron was significantly shorter as compared to Delta (2.63 vs 3.38 days, p = 0.004). The mean empirical serial interval for Omicron was longer for pairs that were boosted as compared to pairs that were vaccinated with only two doses (3.34 vs 2.63 days, p = 0.065).
Diagnostics

Although most current molecular tests for SARS-CoV-2 are expected to be able to detect Omicron, there is increasing evidence of variable sensitivity, optimal detection windows and optimal specimen site for rapid antigen tests (RATs), as described in previous PHO Risk Assessments,2,9,10,44 and elsewhere.45-48 A few recent primary studies are highlighted below.

- A recent review of RATs during the Omicron wave by the Ontario Science Table concluded that these tests are less sensitive against Omicron compared to Delta when nasal specimens are used; but, sensitivity can be improved by combining oral and nasal samples.44 As with other variants, the authors concluded that a single negative RAT result cannot reliably rule out infection. Currently, a positive result should be considered and managed as a case of COVID-19 without PCR confirmation in the majority settings, as the prevalence of Omicron infections remain high and consequently the likelihood of a false positive result will be low. With Ontario’s current testing strategy, it presumed that once the reported rate falls below 35 cases per 100,000 inhabitants per week, 2 out of 3 positive rapid antigen tests could be false positive, and would therefore require confirmation of a positive RAT result by PCR should be considered. In addition, the authors assessed that if asymptomatic testing strategies are considered, RATs need to be performed frequently to be effective.

- An analysis of the sensitivity of the E25Bio, Inc., Cambridge, MA and Perkin Elmer, Waltham, MA rapid antigen test against the Omicron, Delta, Alpha and Gamma variants revealed the test to have the most sensitive limit of detection (10 plaque forming units [PFU]/mL) for the Alpha and Gamma variants, followed by the Omicron (100 PFU/mL) and Delta (1,000 PFU/mL) variants.46

- A study was conducted to qualify the BinaxNOW™ test for use in a university testing program as a tool to rule in positive or rule out negative individuals quickly.48 Of 110 samples, 48 tested positive for SARS-CoV-2, and all samples for which there was WGS were Omicron. The authors estimated BinaxNOW to have a sensitivity of 52.1%, specificity of 100%, a positive predictive value (PPV) of 100%, and a negative predictive value (NPV) of 72.9% (n=110). The receiver operating characteristic (ROC) curve showed that for qRT-PCR positive Ct values between 23 and 40, the BinaxNOW™ test is of limited diagnostic value. The authors conclude that RDT tests could be used to confirm SARS-CoV-2 infection in individuals with substantial viral load, but that a significant fraction of infected individuals would be missed if testing is performed in situations of lower viral load (e.g. early or late infection).

- A prospective study of 244 patients (232 adults and 12 children) with clinical suspicion of COVID-19 evaluated the clinical performance of the Panbio™ COVID-19 Ag Rapid Test Device in nasopharyngeal specimens (NP).47 Patients were tested by RT-PCR and RAT within 5 days since symptom-onset. The study reported that 126 patients (51.6%) tested positive by both RT-PCR and RADT, 90 patients (36.8%) had negative results by both assays and 28 patients (11.4%) had discordant results (RT-PCR+/RADT-). No patients tested negative by RT-PCR and positive by RAT. The study estimated the specificity and sensitivity of RADT to be 100% (95% CI, 95.9–100%) and 81.8% (95% CI, 75–87.1%), respectively. The sensitivity increased from 79.6% (95% CI, 66.4–88.5) for specimens collected at days 0–1 after symptoms onset, to 86.4% (95% CI, 66.7–95.3) when grouping the specimens obtained on days 4–5.
• Using live virus, a study assessed the limit of detection (LoD) for the Omicron variant compared to wildtype for three RATs with emergency use authorization in the US. The authors reported that the 95% detection threshold for antigen tests was at least as good for Omicron as for the wildtype strain, meaning the three RATs tests are just as suitable for detection of Omicron as for wildtype. The authors noted that the relationship of genome copies to plaque forming units for Omicron and wildtype overlapped, suggesting the LoD equivalency also applies if the quantitative comparator is genome copies determined from live virus preparations.

Additional studies have attempted to create novel molecular assays to rapidly identify and distinguish Omicron and new variants, without reliance on WGS. One study is highlighted below.

• A study to identify a rapid method for the identification of Omicron and discrimination between Omicron and other variants described a two single nucleotide polymorphism (SNP) genotyping assay targeting the G339D or T547K mutation of the spike protein for screening of the Omicron variant. In terms of specificity, the two assays could discriminate the Omicron variant from the Delta variant and Alpha variant each with one nucleotide mismatch. The sensitivity test showed that the G339D and T547K assays detected at least 2.60 and 3.36 RNA copies of the Omicron variant, respectively, and 1.59 RNA copies of the Delta variant. The authors conclude that both assays could be useful for detecting and discriminating Omicron from other strains, and could be applied to create more accurate diagnosis systems. Pinkhover et al. also reported a SNP-based assay for Omicron.

Clinical Presentation

Information continues to emerge regarding the signs and symptoms of Omicron and how they may differ from infection with other SARS-CoV-2 variants, with several studies reporting that Omicron cases were less likely to report loss of taste or smell as compared to other SARS-CoV-2 infections.
Disease Severity

There remain limitations with the Omicron severity literature (e.g., lag time to observe hospitalizations and mortality); however, most of the evidence suggests Omicron causes less severe disease than Delta. Additional studies reported on the cytokine response to Omicron, building on previous evidence. There remains insufficient data to comment on hospitalization outcomes, including progression of severity of illness, complications, and mortality.

Select studies are highlighted below:

- A study of Omicron disease severity in risk groups defined by sex, age and comorbidities in addition to vaccination status was conducted in Sweden based on three calendar periods (55,269 cases): i) Delta dominant, 2021 week 27-47, ii) transition to Omicron period, 2021 week 48-51, and iii) Omicron dominant, 2021 week 52 (74% sample prevalence) and 2022 week 1 (88% sample prevalence). After adjusting for age, sex, comorbidities and prior infection, booster dose and time since last dose among the vaccinated, the odds of severe COVID-19 was 40% lower (95% CI 18 – 56% lower) among unvaccinated and 71% lower (95% CI 54 – 82% lower) among vaccinated individuals during the Omicron period Compared to the Delta period. In terms of age, sex, number of comorbidities, and vaccination status, the risk for severe COVID-19 remained high among unvaccinated, first-time infected, cases of both sexes during the Omicron period in the age group 65+, and among males in the age group 40-64 years with two or more comorbidities. The risk of severe COVID-19 for vaccinated cases below 65 years was low for both sexes during Omicron, even with comorbidities. Risk of severe COVID-19 remained elevated among vaccinated 65+ cases during Omicron only in the presence of at least one (males) or at least two comorbidities (females). Vaccine effectiveness against infection and severe disease was estimated using continuous density case-control sampling (10 controls per case) nested within the study cohort, with conditional logistic regression. The median weekly VE against infection was 67% during the Delta period, with a substantial decline in VE against infection starting in the last week of the transition period. In the Omicron period, no vaccine protection against infection remained. VE against severe COVID-19 was estimated monthly, and remained stable around 90% across all periods.

- Using COVID-19 surveillance and immunization registry data, the Los Angeles County Department of Public Health explored COVID-19 hospitalization rates by COVID-19 vaccination status and variant predominance. In the last week of Delta predominance, the hospitalization rates among unvaccinated persons were 83.0 times that of fully vaccinated persons with a booster and 12.9 times that of fully vaccinated persons without a booster. During the Omicron period, unvaccinated persons had a hospitalization rate 23.0 times that of fully vaccinated persons with a booster and 5.3 times that of fully vaccinated persons without a booster.

- Preliminary analysis of case-based data submitted by 15 EU/EEA countries to The European Surveillance System (TESSy) between week 46, 2021 and week 2, 2022 reported that Omicron infection was less likely to be reported with admission to hospital compared to Delta infections (aOR 0.41; 95% CI: 0.37-0.46). Among Omicron cases with known outcomes reported into TESSy as of January 19, 2022, 884 (1.14%) were hospitalised, 120 (0.16%) required ICU admission/respiratory support, and 48 (0.06%) died.
• Using remnant clinical specimens, an evaluation of clinical outcomes between Delta and Omicron infections in the US during the period when both variants were co-circulating revealed that patients with Omicron infections (N= 1121) were more likely to be vaccinated compared to Delta cases (N = 910), but were less likely to be admitted to hospital (3 % vs 13.8 %, p < 0.00001), require ICU care (0.5% vs 3.5%, p < 0.00001), or succumb to infection (0.1 vs 1.1, p = 0.004), regardless of vaccination status.\textsuperscript{38}

• The CDC analyzed Omicron disease severity and health care utilization in the US using three surveillance systems and a large health care database, and compared severity indicators across three periods: winter 2020–21, Delta predominance, and Omicron predominance.\textsuperscript{60} The authors conclude that the Omicron period showed lower disease severity than previous periods of high transmission, which is likely related to higher vaccination coverage reducing disease severity, lower virulence of Omicron, and immunity from previous infections. Overall, the data suggests the Omicron wave has lower disease severity indicators than previous pandemic peaks, but can cause higher volume healthcare utilization due to the number of cases.

• Individual-level data from the Norwegian Preparedness Registry was used to estimate the risk of hospitalization for Omicron cases (39,524) compared with Delta cases (51,481), as well as the length of hospital stay (LoS), risk of admission to an ICU and deaths.\textsuperscript{61} 91 (0.2%) Omicron and 552 (1.1%) Delta cases were hospitalized. The median time from positive test to admission was 1 day (IQR: 0–3) for Omicron and 4 days (IQR: 0–7) for Delta. Omicron was associated with an overall 73% reduced risk of hospitalization (aHR = 0.27; 95% CI: 0.20–0.36) compared with Delta. In a subgroup analysis, the reduced risk of hospitalization for Omicron as compared to Delta was smaller among cases who completed a primary vaccination schedule 7–179 days before positive test, as compared with unvaccinated cases (66% for Omicron vs 93% for Delta with CI that did not overlap). Having a third vaccine dose yielded a similar reduction in hospitalization risk for Omicron and Delta cases, compared to unvaccinated cases (86% and 88% respectively with overlapping CI). Of note, Omicron cases who had partially completed a primary vaccination series or who had completed primary vaccination with maximum two doses ≥ 180 days before positive test had no significant decrease in risk compared with unvaccinated. The crude median LoS for Omicron patients was 2.8 days (IQR: 1.6–6.8) compared with 6.5 (IQR: 3.2–12.3) among Delta patients. Seven Omicron patients (7.7%) were admitted to an ICU, compared with 135 (24%) Delta patients. The aHR for discharge for Omicron patients compared with Delta patients was 1.44 (95% CI: 0.99–2.07), which represents an expected 31% shorter LoS (95% CI: 1% longer–52% shorter). The aHR for the risk of ICU admission for Omicron patients compared with Delta patients was 0.51 (95% CI: 0.20–1.29).

• A retrospective cohort study in France investigated 149,064 COVID-19 cases, of which 497 had a serious hospital event (447 Delta, 50 Omicron), meaning admission to ICU unit or admission to critical care unit or death.\textsuperscript{62} The risk of serious event was lower among Omicron cases compared to Delta cases (aHR=0.13 95% CI 0.09-0.18 in 18 to 79 year olds, aHR=0.30 95% CI 0.17-0.54 in 80 years and older; risk adjusted for age, sex, vaccination status, presence of comorbidity and region of residence). Risk increased with age and was lower in vaccinated compared to unvaccinated cases, without interaction between variant and vaccination status (aHR=0.15 95% CI 0.11-0.19 for 18-79 year olds with primary vaccination versus unvaccinated), was higher in cases with comorbidities (aHR = 3.70, 95% CI 2.66-5.13 for 18-79 year olds with very-high-risk comorbidity versus no comorbidity) and in males.
VE
Since the last PHO Risk Assessment,² more evidence has emerged demonstrating that two doses of COVID-19 vaccines are less effective at preventing Omicron breakthrough infections compared to other VOCs and ‘wild-type’ SARS-CoV-2, and a third COVID-19 vaccine dose increases protection against symptomatic Omicron infection and severe disease.⁶³-⁶⁶ Pfizer-BioNTech announced January 25, 2022 that they have started a clinical trial of a modified COVID-19 vaccine specific to Omicron,⁶⁷ but data are not yet available. Another study reported monovalent Omicron-specific vaccine results in mice.⁶⁸

Epidemiological Studies
- A test-negative study design using linked Ontario databases, estimated VE of mRNA vaccines against symptomatic infection and severe outcomes caused by Omicron (16,807) or Delta (4,261, and 114,087 test-negative controls) using multivariable logistic regression.⁶⁹ **VE against symptomatic Omicron infection was only 36% (95%CI, 24-45%) 7-59 days after a second dose and provided no protection after ≥180 days, but increased to 61% (95%CI, 56-65%) ≥7 days after a third dose.** VE against severe outcomes was very high following a third dose for both Delta and Omicron (99% [95%CI, 98-99%] and 95% [95%CI, 87-98%], respectively). VE against symptomatic Omicron infection was lower as compared to Delta for the entire period and waned more rapidly The authors conclude that 2 doses of COVID-19 vaccines offer modest and short-term protection against symptomatic Omicron infection, but a third dose improves protection against symptomatic infection and provides excellent protection against severe outcomes for both variants.

- A study was conducted in Israel to compare the rate of confirmed COVID-19 and severe illness between those who had received a fourth dose of the Pfizer vaccine at least 12 days earlier, those who had received only three doses, and those 3 to 7 days after receiving the fourth dose.⁷⁰ **The rate of infection was lower in people 12 or more days after their fourth dose than among those who received only three doses and those 3 to 7 days after receiving their fourth dose by factors of 2.0 (95% confidence interval [CI], 2.0 to 2.1) and 1.9 (95% CI, 1.8 to 2.0), respectively.** The rate of severe illness in the group who received the fourth dose 12 days or more before was lower by a factor of 4.3 (95% CI 2.4 to 7.6) compared to the three dose group, and was lower by a factor of 4.0 (95% CI 2.2 to 7.5) compared to those who had the fourth dose 3-7 days previously. The adjusted rate differences were 3.8 (95% CI, 2.8 to 4.8) and 3.5 (95% CI, 2.1 to 5.1) cases per 100,000 person-days at risk compared to the two control groups, respectively.

- The VISION Network analyzed 222,772 encounters from 383 EDs and urgent care (UC) clinics and 87,904 hospitalizations from 259 hospitals among adults aged ≥18 years across 10 states to investigate third dose VE against Omicron as compared to Delta.⁷¹ During the Delta period, VE against ED and UC encounters was 86% 14–179 days after dose 2, 76% ≥180 days after dose 2, and 94% ≥14 days after dose 3. Estimates of VE for the same intervals after vaccination during the Omicron period were 52%, 38%, and 82%, respectively. During the Delta period, VE against hospitalizations was 90% 14–179 days after dose 2, 81% ≥180 days after dose 2, and 94% ≥14 days after dose 3. During the Omicron period, VE estimates for the same intervals after vaccination were 81%, 57%, and 90%, respectively.
**In vitro serology studies**

The body of in vitro evidence of Omicron immune evasion, based largely on serological studies of antibodies, continues to grow. In general, neutralizing antibody titers against Omicron are significantly lower than neutralizing titers against wildtype or other VOCs, and a third vaccine dose at least temporarily boosts neutralizing antibody levels against Omicron. In contrast to previous reports that T cell recognition of Omicron is largely preserved despite antibody immune evasion, one study concluded that T cell function against Omicron may not be well conserved in all people. Some studies are highlighted below.

- Results were recently published from the COVE, TeenCOVE (12-17 years old), and kidCOVE (6 to <12 year olds, administered two doses of 50 µg mRNA-1273) vaccine efficacy trials. In adults, the primary 2-dose mRNA-1273 (100 µg) regimen of elicited detectable Omicron neutralizing antibodies in 95% of participants, 4 weeks post-second dose, but the geometric mean ID50 titer (GMT) was reduced 28.8-fold as compared to D614G. In adolescents, the primary two dose regimen resulted in detectable neutralizing antibodies in 100% of participants 4 weeks post-second dose, but Omicron GMTs were 11.8-fold lower than D614G titers. Compared with adults, GMTs in adolescents were 1.5- and 3.8-fold higher for D614G and Omicron variant, respectively. In children, the primary two dose regimen resulted in Omicron neutralizing antibodies in 100% of participants at 4 weeks post-second dose, but GMTs were reduced 22.1-fold versus D614G. Neutralizing titers in children were 2.0-fold higher for D614G and 2.5-fold higher for Omicron compared with those of adults. Overall, D614G and Omicron neutralizing titers were higher in adolescents and children than adults, 4 weeks following the second dose of a two-dose primary vaccination regimen of mRNA-1273. The Omicron neutralization titers in adolescents and children were also reduced less compared with D614G neutralization than in adults.

- A longitudinal study of 37 older adults (median age of 82 years, range 76-96 years) measured SARS-CoV-2-neutralizing serum activity after two and three doses of the Pfizer vaccine. The third dose of BNT162b2 was given at 7 months (median 209 days, IQR 189-101 228). Serum samples that were collected 1 month post-booster (median 23 days, IQR 102 21-29) showed a more than 50-fold increase in neutralizing titers against wildtype and Delta (GeoMean ID50s of 2912 and 750, respectively), and Omicron (GeoMean ID50 of 256) in 33 out of the 37 participants (89%). Serum samples collected at 3.5 months post-booster (median 106 days, IQR 86-125) revealed that neutralizing titers declined by 2.7-, 2.3-, and 3.0-fold to GeoMean ID50s of 1077, 345, and 85 against the wildtype, Delta, and Omicron, respectively; but, detectable neutralization remained Wu01 (97%), Delta (95%), and Omicron (81% total; 91% of individuals with detectable activity at the early post-boost visit). Using linear mixed-effects models, the authors estimated that neutralizing activity against the different variants showed similar changes after the booster immunization with estimated half-lives of roughly 52 (95% CI, 46-59), 64 (95% CI 52-83), and 41 (95% CI 34-52) days against wildtype, Delta, and Omicron, respectively.
• Analysis of the bronchoalveolar lavage fluid (BAL) and blood of COVID-19 mRNA vaccinated individuals and hospitalized patients revealed that vaccinated individuals had significantly lower levels of neutralizing antibodies against D614G, Delta and Omicron in the BAL as compared to COVID-19 convalescents, despite exhibiting robust S-specific antibody responses in the blood. The authors report that this suggests vaccination does not induce tissue-residing memory B cell responses as effectively as an infection. **mRNA-vaccinated individuals had S-specific B and T cells in their circulation but unlike convalescents, they were absent in the BAL.** Similar to previous studies, the authors observed immune evasion of Omicron, which resulted in a 10-fold decrease in neutralization titer (NT50) compared to D614G. Using an animal model, the authors reported that systemic mRNA vaccination induces weak respiratory mucosal neutralizing antibody responses, especially against SARS-CoV-2 Omicron; however, when combined with mucosal adenovirus-S immunization, they observed a strong neutralizing antibody response, against all strains, including Omicron. The authors conclude that current COVID-19 vaccines are highly effective against severe disease likely by recruiting circulating B and T cell responses during reinfection, but provide limited protection against breakthrough infection, in particular by Omicron. The authors suggest mucosal booster vaccination is needed to establish robust sterilizing immunity in the respiratory tract against SARS-CoV-2.

**Breakthrough Infections and Reinfections**

As more individuals in a population become vaccinated, a greater proportion of SARS-CoV-2 infections will occur in vaccinated individuals. However, this does not mean that vaccinated individuals are more likely to get infected. Since the last PHO Risk Assessment, more evidence has emerged characterizing reinfections and breakthrough infections caused by Omicron. Some studies are highlighted below.

• **Epidemiological characterization of the first 500 identified Omicron infections in Jordan reported that 66.6% of the cases were fully vaccinated (had received their complete vaccine doses, and 14 days had already passed since their last dose).** The fully vaccinated group reported mostly mild symptoms, but of the boosted group (19% of vaccinated group) mostly reported asymptomatic infections (44.1%) or mild symptoms (45.5%), followed by moderate symptoms (3.9%), and none had severe disease. **Forty-three (8.6%) of study participants were reinfected with Omicron after 90 days from a prior SARS-CoV-2 infection.** Reinfections were mostly asymptomatic (41.9%) or mild (44.2%), with 2.3% being moderate, and 2.3% severe.

• **Analysis of 37,877 nasal swab PCR tests was conducted to investigate if Omicron is more likely than Delta to cause infections in vaccinated persons (sample: Delta = 1463/2987, 49.0%; Omicron =1524/2987, 51.0%).** Omicron had higher positivity rates than Delta among those who received two doses within five months (Omicron = 4.7% [95% CI: 3.5-5.8%] vs. Delta = 2.6% [95% CI: 1.8-3.5%]), two doses more than five months ago (4.2% [95% CI: 3.9-4.6%] vs. 2.9% [95% CI: 2.5-3.2%]), and three vaccine doses (2.2% [95% CI: 1.7-2.7%] vs. 0.9% [95% CI: 0.5-1.2%]. **Omicron positivity rates in participants with one or two vaccine doses were not significantly lower than unvaccinated persons but were 49.7% lower after three doses.** In contrast, the reduction in Delta positivity rates from unvaccinated to 2 vaccine doses was 45.6-49.6% and to 3 vaccine doses was 83.2%.
• An analysis in Norway of the immune recall responses to Omicron and Delta was analyzed at day 7 and 14 post-symptom onset by measuring inflammatory mediators, antibodies to the SARS-CoV-2 spike (S) and nucleocapsid (N) proteins, and spike peptide-induced release of interferon gamma (IFN-γ) in whole blood. A total of 51 vaccinated individuals infected with Omicron, 14 infected with Delta, and 18 healthy controls, were included in the study. Infection with Omicron or Delta led to a similar increase in antibodies to the SARS-CoV-2 S and N proteins and S peptide-IFN-γ in whole blood. Secreted IFN-γ levels were similar in Omicron and Delta cases. Both Omicron and Delta cases also had a similar increase in IgA antibodies to RBD and IgG antibodies to nucleocapsid. Overall, both the Omicron and the Delta cases had a mild and transient increase in inflammatory parameters.

• A study was conducted of hybrid immune individuals: vaccinated without prior history of infection (n=15), unvaccinated without prior history of infection (n=13), vaccinated with prior infection (n=10), and unvaccinated with prior infection (n=13). After BA.1 breakthrough infection, individuals with a previous pre-Omicron variant infection or vaccinated individuals all had high neutralizing antibody titers. Of note, BA.1 neutralizing antibody titers were lower compared to titers to other variants in vaccinated individuals but comparable in unvaccinated individuals with D614G or B.1.617.2 infection followed by BA.1 infection. Samples from naive unvaccinated individuals after BA.1 infection mainly contained neutralizing antibodies against BA.1 and only occasionally against other variants.

Measures in Response to Omicron

This section was informed by scanning government websites and searches in the Google search engine for literature related to Omicron, public health measures, and vaccination programming. The following jurisdictions were searched on February 8, 2022: Denmark, England, Finland, France, Germany, Ireland, Israel, Italy, Netherlands, Norway, Portugal, New York State, and California. For more detail regarding the public health measures in these jurisdictions, please see to the recent environmental scan, ‘Public Health Measures and COVID-19 Epidemiology in Select Jurisdictions (Current up to February 2, 2022)’.

• All included jurisdictions implemented public health measures in response to the emergence of Omicron. Currently, there is variation in the status of implemented public health measures across jurisdictions. Most jurisdictions scanned continue to require masks in multiple community indoor settings, with the exception of England and Finland (recommendation) and Denmark (airports only). In January 2022, due to reported stabilizing hospitalizations, many jurisdictions eased or lifted public health measures, while at the same time, encouraged vaccination, including proof of vaccination and vaccine mandates. Some jurisdictions with immunity or vaccine certificate systems are increasing the stringency of the system by shortening the length of time the certificate is considered valid. Some jurisdictions have accelerated their booster programs, and expanded eligibility to include those aged 12 to 17 years old (e.g., Israel, Germany) or shortened the interval between third and fourth doses (e.g., US). The jurisdictions removing most or all measures (i.e., Denmark, England, Ireland, and Norway) have higher rates of additional dose coverage than many of the other jurisdictions.
Ontario Risk Assessment

- The current risk of Omicron transmission in Ontario is high, with a low degree of uncertainty. The risk of reinfection and breakthrough infection in Ontario is high with a low degree of uncertainty, while the risk of severe disease, particularly amongst unvaccinated individuals, is moderate, with a low degree of uncertainty. Changes to limit eligibility for molecular testing in Ontario were implemented as of December 31, 2021; these changes mean that reported cases of SARS-CoV-2 in Ontario are an underestimate of the true epidemiology of infections and have impacts on surveillance quality. The incidence of severe cases due to increased transmission is a threat to health system capacity.

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

Table 1. Risk Assessment for Omicron B.1.1.529

<table>
<thead>
<tr>
<th>Issues</th>
<th>Risk Level</th>
<th>Degree of Uncertainty</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased Transmissibility</td>
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<td>Low</td>
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<tr>
<td>Disease Severity</td>
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<td>Low</td>
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<tr>
<td>COVID-19 Re-infection</td>
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<tr>
<td>Lowered Vaccine Effectiveness/Breakthrough Infections</td>
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<tr>
<td>Impacts on Testing</td>
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<td>Low</td>
</tr>
<tr>
<td>Impacts on Surveillance</td>
<td>Moderate</td>
<td>Low</td>
</tr>
</tbody>
</table>

Implications for Practice

The epidemiology of Omicron in Ontario is more challenging to interpret due to the rapid increase in Omicron cases and changes in eligibility for PCR testing, which makes metrics such as the reproduction number and confirmed case rate an underestimate. As a result, it is difficult to track the epidemiology of Omicron in Ontario and other jurisdictions. Changes to testing strategy also require the identification of new data sources and new models for projections. Of note, differences in health system capacity across jurisdictions means the same changes in hospitalization rate may be met with different changes to public health measures, based on what is most suitable to a given jurisdictions health system and critical infrastructure capacities.

The evidence for three vaccine doses providing additional protection against symptomatic infection and good protection from hospitalization is strong, making three dose vaccinations (and four doses, in those eligible) a key public health tool in the current Omicron context.

There remain unknowns related to the trajectory of Ontario’s Omicron wave, which are important to consider in relation to a benefit and/or need for community-based public health measures. The emergence of the BA.2 sub lineage, for example, or other VOCs, introduces additional unknowns and therefore risks to anticipation of a decline in SARS-CoV-2 burden. A gradual approach to removal of public health measures across multiple settings can help mitigate risk of resurgence and health system impacts. Public health measures (e.g., masking, capacity limits), ongoing efforts to vaccinate all eligible individuals and accelerated booster vaccinations are important to control the transmission of Omicron, reduce population morbidity and mortality, and address impacts to the health system.
References


