

## **Neurological Events following COVID-19 Vaccination: Does Ethnicity Matter?**

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## **KEY POINTS**

**Question:** Do the rates of neurological events in the six weeks following COVID-19 vaccine vary by ethnicity?

**Findings:** In this retrospective cohort study of 10 million adult Ontarians, who received at least one dose of COVID-19 vaccine, the crude rates of neurological events were lower in Chinese and South Asians compared to the general population, and some events were so rare that the ethnic differences could not be evaluated. The observed differences were eliminated after adjusting for age, sex, and vaccine type, except for lower odds of ischemic stroke in Chinese compared to the general population (aOR 0.74, 95% CI 0.59-0.91).

**Meaning:** The rate of neurological events in the six weeks following COVID-19 vaccine is low and does not vary by ethnicity. The observed lower rate of ischemic stroke in Chinese could be due to the known lower incidence rate of ischemic stroke in this ethnic group.

## ABSTRACT

**Importance** Ethnic differences in the uptake of vaccination have been described before, but population-based studies on ethnic differences in the rates of neurological events after vaccination are scarce.

**Objective** To evaluate the association between ethnicity and the odds of having a neurological event within six weeks of COVID-19 vaccine.

**Design, Setting and Participants** We conducted a retrospective cohort study of Ontario residents aged  $\geq$  18 years who received at least one COVID-19 vaccine (freely available to all Ontarians) between December 1, 2020 and June 31, 2021.

**Exposure** Ethnicity was based on a last name algorithm, and classified as Chinese, South Asians or the general population.

**Main Outcomes** Our primary outcomes were the incidence of following neurological events within 42 days of COVID-19 vaccination requiring a hospitalization or emergency department (ED) visit: Bell's palsy, ischemic stroke, intracerebral hemorrhage (ICH), cerebrovenous sinus thrombosis (CVST), transverse myelitis (TM), and Guillain Barre Syndrome (GBS). We used multivariable logistic regression models to calculate adjusted odds ratios (aOR) of each neurological event in Chinese and South Asians compared to the general population, adjusting for age, sex, and vaccine type (Pfizer, Moderna or others). We did the same analyses for neurological events after first and second COVID-19 vaccine.

**Results** We included 10,063,466 adult Ontario residents, who received 19,933,221 vaccinations during the observation period. The rate of CVST, TM, and GBS was very low to explore ethnic differences. Compared to the general population, the crude rates after the first dose of vaccine for Bell's palsy, ischemic stroke and ICH were lower in Chinese (34, 159 and 48 per 1,000,000 doses) and South Asians (44, 148 and 32). However, these differences were not significant in adjusted models, except lower odds of ischemic stroke in the Chinese compared to the general population (first dose: aOR 0.74; 95% CI 0.59-0.91; second dose: 0.66; 95% CI 0.53-0.83).

**Conclusions** The adjusted odds of neurological events within six weeks of COVID-19 vaccine were similar in Canadian Chinese and South Asians compared to the general population. Lack of major ethnic differences in neurological events following COVID-19 vaccine should encourage vaccination for all.

## **INTRODUCTION**

Neurological events, particularly Bell's Palsy and transverse myelitis (TM), following vaccination have been described in case reports or case series.<sup>1,2</sup> While racial and ethnic differences in vaccine uptake have been observed<sup>3,4</sup>, it is unknown if rates of neurological events differ by ethnicity following vaccination. As up to 76% of the world's population received at least one dose of COVID-19 vaccine (WHO estimate), it may be an ideal setting to evaluate rates of neurological events after a vaccine as well as potential ethnic differences. A large-scale study in the UK found no association between COVID-19 vaccination and neurological events<sup>5</sup>, but ethnic differences were not studied.

Our objective was to estimate the rate of neurological events within 42 days (6 weeks) of receiving COVID-19 vaccine in adult Ontarians, and its variation by ethnicity. We compared the rates of neurological events in Chinese and South Asian ethnic groups because together they form the largest non-Caucasian ethnic group in Canada, making up 11.8% of its total population.

## **METHODS**

We conducted a retrospective cohort study in Ontario, Canada using linked health administrative databases. These datasets were linked using unique encoded identifiers and analyzed at ICES (formerly known as the Institute for Clinical Evaluative Sciences). Use of these data is authorized under section 45 of the Ontario Personal Health Information Protection Act and does not require review by a research ethics board.

Ontario residents have access to the Ontario Health Insurance Program (OHIP), a universal, publicly funded health insurance plan which covers the cost of COVID-19 vaccines, inpatient care, and emergency department (ED) visits.

## **Study Population**

We included all persons identified in the Ontario Registered Persons Database (RPDB) who were alive, eligible for OHIP, and between 18-105 years of age on December 1, 2020 (index date) (e-figure 1). Non-Ontario residents, those who had no contact with the health system in the 5 years prior to index date, and those who were not continuously eligible for OHIP services in the year prior to index date were excluded. Information on the dates and types of COVID-19 vaccines administered were ascertained using the provincial COVID-19 vaccine registry (COVaxON). We collected data on first and second dose vaccinations provided between the index date and June 30, 2021. Second dose vaccinations administered less than 21 days after the first dose were excluded.

## **Exposure**

We used the ETHNIC dataset, a version of the RPDB where a surname-based algorithm was used to classify Ontario residents as Chinese, South Asian, or Others (regarded as ‘general population’) to define our exposure groups.<sup>6</sup> Individuals who could not be linked to the ETHNIC database were excluded.

## **Outcomes**

We used the Canadian Institute for Health Information Discharge Abstract Database and the National Ambulatory Care Reporting System to ascertain hospitalizations and ED visits for the following neurological conditions occurring within 42 days of either the first or second COVID-19 vaccination dose: Bell’s palsy, TM, Guillain Barre syndrome (GBS), ischemic stroke, intracerebral hemorrhage (ICH), and cerebrosinus thrombosis (CVST). We included

hospitalizations/ED visits where the diagnosis of an outcome of interest was suspected and/or included in any diagnostic code space on the record (e-Table 1 for details).

### **Covariates of interest**

We obtained information on age, sex, rural residence, and neighbourhood income quintile from the RPDB, and information on residence in a long-term care home based on the Ontario Drug Benefit and Continuing Care Reporting System datasets. We used hospitalization data in the five years prior to index date to compute the Charlson Comorbidity score. Information on vaccine type was collected from COVaxON: Pfizer, Moderna, or Other (e-Table 1).

### **Statistical Analyses**

We computed crude outcome rates (per 1,000,000 doses) of each outcome in the 42 days following first and second dose COVID-19 vaccination for each exposure group. We used multivariable logistic regression to determine whether ethnicity was associated with outcome rates after controlling for age, sex, and vaccine type. We used separate models for first and second dose vaccinations. Given low event rates, we did not adjust for medical comorbidities.

## **RESULTS**

We included 10,063,466 Ontario residents aged 18 years and over, who received 19,933,221 vaccinations. Of these, 857,289 vaccinations were received by South Asians and 1,112,832 by Chinese. Compared to Chinese and the general population, South Asians were younger and less likely to live in the highest neighbourhood-income quintile. Both Chinese and South Asians had lower comorbidity scores than the general population and were less likely to reside in long-term care homes (Table 1).

In total, 2,419 people developed ischemic stroke, 505 developed ICH, and 542 developed Bell's Palsy within 42 days following first dose of vaccine. The total number of people developing CVST (n=52), GBS (n=72), and TM (n=25) was low which did not allow us to evaluate the differential effect of ethnicity on these outcomes.

Overall, crude rates of ischemic stroke and ICH after the first dose of COVID-19 were lowest in South Asians while Bell's palsy were the lowest in Chinese (Table 2). Chinese ethnicity was associated with a lower adjusted odds of ischemic stroke (adjusted odds ratio [aOR] 0.74; 95% CI, 0.59-0.91) and Bell's Palsy (0.62, 0.39-0.98). Compared to the general population, South Asians had lower adjusted odds for each of the three complications albeit with wide confidence intervals that included null values (Table 2). Similar results were observed for crude rates after second dose (Table 2). Again, Chinese ethnicity was associated with a lower adjusted odds of ischemic stroke compared to the general population (0.66; 0.53-0.83), but not Bell's Palsy (0.63; 0.39-1.01); whereas, like the first dose, odds of ICH were non-significantly lower in South Asians compared to the general population.

## **DISCUSSION**

In this population-based retrospective cohort study in Ontario, rates of neurological events following the first or the second dose of COVID-19 were low and were largely similar after both doses. The crude rates were lower in South Asians and Chinese, with no ethnic differences in these rates after accounting for age, sex, and vaccine type.

In Georgia, United States of America (USA), the rate of ischemic stroke within 21 days of COVID-19 vaccination was 8.14 to 10.48 per 100,000 doses, depending on vaccine type.<sup>7</sup> In a large-scale study across the entire US, among people  $\geq 65$  years with Medicare benefits, rates of



ICH were 48% higher (IRR 1.48; 1.41-1.56) and that of ischemic stroke were 7% lower (IRR 0.93; 0.90-0.96) in Asians compared to Whites. We too found a lower rate of ischemic stroke in Chinese in Ontario, but no difference in the rate of ICH. Further, our observed rates of these events are similar to the baseline rates observed in Ontario in the years preceding COVID-19 infection<sup>9</sup>, and the known ethnic differences in the incidence of stroke and its subtypes.<sup>10</sup>

While our strength includes use of population-based registry to track COVID-19 vaccination, and linked health records to identify incident neurological events, the use of latter can lead to some misclassification inherent to use of health administrative data.<sup>11</sup> Our surname algorithm is specific although for those with hyphenated names or those who change surnames after marriage could be incorrectly classified. Lastly, the incidence of a neurological event in the weeks after vaccination cannot be attributed directly to the vaccine itself.

We observed overall low rates of neurological events following COVID-19 vaccine in Ontario adults, without significant ethnic differences. This should encourage all ethnic groups to be vaccinated by showing lack of vaccine-associated complications by ethnicity.

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**Authors' Contributions:** Study conceptualization- JYC, MVV, RC; Writing of manuscript- MVV; Statistical analysis – IS. All authors interpreted the results, critically revised the manuscript for important intellectual content, and approved the final version for publication.

**Conflicts of Interests:** None.

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**Table 1.** Characteristics of the included cohort with at least one COVID-19 vaccine in Ontario, Canada

<b>Characteristics of interest</b>	<b>Chinese N = 560,087</b>	<b>South Asians N = 431,504</b>	<b>General Population N = 9,071,875</b>
Female, n (%)	299,453 (53.5%)	213,980 (49.6%)	4,710,420 (51.9%)
Median age in years (Q1-Q3)	48 (33-61)	43 (31-57)	50 (34-64)
Neighbourhood-level income in quintiles, n (%)			
Q1 (lowest)	100,715 (18.0%)	70,784 (16.4%)	1,699,277 (18.7%)
Q2	116,706 (20.8%)	100,397 (23.3%)	1,750,870 (19.3%)
Q3	101,946 (18.2%)	117,352 (27.2%)	1,819,542 (20.1%)
Q4	124,597 (22.2%)	84,155 (19.5%)	1,853,706 (20.4%)
Q5 (Highest)	114,564 (20.5%)	58,041 (13.5%)	1,924,658 (21.2%)
Missing	1,559 (0.3%)	775 (0.2%)	23,822 (0.3%)
Rural vs. urban residence, n (%)			
Missing	1,551 (0.3%)	773 (0.2%)	20,353 (0.2%)
Rural	3,642 (0.7%)	3,650 (0.8%)	1,008,899 (11.1%)
Urban	554,894 (99.1%)	427,081 (99.0%)	8,042,623 (88.7%)
Charlson comorbidity score, n (%)	0.07 ± 0.50	0.10 ± 0.55	0.14 ± 0.67
0	541,946 (96.8%)	411,756 (95.4%)	8,468,628 (93.4%)
1	6,796 (1.2%)	8,062 (1.9%)	254,486 (2.8%)
≥ 2	11,345 (2.0%)	11,686 (2.7%)	348,761 (3.8%)
Residence in a long-term residence, n (%)	2,082 (0.4%)	574 (0.1%)	60,509 (0.7%)

**Table 2.** Neurological events within 42 days following the first and second COVID-19 vaccine.

Outcomes of interest	Overall population	Ethnicity					
		Other (ref)		Chinese		South Asians	
	Crude rate <sup>§</sup>	Crude rate <sup>§</sup>	Odds ratio [reference]	Crude rate <sup>§</sup>	Adjusted odds ratio* (95% CI)	Crude rate <sup>§</sup>	Adjusted odds ratio* (95%CI)
<b>First dose of COVID-19 vaccine</b>							
Bell's palsy	53.9 (49.4-58.6)	55.6 (50.8-60.6)	1.00	33.9 (20.4-53.0)	0.62 (0.39-0.98)	44.0 (26.5-68.8)	0.83 (0.52-1.31)
Ischemic stroke	240.4 (230.9-250.2)	249.8 (239.6-260.3)	1.00	158.9 (127.6-195.5)	0.74 (0.59-0.91)	148.3 (114.2-189.4)	0.84 (0.65-1.08)
Intracerebral hemorrhage	50.2 (45.9-54.8)	51.2 (46.6-56.0)	1.00	48.2 (31.8-70.1)	1.07 (0.72-1.57)	32.4 (17.7-54.4)	0.85 (0.50-1.44)
<b>Second dose of COVID-19 vaccine</b>							
Bell's palsy	52.1 (47.7-56.8)	53.7 (48.9-58.7)	1.00	32.6 (19.3-51.5)	0.63 (0.39-1.01)	44.6 (26.9-69.7)	0.90 (0.57-1.42)
Ischemic stroke	232.8 (223.4-242.6)	242.0 (231.9-252.5)	1.00	137.5 (108.3-172.1)	0.66 (0.53-0.83)	164.4 (128.2-207.7)	0.98 (0.77-1.24)
Intracerebral hemorrhage	47.4 (43.2-51.9)	49.0 (44.5-53.9)	1.00	39.8 (24.9-60.3)	0.93 (0.60-1.42)	23.5 (11.3-43.2)	0.65 (0.35-1.21)

<sup>§</sup>Crude rates are per 1,000,000 people. \*Adjusted for age, sex, and type of COVID-19 vaccine (Pfizer [ref], Moderna vs. Other)