RESEARCH LETTER

Estimates of SARS-CoV-2 Omicron Variant Severity in Ontario, Canada

The World Health Organization designated Omicron as a variant of concern on November 26, 2021. Omicron has 37 mutations in the spike protein and has rapidly replaced Delta as the dominant variant globally, due to increased immune evasion.[1]

Multimedia

It is less clear how the severity of Omicron compares with that of Delta. Early data from South Africa suggest that Omicron may be less severe than prior lineages[2]; however, the low average age of infected individuals, extent of previous infection, and low vaccination rates affect generalizability to certain other countries. In Ontario, Canada, we examined hospitalizations and deaths associated with Omicron compared with matched patients infected with Delta.

Methods | We conducted a retrospective population-wide matched cohort study of patients infected with the Omicron and Delta variants, using Ontario-wide data sets: Public Health Case and Contact Management Solution, containing all SARS-CoV-2 infections diagnosed in Ontario, linked to the COVaxON database, containing all COVID-19 vaccination records. Cases were included if onset occurred between November 22, 2021 (first Omicron BA.1 sublineage case in Ontario), and December 24, 2021. The study period was prior to the January 2022 emergence of the Omicron BA.2 sublineage in Ontario. Case onset date was defined by symptom onset or, for asymptomatic cases, specimen collection. Cases were excluded if they were missing onset date, age, or sex or were hospital acquired.

A representative portion (stepping down from 50% to 10% on December 20, 2021) of case samples with cycle threshold of 30 or less were submitted for whole-genome sequencing (WGS). Between December 6 and 24, 2021, testing for S gene target failure (SGTF) was conducted for all cases in Ontario. Omicron cases were defined as cases identified by WGS, with SGTF and cycle threshold of 30 or less before December 13 (date of 50% Omicron prevalence),[3] or all with SGTF after December 13. Delta cases were defined as cases detected by WGS, cases with amplification of the S gene, or all cases not identified as

Table 1. Demographic Characteristics, Vaccination Status, and Outcomes Among SARS-CoV-2 Delta and Omicron Variant Cases

	No. (%)			
	Full cohort		Matched cohort	
	Delta (n = 24 432)	Omicron (n = 37 296)	Delta (n = 9087)	Omicron (n = 9087)
Age, median (IQR), y	33.0 (13.0-49.0)	30.0 (21.0-44.0)	32.0 (16.0-46.0)	32.0 (17.0-46.0)
Sex				
Female	12 038 (49.3)	18 682 (50.1)	4571 (50.3)	4571 (50.3)
Male	12 331 (50.5)	18 577 (49.8)	4511 (49.6)	4511 (49.6)
Other	63 (0.3)	37 (0.1)	5 (0.1)	5 (0.1)
Vaccination status (doses and time since last dose)				
0 doses	10 900 (44.6)	4784 (12.8)	2823 (31.1)	2823 (31.1)
1 dose				
>14 d-<3 mo	1096 (4.5)	1617 (4.3)	551 (6.1)	551 (6.1)
3-<6 mo	159 (0.7)	110 (0.3)	29 (0.3)	29 (0.3)
≥6 mo	154 (0.6)	132 (0.4)	18 (0.2)	18 (0.2)
2 doses				
>7d-<3 mo	509 (2.1)	865 (2.3)	162 (1.8)	162 (1.8)
3-<6 mo	3392 (13.9)	8714 (23.4)	1724 (19.0)	1724 (19.0)
≥6 mo	6183 (25.3)	17 102 (45.9)	3146 (34.6)	3146 (34.6)
3 doses				
>7d-<3 mo	1975 (8.1)	3841 (10.3)	622 (6.8)	622 (6.8)
3-<6 mo	64 (0.3)	130 (0.3)	12 (0.1)	12 (0.1)
≥6 mo	0	1 (0.003)	0	0
Outcomes				
Hospitalization/death	689 (2.8)	115 (0.3)	129 (1.4)	53 (0.6)
ICU admission/death	248 (1.0)	21 (0.1)	42 (0.5)	8 (0.1)
Deaths	133 (0.5)	12 (0.03)	26 (0.3)	3 (0.03)

Abbreviation: ICU, intensive care unit.

Table 2. Risk of Hospitalization, ICU Admission, or Death Among SARS-CoV-2 Omicron Variant Cases Relative to Delta, Ontario, Canada

		HR (95% CI)[a]		
	Matched pairs, No. (%)	Hospitalization or death	ICU admission or death	Hospitalization or death, sensitivity analysis[b]
Total	9087 (100.0)	0.41 (0.30-0.55)	0.19 (0.09-0.39)	0.33 (0.19-0.56)
Stratified analyses				
Sex				
Female	4571 (50.3)	0.47 (0.31-0.73)	0.23 (0.07-0.74)	0.61 (0.29-1.29)
Male	4511 (49.6)	0.36 (0.24-0.54)	0.17 (0.07-0.43)	0.18 (0.08-0.41)
Age, y				
<60	8215 (90.4)	0.42 (0.25-0.70)	0.10 (0.01-0.78)	0.47 (0.21-1.05)
≥60	872 (9.6)	0.39 (0.28-0.57)	0.21 (0.10-0.46)	0.24 (0.11-0.51)
Vaccine doses				
0 doses	2823 (31.1)	0.41 (0.26-0.64)	0.31 (0.13-0.76)	0.21 (0.07-0.61)
2 doses	5032 (55.4)	0.44 (0.29-0.65)	0.09 (0.02-0.38)	0.40 (0.20-0.80)

Abbreviations: HR, hazard ratio; ICU, intensive care unit.

[a] All analyses based on proportional hazards models and presented as HRs. HRs of 1 indicate equal risk for Omicron relative to Delta, of less than 1 indicate reduced severity of Omicron, and of more than 1 indicate increased severity of Omicron.

[b] Sensitivity analysis excludes Delta or Omicron cases with potential incidental SARS-CoV-2 findings (first positive specimen collection on the day of or the day prior to hospitalization).

Omicron prior to December 3 (date of 5% Omicron prevalence).[3] Omicron cases were matched 1:1 with Delta cases on sex, age in years, vaccination status, time since most recent vaccine dose, region, and onset date (±3 days).

Cox proportional hazards models accounting for clustering within matched sets were used to determine hazard ratios (HRs) for hospitalization, intensive care unit admissions, and deaths for Omicron compared with Delta cases, and 95% CIs, in R (version 4.1.0; R Foundation). Statistical significance was defined as a 95% CI that excluded 1. Stratified analyses were performed to evaluate differences in risk by sex, age group, and vaccination status. In a sensitivity analysis, potential incidental cases (first positive specimen collection on the day of or the day prior to hospitalization) were excluded. The Public Health Ontario Ethics Review Board determined that ethics committee approval or informed consent was not required because deidentified population data were used.

Results | We identified 37 296 Omicron cases that met eligibility criteria, of which 9087 (24.4%) were matched 1:1 with Delta cases (**Table 1**). The median follow-up time was 24 days (IQR, 21.0-28.0). There were 53 hospitalizations (0.6%) and 3 deaths (0.03%) among matched Omicron cases compared with 129 hospitalizations (1.4%) and 26 deaths (0.3%) among matched Delta cases. The HR for hospitalization or death among Omicron cases compared with Delta cases was 0.41 (95% CI, 0.30-0.55; 0.33 [95% CI, 0.19-0.56] in sensitivity analysis), while the HR for intensive care unit admission or death was 0.19 (95% CI, 0.09-0.39), and the HR for death was 0.12 (95% CI, 0.04-0.37). Stratified estimates of Omicron severity by age, sex, and vaccination status all indicated reduced Omicron severity (**Table 2**).

Discussion | In this matched study of more than 9000 Omicron cases in Ontario, the risk of hospitalization or death was lower for Omicron cases compared with Delta cases. The results align with findings from South Africa, Scotland, and England, all of which have demonstrated substantial decreases in risk associated with Omicron.[4-6]

This study has some limitations, in particular the short follow-up duration, potential misclassification due to incidental findings from hospital admission screening, and incomplete public health follow-up as incidence increased. While severity may be reduced among Omicron cases, the absolute number of hospitalizations and the effects on health care systems are likely to be significant due to the elevated incidence of Omicron.

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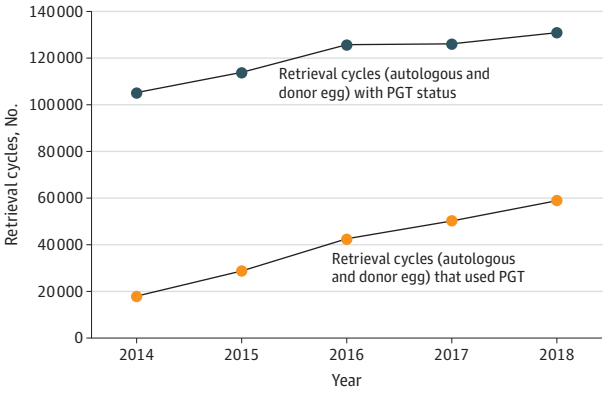
Trends and Outcomes for Preimplantation Genetic Testing in the United States, 2014-2018

Preimplantation genetic testing (PGT) with in vitro fertilization (IVF) is commonly used to screen embryos for chromosome aneuploidy to prioritize embryos for transfer. However, the American Society for Reproductive Medicine states that there is "insufficient evidence to recommend routine use" of the technology[1] because studies preferentially include patients with favorable prognoses and concerns exist regarding costs, risk of false-positive results, and embryo damage.[2] In 2011-2012, PGT use was reported in 4.5% of all IVF cycles.[3] Since then, there have been practice changes, including aneuploidy screening technology and a shift toward blastocyst-stage biopsy with delayed transfer of previously frozen embryos. We used US national surveillance data to describe PGT trends and outcomes between 2014 and 2018.

Methods | This study was reviewed and deemed exempt by the Emory University institutional review board. Data were obtained from the Society for Assisted Reproductive Technology Clinic Outcome Reporting System, estimated to include 90% of IVF cycles in the US. Cycles are entered by member clinics; data validation occurs annually for select clinics. Trends were explored using linear regression to model the number or percentage of cycles using PGT in each year against time.

Given that most transfers using PGT-screened embryos use frozen embryos, we linked originating oocyte retrievals to subsequent frozen transfers to determine cumulative live birth rate (LBR), defined as the rate of achieving 1 live birth after all fresh and frozen embryo transfers within a year of retrieval. To reduce selection bias, we used oocyte retrievals as the denominator instead of embryo transfers. We explored the association between PGT use and cumulative LBR using Mantel-Haenszel χ^2 tests. This analysis was stratified by age and oocyte yield because aneuploidy rates increase with age and directly affect LBR and the decision to perform PGT is often influenced by ovarian response. Analyses were conducted using SAS On-Demand for Academics (SAS Institute Inc). Statistical significance was defined as 2-sided $P < .05$.

Figure 1. Trends in Absolute Number of In Vitro Fertilization Retrieval Cycles and Cycles Using Preimplantation Genetic Testing (PGT), 2014-2018



Results | A total of 115 147 IVF cycles (16.1%) with missing PGT status were excluded from analysis; of these, 57 700 (8.0%) were canceled or yielded no embryos. The absolute number of oocyte retrieval cycles that used PGT increased from 18 059 in 2014 to 58 827 in 2018 ($P < .001$) (**Figure 1**), accounting for 17.2% of cycles in 2014 and 44.9% in 2018 ($P < .001$). In all years combined, PGT was used in 27.0% of autologous oocyte retrieval cycles in women younger than 35 years, 36.5% in women aged 35 to 37 years, 41.3% in women aged 38 to 40 years, 39.7% in women aged 41 to 42 years, and 29.0% in women aged 43 years or older. It was used in 28.6% of cycles using fresh donor oocytes fertilized at the time of retrieval.

In women younger than 35 years, the cumulative LBR was 52.9% with PGT and 54.9% without PGT ($P < .001$). In older women, cumulative LBRs were higher in cycles that used PGT compared with cycles that did not use PGT (35-37 years: 44.0% vs 40.6%; 38-40 years: 31.4% vs 24.4%; 41-42 years: 18.1% vs 11.4%) (**Figure 2**A). Cumulative LBRs were significantly lower in cycles that used PGT than those that did not among women younger than 35 years, regardless of number of oocytes retrieved, but did not significantly differ by use of PGT among older women (Figure 2B).

Discussion | From 2014 to 2018, PGT use increased significantly in the absolute number and percentage of retrieval cycles, accounting for nearly half of all cycles in 2018. These trends could reflect increasing use of IVF among older women[4] at higher risk of aneuploidy or reports of higher LBRs in PGT cycles per transfer in patients with good prognosis.[1,5]

The high use of PGT in young women is inconsistent with their relatively low rates of aneuploidy. In addition, the cumulative LBR was lower for women younger than 35 years who used PGT vs those who did not. Data from a 2019 study[6] showed no improvements in cumulative LBRs for women younger than 35 years. PGT was used relatively more often for