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SARS-CoV-2 vaccination, ABO blood group, and risk of COVID-19: population-based cohort study

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SARS-CoV-2 vaccination, ABO blood group, and risk of COVID-19: population-based cohort study

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1	
2 3 4	Abstract
5	Objective: To compare outcomes between O and non-O blood groups, and by mRNA and Ad-V
6 7	vaccines.
8 9	Design: Population-based cohort study.
10 11	Setting: All of Ontario, Canada. Linked datasets captured clinical encounters, vaccinations and
12 13	laboratory testing for SARS-CoV-2.
14	Participants: Individuals aged 12+ years with known ABO blood group and free of SARS-CoV-2
16	before January 15, 2021.
17 18	Main outcomes measures: The main exposure, first SARS-CoV-2 vaccination, was modeled in a
19 20	time-varying manner. O and non-O blood group was known prior to vaccination. SARS-CoV-2
21 22	infection, and severe COVID-19 (hospitalization or death), were assessed starting 14 days after
23	vaccination, up to June 27, 2021.
25	Results: 2,472,261 individuals were included. 1,743,916 (70.5%) had at least one vaccination, of
26 27	which 24.6% were fully vaccinated. Relative to unvaccinated, after receiving their first mRNA
28 29	(aHR 0.46, 95% CI 0.44-0.47) or Ad-V (aHR 0.49, 95% CI 0.44-0.54) vaccine, the risk of SARS-CoV-
30 31	2 infection was lower, as was severe COVID-19 (aHR 0.29, 95% CI 0.20-0.43 [mRNA]; 0.29, 95%
32 33	CI 0.26-0.33 [Ad-V]). Stratifying by blood group produced similar results. For example, after first
34	mRNA vaccination, the aHR of severe COVID-19 was 0.31 (95% CI 0.27-0.36) among non-O, and
36	0.27 (95% CI 0.22 to 0.32) among O blood groups, relative to unvaccinated. Fully vaccinated
37 38	individuals had the lowest risk of SARS-CoV-2 and severe COVID-19.
39 40	Conclusions SARS-CoV-2 infection and severe COVID-19 are reduced by vaccination. This effect
41 42	does not vary by vaccine type or blood group, but is more pronounced among fully, than
43	partially, vaccinated individuals.
45	
46 47	Keywords : SARS-CoV-2: COVID-19: vaccination: ABO blood group: effectiveness: cohort study.
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54	

Strengths and limitations of this study

- This study was limited to persons who had ABO blood group testing, and who are more likely to have required blood transfusion or to have been pregnant in the past.
- We did not know who had acquired natural immunity to SARS-CoV-2. •
- The potential for immortal time bias was mitigated by treating vaccine exposure as time varying, and by setting follow-up time to a common starting date.
- The current study was largely completed prior to the emergence of the SARS-CoV-2 Delta/B.1.617 variant.

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Introduction

Emergence of the SARS-CoV-2 pandemic, and COVID-19 related disease, led to rapid development of various vaccines. Efficacy was demonstrated for the modified RNA (mRNA) vaccine of the SARS-CoV-2 spike protein, to induce neutralizing antibodies <1>, as well as a recombinant, replication-incompetent adenovirus vector that encodes a full-length and stabilized SARS-CoV-2 spike protein (adenovirus-vectored [Ad-V]) <2>. Demonstrated vaccine efficacy shown from pooled data of randomized clinical trials is 95% (95% CI 94 to 95) and 80% (95% CI 56 to 93), respectively <3>. Even within 14 days of receipt of a first dose, vaccine efficacy can reach 80% <4,5>.

It is of interest that adults with O blood group appear to be at lower risk of SARS-CoV-2 infection and COVID-19-related severe illness, compared to those with A, B and AB (i.e., non-O) blood groups <6,7>. Those with O blood group are identified by their anti-A and anti-B antibodies; these same antibodies may offer immunoprotection against SARS-CoV-2, as they are concomitantly produced by certain epithelial cells within the respiratory and digestive tract – prime targets for COVID-19 tissue injury <7>. What is not known, however, is whether vaccinated persons with O blood group experience different rates of SARS-CoV-2 infection and COVID-19 disease than those of non-O blood group. Such information might guide vaccine type, recipient prioritization, and the need for repeat vaccination.

The current study evaluated SARS-CoV-2 infection and COVID-19 disease in a population with a universal vaccination system offered to those aged 12+ years, a high uptake of at least one vaccine (<u>https://www.ices.on.ca/DAS/AHRQ/COVID-19-Dashboard#vaccinecoverage</u>), and systematic collection of vaccination and infection data. Herein, we compared outcomes between O and non-O blood groups, and by mRNA and Ad-V vaccines.

Method

This population-based retrospective cohort study was performed in Ontario, Canada. Patientlevel datasets included all hospitalizations, emergency department visits, the majority of laboratory tests for SARS-CoV-2, and all SARS-CoV-2 vaccinations administered within Ontario (https://data.ontario.ca/dataset/covid-19-vaccine-data-in-ontario), as further detailed in Table S1 <6,8>. Datasets were linked using unique encoded identifiers and analyzed at ICES.

Study eligibility required that an individual was aged 12+ years, a resident of Ontario, had undergone ABO testing, and also did not have a SARS-CoV-2 positive swab before January 15, 2021 (Table S1 and Figure S1).

Exposures and outcomes

The main study exposure was a first SARS-CoV-2 vaccination, handled in a time-varying manner, with a lag of 14 days after vaccination to ensure that the person had a chance to develop immunity. December 15, 2020 was the date when high-risk persons were first vaccinated, and January 15, 2021 the time when Canada began mass vaccinating its citizens <9>. So, for example, a person who was vaccinated on January 1, 2021 or earlier was considered exposed on January 15, 2021, whereas a person who was vaccinated on February 1, 2021 was considered exposed on February 15, 2021 and unexposed before that date.

The main study outcome was *SARS-CoV-2 infection*, defined as a positive SARS-CoV-2 PCR test – regardless of indication, symptoms or illness severity – arising during the follow-up period, from January 15, 2021 to June 27, 2021. The second study outcome was a *severe COVID-19*, defined as a positive SARS-CoV-2 PCR test in conjunction with either a hospitalization within +/- 3 days, or a death within -1 to +3 days, of that positive PCR test. Both study outcomes were assessed starting at least 14 days after vaccination, among those vaccinated <10> (Table S1).

Data analyses

For the overall cohort, study outcomes were based on population-at-risk denominators, which included both those who did and did not necessarily undergo SARS-CoV-2 PCR testing after January 15, 2021. Time-to-event analyses generated incidence rates, and Cox proportional hazard models produced unadjusted and adjusted hazard ratios (HR), comparing first-vaccinated to unvaccinated persons (referent). Censoring occurred if a person lost their Ontario Health Insurance Plan coverage, were outcome-free by June 27, 2021 (the end of study period), or the day after they died (if a death occurred). HR were adjusted for age, sex, rural residence, area income quintile – each at baseline -- as well as prior diabetes mellitus, malignancy, heart

failure, cardiac ischemia or arrhythmia, chronic kidney disease or venous thromboembolism (Table S1). Additional analysis 1 restricted the at-risk denominator those individuals who underwent SARS-CoV-2 PCR testing at least 14 days after their first vaccination.

The main cohort model was repeated, with each study outcome assessed by more specifically comparing first mRNA vaccination or first Ad-V vaccination to unvaccinated persons (referent).

Next, and central to the study, we examined the risk of each study outcome in relation to first-vaccination status, further stratified by O and non-O blood groups. This was done among the entire cohort, as well as restricted to those who underwent SARS-CoV-2 PCR testing at least 14 days after their first vaccination.

Consideration was given to receipt of a second vaccination as a time-dependent variable. Hence, "fully vaccinated" and "partially vaccinated" persons were each compared to unvaccinated individuals, stratified by O and non-O groups – with these analyses conducted among the whole cohort, as well as limited to just those who had SARS-CoV-2 testing in the observation period.

Analyses were planned *a priori*. Statistical analyses were performed using SAS version 9.4 for UNIX (SAS Institute Inc., Cary, NC).

Patient and public involvement

No patient was consulted or involved in this study.

Did we involve patients/service users/carers/lay people in the design of this study? No.

Was the development of outcome measures informed by patients' priorities, experience, and preferences? No.

Were patients/carers/lay people involved in the recruitment to and conduct of the study? No. How will the results be disseminated to study participants? Not applicable.

Are patients/carers/lay people thanked in the contributorship statement/acknowledgements? Not applicable.

Was the development of the research question and outcome measures informed by patients' priorities, experience, and preferences? No.

Results

Among 2,938,215 individuals, 2,472,261 met the inclusion criteria (Figure S1). Of these, 1,743,916 (70.5%) had at least one vaccination (Table 1). Those vaccinated were more likely to be male, older in age, residing in a higher income area, and have higher rates of certain comorbid conditions, like cancer, diabetes and hypertension (Table 1). Of those vaccinated, 1,600,524 (91.8%) first received an mRNA vaccine, and 143,358 (8.2%) an Ad-V vaccine. A second vaccine was administered to 24.6% of individuals by June 13, 2021 (i.e., by 2 weeks before the end of the study observation period), comprising the mRNA vaccine among 415,632 (23.8%), and the Ad-V among 12,855 (0.7%) (Table 1).

After a median follow-up of 163 days (IQR 163 to 163), the rate of SARS-CoV-2 positivity was 0.54 per 10,000 person-days among first-vaccinated persons, and 1.69 per 10,000 person-days among non-vaccinated persons -- an unadjusted HR of 0.38 (95% CI 0.37 to 0.39) and an adjusted HR of 0.46 (95% CI 0.45 to 0.48). The corresponding HR were equally protective for those receiving a first mRNA vaccine (adjusted HR 0.46, 95% CI 0.44 to 0.47) or first Ad-V vaccine (adjusted HR 0.49, 95% CI 0.44 to 0.54), each relative to being unvaccinated (Table 2). The adjusted HR for severe COVID-19 was 0.29 (95% CI 0.26 to 0.33) comparing vaccinated to unvaccinated persons, with similar estimates by vaccine type (Table 2).

There were 439,058 (25.2%) vaccinated people who had SARS-CoV-2 PCR testing during followup period, from January 15, 2021 onward, compared to 175,397 (24.1%) unvaccinated individuals – a small standardized difference of 0.03. Restricting the at-risk denominator these 614,455 individuals, and comparing the vaccinated to the unvaccinated, the adjusted HR were 0.28 (95% CI 0.27 to 0.29) for SARS-CoV-2 positivity, and 0.22 (95% CI 0.20 to 0.25) for severe COVID-19, albeit, at much higher event rates than seen in the entire cohort (Additional analysis 1, Table S2)

Among the entire cohort, the protective effect associated with a first mRNA or Ad-V vaccine against SARS-CoV-2 infection or severe COVID-19 was equally seen among those with O and non-O blood groups, and the expected slightly lower outcome event rates among those with O blood group (Figure 1, upper). This pattern was also seen by vaccine type (Table S3), and among the 614,455 individuals who had SARS-CoV-2 PCR testing (Figure 1, lower).

In the entire cohort, relative to the unvaccinated, fully vaccinated individuals had the lowest

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risk of SARS-CoV-2 infection, followed by partially vaccinated persons (Figure 2, upper). For example, among those with blood group O, the corresponding adjusted HR were 0.39 (95% Cl 0.34 to 0.43) and 0.48 (95% Cl 0.45 to 0.50). Moreover, the HRs did not differ by blood group. The same was evident for severe COVID-19 (Figure 2, upper). Restricting to the sub-cohort who had SARS-CoV-2 testing, the protective effect conferred by full and partial vaccination was similar by blood groups (Figure 2, lower)

Discussion

Main findings

This population-based cohort study observed a lower risk of SARS-CoV-2 infection, as well as severe COVID-19 hospitalization or death, in association with SARS-CoV-2 vaccination. This conferred protective effect did not vary by vaccine type or blood group, but was more pronounced among fully, than partially, vaccinated individuals.

Comparison with other studies

A 2021 meta-analysis observed a lower risk of 54,218 persons showed a lower risk of SARS-CoV-2 infection comparing O vs. non-O blood group (odds ratio 0.71, 95% CI 0.60 to 0.84) <11>. In a cohort study of 225,556 adults and children in Ontario, before SARS-CoV-2 vaccination, we previously observed a lower relative risk of SARS-CoV-2 infection (0.88, 95% CI 0.84 to 0.92) and severe COVID-19 illness or death (0.87, 0.78 to 0.97) among those with O vs. non-O blood group <6>. The current study is the first to explore effect modification of O blood group on vaccine effectiveness against SARS-CoV-2 infection or related illness. Just as we found no effect modification, prior research on the smallpox vaccine suggested no differences in "vaccine success" by ABO blood group <12>, nor for influenza A <13>, rabies <14> and cholera <15> vaccines. Thus, if O blood group is somehow protective against SARS-CoV-2 infection or illness, it is unlikely to generate any additive benefit to that conferred by available mRNA and Ad-V vaccines.

The current study observed a relative risk reduction against severe COVID-19 of between 82-85% after full vaccination, and between 67-70% following partial vaccination (Figure 2). In Chile, Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies

among those aged 60+ years and fully vaccinated, vaccine effectiveness was 67% against infection, 85% for the prevention of hospitalization, and 87% for the prevention of Covid-19related death, with corresponding estimates of 16%, 37% and 46% after partial vaccination <16>. Our findings about vaccine effectiveness are similar to those of randomized clinical trials of SARS-CoV-2 vaccination <1-4>, or another observational study from Ontario <8>. Taken together, SARS-CoV-2 vaccination by mRNA or Ad-V is effective at preventing serious disease.

Limitations

This study was limited to persons who had ABO blood group testing, and who are more likely to have required blood transfusion or to have been pregnant in the past <6>. As a study strength, identification of blood group status preceded SARS-CoV-2 vaccination or index PCR testing. While we excluded those with SARS-CoV-2 infection prior January 15, 2021, we did not know who had acquired natural immunity. While vaccination and study outcomes were fully ascertained within a universal healthcare system, a minority of individuals may have been vaccinated outside of Ontario, and not identified herein. The potential for immortal time bias – the influence of misclassified follow-up time for individuals who were vaccinated, which could differentially favour their survival – was mitigated by treating vaccine exposure as time varying, and by setting follow-up time to a common starting date of January 15, 2021 <17>. All study covariates, including demographic and clinical variables, were captured prior to time zero. A protective effect of vaccination was seen in the additional analyses restricted to those who underwent PCR testing. This was akin to using a test-negative design, in which common access to, and uptake of, medical care can reduces unmeasured confounding related to healthcareseeking behaviours <18>. Last, while the current study was largely completed prior to the emergence of the SARS-CoV-2 Delta/B.1.617 variant, it is unlikely that ABO blood group would be expected to modify vaccine effectiveness within the subsequent period.

Conclusions

The protective benefit offered by mRNA or Ad-V SARS-CoV-2 vaccination – especially full vaccination — is not further modulated by ABO blood group status. Large-scale population or

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targeted vaccination programs should continue, with ongoing research about how to mitigate emerging viral variants.

Contributions to authorship

JGR, AP: Study concept, analysis and interpretation of the data, drafting of manuscript, manuscript revision, approval of final version.

Data sharing statement

No additional data available.

Ethics approval

The use of data in this project was authorized under section 45 of Ontario's Personal Health Information Protection Act, which does not require review by a Research Ethics Board.

Funding

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No grant number is assigned to either funding source.

Competing interests

None.

Figure legends

Figure 1. SARS-CoV-2 vaccination and associated risk of SARS-CoV-2 infection, or severe COVID-19 (hospitalization or death), stratified by O and non-O blood groups. Data are presented for the entire cohort (upper panel), and 614,455 individuals who had SARS-CoV-2 PCR testing during the follow-up period (lower panel). Analyses are by time-varying exposure after first vaccination. Unadjusted hazard ratios are in red, and adjusted hazard ratios in blue, adjusted for age, sex, rural residence, area income quintile – each at baseline -- as well as prior diabetes mellitus, malignancy, heart failure, cardiac ischemia or arrhythmia, chronic kidney disease or venous thromboembolism.

Figure 2. Full or partial SARS-CoV-2 vaccination and associated risk of SARS-CoV-2 infection, or severe COVID-19 (hospitalization or death), stratified by O and non-O blood groups. Data are presented for the entire cohort (upper panel), and 614,455 individuals who had SARS-CoV-2 PCR testing during the follow-up period (lower panel). Analyses are by time-varying exposure after first vaccination. Unadjusted hazard ratios are in red, and adjusted hazard ratios in blue, adjusted for age, sex, rural residence, area income quintile – each at baseline -- as well as prior diabetes mellitus, malignancy, heart failure, cardiac ischemia or arrhythmia, chronic kidney disease or venous thromboembolism.

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Table 1. Characteristics of 2,472,261 individuals in Ontario, Canada aged 12 years and older, with known ABOblood group, and without evidence of SARS-CoV-2 infection before January 15, 2021. All data are presented as anumber (%) unless otherwise indicated.

Characteristic		Any SARS-Cov-2 vaccination (N = 1.743.916)	No SARS-COV-2 vaccination (N = 728.345)	Standardize difference
On January 15, 2021 (time zero)			(
Mean (SD) age, y		50.8 (18.4)	40.6 (15.4)	0.60
12-17		13,009 (0.7)	11,509 (1.6)	0.08
18-39		589,158 (33.8)	415,983 (57.1)	0.48
40-59		568,693 (32.6)	208,310 (28.6)	0.09
60-69		218,653 (12.5)	42,386 (5.8)	0.23
70-79		209,118 (12.0)	29,116 (4.0)	0.30
80+		145,285 (8.3)	21,041 (2.9)	0.24
Female		1,200,499 (68.8)	548,647 (75.3)	0.15
Area income quintile (Q) ^a	Q1 (lowest)	298,360 (17.1)	182,483 (25.1)	0.20
	Q2	332,128 (19.0)	153,526 (21.1)	0.05
	Q3	360,666 (20.7)	147,174 (20.2)	0.01
	Q4	375,199 (21.5)	134,421 (18.5)	0.08
	Q5 (highest)	373,655 (21.4)	108,469 (14.9)	0.17
Rural residence ^b	Rural	164,607 (9.4)	76,733 (10.5)	0.04
Pregnant		23,137 (1.3)	19,410 (2.7)	0.10
O blood group	6	315,903 (43.4)	751,212 (43.1)	0.01
Pre-existing conditions			· · · ·	
Diabetes mellitus		292,661 (16.8)	70,062 (9.6)	0.21
Malignancy		405,034 (23.2)	104,741 (14.4)	0.23
Heart failure		89,604 (5.1)	18,085 (2.5)	0.14
Cardiac ischemia or arrhythmia		144,692 (8.3)	27,106 (3.7)	0.19
Chronic kidney disease		90,732 (5.2)	19,760 (2.7)	0.13
Venous thromboembolism		41,006 (2.4)	13,342 (1.8)	0.04
Stroke or transient ischemic attack		31,638 (1.8)	6,763 (0.9)	0.08
Chronic hypertension		571,167 (32.8)	116,201 (16.0)	0.40
Asthma		300,546 (17.2)	126,172 (17.3)	0.00
Dementia, or frailty		264,694 (15.2)	107,972 (14.8)	0.01
Anemia		265,861 (15.2)	96,060 (13.2)	0.06
Chronic obstructive pulmonary disease		89,413 (5.1)	20,352 (2.8)	0.12
HIV or organ transplant		9,754 (0.6)	2,770 (0.4)	0.03
At time of first vaccination				
Vaccine type	Modified RNA	1,600,524 (91.8)		
	Adenovirus-vectored	143,358 (8.2)		
	Unspecified	34 (0.0)		
Vaccine name	Astrazeneca	117,100 (6.7)		
	Covishield	26,086 (1.5)		
	Janssen	172 (0.0)		
	Moderna	315,370 (18.1)		
	Pfizer	1,285,154 (73.7)		
	Unspecified	34 (0.0)		

Characteristic		Any SARS-Cov-2 vaccination (N = 1,743,916)	No SARS-COV-2 vaccination (N = 728,345)	Standardized difference
At time of second vaccination				
Vaccine type	Modified RNA	415,632 (23.8)		
	Adenovirus-vectored	12,855 (0.7)		
	Unspecified	16 (0.0)		
	No second dose	1,315,413 (75.4)		
Vaccine name	Astrazeneca	12,692 (0.7)		
	Covishield	157 (0.0)		
	Janssen	6 (0.0)		
	Moderna	86,791 (5.0)		
	Pfizer	328,841 (18.9)		
	Unspecified	16 (0.0)		
	No second dose	1,315,413 (75.4)		
Received two vaccine doses by		428,503 (24.6)		
of follow-up)				
Vaccine dose 2 same as dose 1	Same	121 517 (21 3)		
	Different	3 969 (0 2)		
	Unknown	17 (0 0)		
	No second dose	1 315 <i>J</i> 13 (75 <i>J</i>)		
Median (IQR) follow-up for assessing the primary study outcome, d	10	163.0 (163.0-163.0)	163.0 (163.0-163.0)	0.39
Median (IQR) follow-up for assessing the secondary study outcome, d	2	163.0 (163.0-163.0)	163.0 (163.0-163.0)	0.16
Had SARS-CoV-2 PCR testing during follow-up period, from January 15, 2021 onward		439,058 (25.2)	175,397 (24.1)	0.03
Missing for 6180 (0.25%) of all person Missing for 5247 (0.21%) of all person Before January 15, 2021	ns ns			

7 of 35 Table 2. SARS-CoV-2 vaccination and associated risk of SARS-CoV-2 infection, or severe COVID-19 (hospitalization or death) – eacling assessed starting at least 14 days after the first vaccination, among the entire cohort. Data are presented by time-varying exposure after first vaccination vs. unvaccination vs. unvaccination, among the entire cohort. Data are presented by time-varying exposure after first vaccination vs. unvaccination vs. unvaccinatio vs. unvaccina includi)59944 vaccination type vs. unvaccinated (lower maroon).

			No. with outcome (rate	Unลdjusted	Adjusted
		No. person-days of	per 10,000 person-	hazardratio	hazard ratio
Study outcome	Exposure state ^a	follow-up ^a	days)	(95 x 10 k)	(95% CI%) ^ь
CARC Cold 2 infection	Unvaccinated (N = 2,464,998)	303,209,192	51,187 (1.69)	1.00 kg kg rent)	1.00 (referent)
SARS-COV-2 INJECTION	Vaccinated (N = 1,743,916)	93,324,805	4995 (0.54)	0.38 (9 , 3 7 0 0.39)	0.46 (0.45 to 0.48)
				o tej	
Severe COVID-19 ^c	Unvaccinated (N = 2,464,998)	307,438,194	2890 (0.09)	1.00 () () () () () () () () () (1.00 (referent)
	Vaccinated (N = 1,743,916)	93,575,031	491 (0.05)	0.71 (0 .044 0 0.79)	0.29 (0.26 to 0.33)
	()	0		om ata	
				mini SES	
	Unvaccinated (N = 2,464,998)	303,209,192	51,187 (1.69)	1.0@(reprent)	1.00 (referent)
SARS-CoV-2 infection	Adenovirus-vectored (N = 143,358)	8,263,735	434 (0.53)	0.39 (4 .36 5 o 0.43)	0.49 (0.44 to 0.54)
	Modified RNA (N = 1,600,524)	85,059,246	4561 (0.54)	0.38 (🚆 37 <mark> 1</mark> 0 0.39)	0.46 (0.44 to 0.47)
				ng,	
	Unvaccinated (N = 2,464,998)	307,438,194	2890 (0.09)	1.00 <mark>2(</mark> reerent)	1.00 (referent)
Severe COVID-19 ^c	Adenovirus-vectored (N = 143,358)	8,284,162	27 (0.03)	0.46 (🛱:31 do 0.68)	0.29 (0.20 to 0.43)
	Modified RNA (N = 1,600,524)	85,289,045	464 (0.05)	∕0.73 (0 .66 ± 0 0.82)	0.29 (0.26 to 0.33)

^aExposure is time-varying, therefore, some individuals may have contributed time as unvaccinated, and then subsequen $\mathbf{\bar{d}}$ y, $\mathbf{\bar{s}}$ vaccinated.

^bAdjusted for age, sex, rural residence, area income quintile – each at baseline -- as well as prior diabetes mellitus, maligandy, heart failure, cardiac

ischemia or arrhythmia, chronic kidney disease or venous thromboembolism.

^cIn the vaccinated and unvaccinated groups, respectively, there were 21 and 133 deaths, from 1 day before, up to 3 days after, a SARS-CoV-2 positive PCR ce Bibliographique de l test.



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Hazard ratio (95% confidence interval)

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Assessment	Timing	Disease, procedure or condition	CIHI-DAD, SDS or NACRS ICD-10-CA diagnosis or CCI procedure codes	OHIP ICD-9 diagnosts orstee codes; or other data source 84 in 9 g t	Validation studies or documentation for some codes
Inclusion criteria	ABO-Rh specimen date January 2007 to December 2020	Individuals with an ABO blood group test result in Ontario, Canada		LOINC codes 882-1, 283, 10331-7 in the Ontario Labor 55 Information System 4 2 5 most outpatient lab 7 5 information in Ontar 5	
Exclusion criteria	SARS-CoV-2 specimen date January 15, 2020 to January 14, 2021	Individuals with a SARS-CoV- 2 RNA PCR positive laboratory result in Ontario, Canada prior to time zero		OLISC19 - includes Test, equest (TR)/LOINC codes for the S-CoV-2 and other respirator the seting: TR12936-1, TR1293 5, \$4315-9, 94314-2, 94316-7, XOR 55, XON13529-3, XON1357, 5, XON13531-9, XON1357, 5, XON13531-9, XON1357, 7. These codes, plus keywords such as "COVID", "SARS-CoV 7, "Ovel coronavirus" or "nCOV" or microorganism SNOV/LE2.codes (840533007 [SARS-CoV-2], 168209000 [No Virus Identified]), were used to define the data pull from OLIS.	For the ICES methodology and Python script for cleaning and parsing OLIS lab results for SARS CoV-2 and othe respiratory viruses, see <u>https://github.c</u> <u>m/icescentral/C</u> <u>OVID19-Lab- Results</u>
	January 15, 2021 (time zero)	Implausible or missing sex, birth date or death date		Registered Persons Batabase (<u>RPDB</u>) - contains demogration and encrypted health cafe numbers for all individuals eligible for OHIP	
	Same as above	Non-Ontario resident or not eligible for OHIP at time zero		RPDB Agenc	
	Same as above	Aged less < 12 years at time		RPDB B	

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Assessment	Timing	Disease, procedure or condition	CIHI-DAD, SDS or NACRS ICD-10-CA diagnosis or CCI procedure codes	OHIP ICD-9 diagnosis or tee codes; or other data source 24	Validation studies or documentatio for some code
	Same as above	Death occurred before baseline, before the vaccination date, or > 1 day before the SARS-CoV-2 specimen date	Discharge disposition is not alive (<u>DAD</u> , <u>NACRS</u>)	RPDB, COVAXON, Og Brog for uses reeig RPDB, COVAXON, COVAXO	
	December 15, 2020 to June 13, 2021	Duplicate vaccination record		COVAXON lated to Do	
Study exposures	December 15, 2020 to June 13, 2021	COVID-19 partially vaccinated status		COVAXON texts	
·	Same as above	COVID-19 1 st dose type (mRNA, viral vector, unknown, none)		COVAXON data r	
	Same as above	COVID-19 fully-vaccinated status (fully-vaccinated, partially-vaccinated, unvaccinated)		COVAXON ning, Al trai	
Stratification variable	January 2007 to December 2020	ABO blood group (O, other)	- 0	LOINC codes 882-1, 3839, 10331-7	
Main study outcome	SARS-CoV-2 specimen date January 15, 2021 (time zero) to June 27, 2021, censored at loss OHIP eligibility or the day after death.	Earliest SARS-CoV-2 positive test.		OLISC19 OLISC19 OLISC19	

Assessment	Timing	Disease, procedure or condition	CIHI-DAD, SDS or NACRS ICD-10-CA diagnosis or CCI procedure codes	OHIP ICD-9 diagnosits or fee codes; or other data source in	Validation studies or documentation for some codes
Secondary study outcome	SARS-CoV-2 specimen date January 15, 2021 (time zero) to June 30, 2021, censored at loss OHIP eligibility or the day after death.	Earliest SARS-CoV-2 positive test <u>AND</u> a hospital admission within -/+ 3 days or death within -1 to +3 days of the SARS-CoV-2 specimen date.	DAD (hospital admission, not alive at discharge), NACRS (hospital admission, not alive at discharge), SDS (not alive at discharge)	OLISC19 (SARS-CoV teon 18 July 2022. Downloaded from Enseignement Superieur (AE (AE	
Covariates	January 15, 2021 (time zero)	Age	E K	RPDB	
	Same as above	Sex	- 0	RPDB $\geq \overline{\underline{3}}$	
	Same as above	Area income guintile		Statistics Canada Ceasura	
	Same as above	Rural residence		Statistics Canada Ceasus	
	Any time before January 15, 2021 (time zero)	Diabetes mellitus	The ICES-derived ODD database was used to identify patients with diagnosed diabetes before the index date, based on 2 OHIP diagnostic codes or 1 OHIP fee code or 1 DAD/SDS diagnostic code, within 2 years. ICD-10-CA: E10, E11, E13, E14	OHIP ICD-9: 250 OHIP fee codes: Q040, K029, K030, K045, K046 Similar technologies.	https://pubme ncbi.nlm.nih.gr /11874939/

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Assessment	Timing	Disease, procedure or condition	CIHI-DAD, SDS or NACRS ICD-10-CA diagnosis or CCI procedure codes	OHIP ICD-9 diagnosits or the data source in the dat	ee codes; V si d	alidation tudies or ocumentatio
	Same as above	History of heart failure	The ICES-derived CHF database was used to identify patients with CHF, based on 1 ED, hospitalization or outpatient claim, and a second claim in 1 year. The CHF database is limited to those 40 years of age or older. ICD-10-CA (DAD, SDS): 1500, 1501, 1509	944 on 18 July 2022. Downloaded from htt Enseignement Superieur (ABEs 944 on 18 July 2022. Downloaded from htt Enseignement Superieur (ABEs 944 on 18 July 2022. Downloaded from htt 944 on 18 July 2022. Downloaded from htt 944 on 18 July 2022. Downloaded from htt 944 on 18 July 2022. Downloaded from htt 945 Other Superior Supe	h n /	ttps://pubme cbi.nlm.nih.go 23735455/
	Within 5 years before January 15, 2021 (time zero)	History of malignant neoplasm	ICD-10-CA (DAD, SDS, NACRS): C00-C97	ing, Al tra		
	Same as above	Chronic kidney disease (CKD)	<u>CKD diagnosis</u> ICD-10-CA (DAD, NACRS): E102, E112, E132, E142, I12, I13, N08, N18, N19	CKD diagnosis ICD-9 (OHIP): 403, 585 icom c	h n /	ttps://pubme cbi.nlm.nih.g 23560464/
				n June 10, 2025 at Agence Bibliographique nilar technologies.		
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ning Disease, procedure or condition	CIHI-DAD, SDS or NACRS		
	ICD-10-CA diagnosis or CCI procedure codes	OHIP ICD-9 diagnos 과 or ther data source 역 2 or other data source 2 	Validation studies or documentation for some cod
	Chronic dialysis At least 2 of the following CCI (DAD, SDS) codes separated by 90 days, but < 150 days, in the year before the index date: 1PZ21	Chronic dialysis At least 2 of the following OHIP fee codes separated by 20 days, but <	https://pubm ncbi.nlm.nih.g /20613656/
	Exclude kidney transplant CCI (DAD): 1PC85	Exclude kidney transplantOHIP fee codes: S435, S434 \mathcal{G} <	https://pubm ncbi.nlm.nih. _ł /26019887/
		June 10, 2025 at Agence Bibliographique ar technologies.	
		Chronic dialysis At least 2 of the following CCI (DAD, SDS) codes separated by 90 days, but < 150 days, in the year	Chronic dialysis Chronic dialysis Chronic dialysis At least 2 of the following CCI (DAD, SDS) codes separated by 90 days, but < 150 days, in the year before the index date: Chronic dialysis Chronic dialysis

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Assessment	Timing	Disease, procedure or condition	CIHI-DAD, SDS or NACRS ICD-10-CA diagnosis or CCI procedure codes	OHIP ICD-9 diagnosits or the codes; or other data sourcer 24	Validation studies or documentatio
	Same as above	History of cardiac ischemia	At least 1 hospitalization (DAD) or ED (NACRS) visit with a diagnosis or procedure coded with 1 of the following codes:Angina: ICD-10-CA: I20, I2382, I24Chronic Ischemic Heart Disease: ICD-10-CA: I25Myocardial infarction: ICD-10-CA: I21, I22Coronary Artery Bypass Grafting: CCI: 1IJ76, 1IJ80Percutaneous Coronary Intervention: CCI: 1IJ26, 1IJ50, 1IJ55, 1IJ57	944 on 18 July 2022. Downloaded from http://bmjopen.bmj.com/ on June 10, 20 Enseignement Superieur (ABES) . uding for uses related to text and data mining, Al training, and similar technolo	https://pubme ncbi.nlm.nih.go /20847972/
		For peer review only - http	p://bmjopen.bmj.com/site/about	es si Agence Bibliographique de I t/guidelines.xhtml	6

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Assessment	Timing	Disease, procedure or condition	CIHI-DAD, SDS or NACRS ICD-10-CA diagnosis or CCI procedure codes	OHIP ICD-9 diagnosition; fee codes; or other data source	Validation studies or documentatio for some code
	Same as above	History of cardiac arrhythmia	At least 1 hospitalization (DAD) or ED (NACRS) visit with a diagnosis or procedure coded with 1 of the following codes: Atrial Fibrillation/Atrial	44 on 18 July 2022. Do Enseigneme ding for uses related t	https://pubme ncbi.nlm.nih.g /19433698/ https://www.i .on.ca/Publica ns/Atlases-and
		De Co	Flutter: ICD-10-CA: I48 <u>Ventricular Arrhythmia &</u> Tachycardia:	wnloaded from I nt Superieur (AE o text and data r	Reports/2006/ nadian-Institut for-Health- Information
			ICD-10-CA: I470, I472, I490, I493 <u>Permanent Pacemaker:</u> CCI: 1HZ53GRNM,	http://bmjopen.l IES) . nining, Al traini	https://pubme ncbi.nlm.nih.g /17599603/
			1HZ53LANM, 1HZ53GRNK, 1HZ53LANK, 1HZ53GRNL, 1HZ53LANL	ng, and similar	
			Implantable Cardioverter- Defibrillator:Defibrillator: CCI: 1HZ53GRFS, 1HZ53LAFS, 1HZ53SYFS, 1HZ53HAFS	ine 10, 2025 at technologies.	
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Assessment	Timing	Disease, procedure or	CIHI-DAD. SDS or NACRS	OHIP ICD-9 diagnosts orkfee codes:	Validation
	0	condition	ICD-10-CA diagnosis or	or other data source	studies or
			CCI procedure codes	, in 1-0,	documenta
				10. 10. 10.	for some co
	Same as above	History of pulmonary	ICD-10-CA (DAD, SDS,	OHIP ICD-9: 677, 415, 62, 451, 452	
		embolism, deep vein	NACRS): 1260, 1269,	y fo	
		thrombosis, or other venous	088201, 088202, 088203,	AND r	
		thromboembolism	088204, 088209, 1636,	uly ses	
			1822, 1828, 1829, 1801,	one of the following	
			1802, 1803, 1808, 1809,	radiological professដ្ឋាធ្មើរអ៊ីee codes	
			022301, 022303, 022309,	for a VTE diagnostic	
			022501, 022503, 022509,	3 days: J198, J498, Jຊ້ອີຊີ2493, J202,	
			087102, 087104, 087109,	၂502, J206, J506, J18 ခုနှစ် နို 82, X406,	
			087304, 087309, 1676,	X407, X125, X188, Xā 🛱 🛱 🕅 405, X408,	
			I81, I820, I823, O228,	X126, X410, X231, X 🕃 🛱 式 X233, X127,	
			0229, 0878, 0879	X413, X421, X425, J∰ 2660, J859,	
				J860	
			AND	ng.	
				A B	
			one of the following CCI	tra	
			codes for diagnostic	ini p	
			imaging during the same	Ģ <u>ē</u>	
			admission: 3KX30DA,	and cor	
			3KX30DB, 3KX30DC,	l sir	
			3KX30DD, 3KR10VC,		
			3KR10VN, 3KR12VA,	ar te	
			3KX10VA, 3KX10VC,	sch	
			3KX10VN, 3KX10VX,	nol	
			3KX12VA, 3IM10VC,	ogi	
			3IM10VX, 3IM10VY,	es. at	
			3IM12VA, 3GT70CA,	Age	
			3GT70CC, 3GT70CE,) ore	
			3GT70KC, 3GT70KD,	е — — — — — — — — — — — — — — — — — — —	
			3GT70KE, 3JY10VA,	l ibi	
			3JY10VC, 3JY10VN,	ogr	
			3JY10VX, 3JY12VA ,	a p	

Assessment	Timing	Disease, procedure or condition	CIHI-DAD, SDS or NACRS ICD-10-CA diagnosis or CCI procedure codes	OHIP ICD-9 diagnosts or tee codes; or other data source	Validation studies or document for some c
Other baseline variables	Any time before January 15, 2021 (time zero)	Asthma	The ICES-derived <u>ASTHMA</u> database was used to identify patients with diagnosed asthma before the index date, based on 2 OHIP diagnostic codes or 1 DAD diagnostic code.	OHIP ICD-9: 493 ding for uses related to text a	https://puk ncbi.nlm.ni /20011725
	Same as above	Chronic obstructive pulmonary disease (COPD)	The ICES-derived <u>COPD</u> database was used to identify patients with diagnosed COPD before the index date, based on 1 OHIP diagnostic code or 1 DAD diagnostic code.	OHIP ICD-9: 491, 49 effeur (ABES) . Al training, Al training,	https://pub ncbi.nlm.nii /19863368, COPD algor was validat those aged years.
	Same as above	Chronic hypertension	The ICES-derived HYPER database was used to identify patients with: a) 1 hospital admission with a hypertension diagnosis, or b) an OHIP claim with a hypertension diagnosis followed within 2 years by either an OHIP claim or a hospital admission with a hypertension diagnosis.	OHIP ICD-9: 401-40 and similar technologies.	https://pub ncbi.nlm.nil /20101286/
			ICD-10-CA (DAD, SDS): 110- 113, 115	Iraphi	

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Assessment	Timing	Disease, procedure or condition	CIHI-DAD, SDS or NACRS ICD-10-CA diagnosis or CCI procedure codes	OHIP ICD-9 diagnosts or tee codes; or other data source 22	Validation studies or documentation for some code
	Same as above	Immunocompromised (HIV or organ transplant)		The ICES-derived Hig database was used to identify patients with pre- existing HIV, based on 30 hysician claims in 3 years.	https://pubme ncbi.nlm.nih.go /21738786/
Same as	Same as above	Dementia	The ICES-derived <u>DEMENTIA</u> database was used to identify individuals with 1 hospitalization for dementia and/or 3 outpatient visits for dementia, each separated by 30 days, within 2 years, or 1 prescription from ODB. ICD-10-CA (DAD, SDS): F00-F03, G30	OHIP ICD-9: 290, 33 Amining ODB	https://pubme ncbi.nlm.nih.go /27567819/
		For peer review only - http	v//hmianan hmi.com/cita/ahaut)25 at Agence Bibliographique de I ogies.	

Assessment	Timing	Disease, procedure or condition	CIHI-DAD, SDS or NACRS ICD-10-CA diagnosis or CCI procedure codes	OHIP ICD-9 diagnos弦 orびee codes; or other data sourc로 것 	Validation studies or documenta for some c
	Within 1 year before January 15, 2021 (time zero)	Frailty	 Identified based on the following rules, using DAD and OHIP databases: 1. Long-term care residence (i.e., admitted from/discharged to, a nursing home after hospital stay, or location of physician billing claim was long-term care facility); 2. Receipt of palliative care; 3. Two or more domains derived from frailty scales (i.e., cognitive impairment, falls, general health status, incontinence, nutrition issues, functional performance) and health services utilization (i.e., ≥ 2 hospital stays or ED visits, geriatrician or home care visit). 	44 on 18 July 2022. Downloaded from http://bmjopen.bmj.com/ on June 10, 2025 at Age Enseignement Superieur (ABES) . Iding for uses related to text and data mining, Al training, and similar technologies.	https://pub ncbi.nlm.ni /28974280,
	Within 5 years before January 15, 2021 (time zero)	Anemia	ICD-10-CA (DAD, SDS, NACRS): D50-D53, D55, D56, D572-D574, D58- D61, D63, P55, P560, P570	OHIP ICD-9: 280-285, 77율 Bibliog	

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Assessment	Timing	Disease, procedure or condition	CIHI-DAD, SDS or NACRS ICD-10-CA diagnosis or CCI procedure codes	ତ୍ର୍ରୁ କୁ OHIP ICD-9 diagnosର ordee codes; or other data source ସୁ <u>n</u> ତୁ	Validation studies or documentat
	Same as above	History of transient ischemic attack or acute ischemic stroke	Transient Ischemic Attack: At least 1 hospitalization or ED visit with 1 of the following diagnosis codes:ICD-10-CA (DAD, NACRS): G450-G453, G458, G459, H340Acute Ischemic Stroke: 1 hospitalization with a main diagnosis coded with one of the following codes:	9944 on 18 July 2022. Downloaded from http://bmjop Enseignement Superieur (ABES) . luding for uses related to text and data mining, Al t	for some coc http://canad trokenetwor en/wp- content/uplc /2014/08/Str _Core_ENG.p
ASTHMA: On Health Inforr Ontario Dem Diseases, 9th Network; LO Ontario Diab System COVI	itario Asthma datase nation; CORR: Canac entia dataset; ED: En Revision; ICD-10-CA INC: Logical Observa etes Dataset; OHIP: D-19 Laboratory Dat	et; CCI: Canadian Classification of In dian Organ Replacement Registry; mergency Department; HIV: Ontar A: International Classification of Dis tion Identifiers Names and Codes; Ontario Health Insurance Plan; OL ca; RPDB: Registered Persons Datal	icD-10-CA (DAD): 163 (except 1636), 164, H341 nterventions; CHF: Ontario Co COVAXON: Ontario COVID-19 io HIV dataset; HYPER: Ontari seases, 10th Revision, Canada NACRS: National Ambulatory IS: Ontario Laboratories Inform base; SDS: Same Day Surgery	ngestive Heart Failured dataset; CIHI: Ca Vaccine Data; DAD: Dischorge Abstrac o Hypertension dataset; ICD-9: Interna ; ICU: Intensive Care Unit J HIN: Local I Care Reporting System; ODB: Ontario mation System; OLISC 9: Ontario Labo	anadian Institute t Database; DEN tional Classifica Health Integrati Drug Benefit; O ratories Informa
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BMJ Open Table S2 (Additional analysis 1). SARS-CoV-2 vaccination and associated risk of SARS-CoV-2 infection, or severe COVID-19 (hospitalization or death) – each assessed starting at least 14 days after the first vaccination. This analysis is limited to 614,455 individuals who had SARS-CoV-2 PCR testing diring the follow-up period, from ncludi)59944 January 15, 2021 onward.

Study outcome	Exposure state ^a	No. person-days of	No. with outcome (rate per 10,000 person-days)	Uឆ្អឹdjអ្មីted haærdratio (៨ឆ្នីទីទី%)	Adjusted hazard ratio (95% Cl%) ^b
SARS Cold 2 infection	Unvaccinated (N = 609,129)	67,185,613	51,187 (7.62)	1.00 1.00	1.00 (referent)
SARS-COV-2 Injection	Vaccinated (N = 439,058)	27,220,438	4995 (1.84)	0.25 (0.25 to 0.26)	0.28 (0.27 to 0.29)
				o tey	
Savara COVID 10	Unvaccinated (N = 609,129)	71,414,615	2890 (0.40)	1.00 () () () () () () () () () (1.00 (referent)
Severe COVID-19	Vaccinated (N = 439,058)	27,470,663	491 (0.18)	0.50 (6 .46)	0.22 (0.20 to 0.25)

^aExposure is time-varying, therefore, some individuals may have contributed time as unvaccinated, and then subsequen

^bAdjusted for age, sex, rural residence, area income quintile – each at baseline -- as well as prior diabetes mellitus, mali any, heart failure, cardiac

ischemia or arrhythmia, chronic kidney disease or venous thromboembolism. mbolism.

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among the entire cohort. Data are presented by time-varying exposure after first vaccination type vs. unvaccinated, with study out on starting at least 14 includi days after the first vaccination.

				No. with outeome	Adjusted
	Stratified by		No. person-days of	(rate per 10,000	hazard ratio
Study outcome	blood group	Exposure state ^a	follow-up ^a	person⊭darys)	(95% CI%) ^ь
		Unvaccinated (N = 1,401,213)	172,490,490	30,685	1.00 (referent)
	Non-O	Adenovirus-vectored (N = 80,411)	4,637,314	260 (260	0.49 (0.43 to 0.55)
		Modified RNA (N = 912,274)	48,108,108	2717 (0,56)	0.46 (0.44 to 0.48)
SARS-CoV-2 infection		6		oad xt a	
		Unvaccinated (N = 1,063,785)	130,718,702	20,502 (25)	1.00 (referent)
	0	Adenovirus-vectored (N = 62,947)	3,626,421	174 (b .)	0.49 (0.42 to 0.57)
		Modified RNA (N = 688,250)	36,951,138	1844	0.46 (0.44 to 0.48)
				ing,	
		e e		≥ 1 t	
		Unvaccinated (N = 1,401,213)	175,034,046	1677 D.1 B)	1.00 (referent)
	Non-O	Adenovirus-vectored (N = 80,411)	4,649,419	15 (Ģ 03)	0.27 (0.16 to 0.45)
		Modified RNA (N = 912,274)	48,242,495	296 (ខ្).06	0.31 (0.27 to 0.36)
Severe COVID-19				sim	
		Unvaccinated (N = 1,063,785)	132,404,148	1213 ¥0.02	1.00 (referent)
	0	Adenovirus-vectored (N = 62,947)	3,634,743	12 (¢ 03 °	0.33 (0.18 to 0.58)
		Modified RNA (N = 688,250)	37,046,550	168 (ð .05)	0.27 (0.22 to 0.32)

ግ Exposure is time-varying, therefore, some individuals may have contributed time as unvaccinated, and then subsequently, ଛୁ vaccinated. ^bAdjusted for age, sex, rural residence, area income quintile – each at baseline -- as well as prior diabetes mellitus, malignan y, heart failure, cardiac ischemia or arrhythmia, chronic kidney disease or venous thromboembolism.

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Supplementary file 3.	STROBE	E checklist.		
Section/Topic	Item #	Recommendation	Reported on p	
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract 두 주 프	3	
		لله من ح (b) Provide in the abstract an informative and balanced summary of what was done and what wag figund	3	
Introduction		ate		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported 6	4	
Objectives	3	State specific objectives, including any prespecified hypotheses 폭읍 බ	4	
Methods	1	and a serie d		
Study design	4	Present key elements of study design early in the paper	4	
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, and data collection	4	
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	4,5	
		(b) For matched studies, give matching criteria and number of exposed and unexposed	NA	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifier Give diagnostic criteria, if applicable	5	
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5	
Bias	9	Describe any efforts to address potential sources of bias	6	
Study size	10	Explain how the study size was arrived at	NA	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which good by the second second why	5,6	
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	5,6	
		(b) Describe any methods used to examine subgroups and interactions	5,6	
		(c) Explain how missing data were addressed	NA	
		(d) If applicable, explain how loss to follow-up was addressed		
		(e) Describe any sensitivity analyses	NA	

		BMJ Open by copyrig	Page
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, exan ane for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6, eFig 1
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	eFig 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information of the posterial confounders	Table 1
		(b) Indicate number of participants with missing data for each variable of interest	Table 1
		(c) Summarise follow-up time (eg, average and total amount)	6
Outcome data	15*	Report numbers of outcome events or summary measures over time	Figure 1
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precedent of the second	6, Figure 1
		(b) Report category boundaries when continuous variables were categorized	NA
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful americal	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses 3 .	Figure 2
Discussion		ning	
Key results	18	Summarise key results with reference to study objectives	7
Limitations		si v	
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity af analyses, results from similar studies, and other relevant evidence	7,8
Generalisability	21	Discuss the generalisability (external validity) of the study results	8
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	9

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SARS-CoV-2 vaccination, ABO blood group, and risk of COVID-19: population-based cohort study

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Keywords:	HAEMATOLOGY, INFECTIOUS DISEASES, Epidemiology < INFECTIOUS DISEASES, COVID-19, Blood bank & transfusion medicine < HAEMATOLOGY





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BMJ Open

SARS-CoV-2 vaccination, ABO blood group, and risk of COVID-19: population-based cohort study

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Text word count: 1948 Abstract word count: 272

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G Minⁱ **Primary Funding Source:** Funded by a grant from the Ontario Academic Health Sciences Centre AFP Innovation Fund, and the Ontario Ministry of Health and Ministry of Long-Term Care. No grant number is assigned to either.

57 58 59

1	
3	Abstract
4 5	Objective: To compare outcomes between O and non-O blood groups, and by mRNA and Ad-V
6 7	vaccines.
8 9	Design: Population-based cohort study.
10 11	Setting: All of Ontario, Canada. Linked datasets captured clinical encounters, vaccinations and
12 13	laboratory testing for SARS-CoV-2.
14	Participants: Individuals aged 12+ years with known ABO blood group and free of SARS-CoV-2
16	before January 15, 2021.
17 18	Main outcomes measures: The main exposure, first SARS-CoV-2 vaccination, was modeled in a
19 20	time-varying manner. O and non-O blood group was known prior to vaccination. SARS-CoV-2
21 22	infection, and severe COVID-19 (hospitalization or death), were assessed starting 14 days after
23 24	vaccination, up to June 27, 2021.
25	Results: 2,472,261 individuals were included. 1,743,916 (70.5%) had at least one vaccination, of
27	which 24.6% were fully vaccinated. Those vaccinated were more likely to be female, older in
28 29	age, residing in a higher income area, and have higher rates of certain comorbid conditions, like
30 31	cancer, diabetes and hypertension. Relative to unvaccinated, after receiving their first mRNA
32 33	(aHR 0.46, 95% CI 0.44-0.47) or Ad-V (aHR 0.49, 95% CI 0.44-0.54) vaccine, the risk of SARS-CoV-
34 35	2 infection was lower, as was severe COVID-19 (aHR 0.29, 95% CI 0.20-0.43 [mRNA]; 0.29, 95%
36	CI 0.26-0.33 [Ad-V]). Stratifying by blood group produced similar results. For example, after first
38	mRNA vaccination, the aHR of severe COVID-19 was 0.31 (95% CI 0.27-0.36) among non-O, and
39 40	0.27 (95% CI 0.22 to 0.32) among O blood groups, relative to unvaccinated. Fully vaccinated
41 42	individuals had the lowest risk of SARS-CoV-2 and severe COVID-19.
43 44	Conclusions SARS-CoV-2 infection and severe COVID-19 are reduced by vaccination. This effect
45	does not vary by vaccine type or blood group, but is more pronounced among fully, than
47	partially, vaccinated individuals.
48 49	
50 51	Keywords: SARS-CoV-2; COVID-19; vaccination; ABO blood group; effectiveness; cohort study.
52 53	
54 55	
56	

Strengths and limitations of this study

- This study was limited to persons who had ABO blood group testing, and who are more likely to have required blood transfusion or to have been pregnant in the past.
- We did not know who had acquired natural immunity to SARS-CoV-2. •
- The potential for immortal time bias was mitigated by treating vaccine exposure as time varying, and by setting follow-up time to a common starting date.
- The current study was largely completed prior to the emergence of the SARS-CoV-2 Delta/B.1.617 variant.

ser. Idy was large., variant.

Introduction

Emergence of the SARS-CoV-2 pandemic, and COVID-19 related disease, led to rapid development of various vaccines. Efficacy was demonstrated for the modified RNA (mRNA) vaccine of the SARS-CoV-2 spike protein, to induce neutralizing antibodies,[1] as well as a recombinant, replication-incompetent adenovirus vector that encodes a full-length and stabilized SARS-CoV-2 spike protein (adenovirus-vectored [Ad-V]).[2] Demonstrated vaccine efficacy shown from pooled data of randomized clinical trials is 95% (95% CI 94 to 95) and 80% (95% CI 56 to 93), respectively.[3] Even within 14 days of receipt of a first dose, vaccine efficacy can reach 80%.[4, 5]

It is of interest that adults with O blood group appear to be at lower risk of SARS-CoV-2 infection and COVID-19-related severe illness, compared to those with A, B and AB (i.e., non-O) blood groups.[6, 7] Those with O blood group are identified by their anti-A and anti-B antibodies; these same antibodies may offer immunoprotection against SARS-CoV-2, as they are concomitantly produced by certain epithelial cells within the respiratory and digestive tract – prime targets for COVID-19 tissue injury.[7] What is not known, however, is whether vaccinated persons with O blood group experience different rates of SARS-CoV-2 infection and COVID-19 disease than those of non-O blood group. Such information might guide vaccine type, recipient prioritization, and the need for repeat vaccination.

The current study evaluated SARS-CoV-2 infection and COVID-19 disease in a population with a universal vaccination system offered to those aged 12+ years, a high uptake of at least one vaccine.[8] and systematic collection of vaccination and infection data. Herein, we compared outcomes between O and non-O blood groups, and by mRNA and Ad-V vaccines.

Method

This population-based retrospective cohort study was performed in Ontario, Canada. Patientlevel datasets included all hospitalizations, emergency department visits, the majority of laboratory tests for SARS-CoV-2, and all SARS-CoV-2 vaccinations administered within Ontario,[9] as further detailed in Table S1.[6, 10] Datasets were linked using unique encoded identifiers and analyzed at ICES.

Study eligibility required that an individual was aged 12+ years, a resident of Ontario, had undergone ABO testing, and also did not have a SARS-CoV-2 positive swab before January 15, 2021 (Table S1 and Figure S1).

Exposures and outcomes

The main study exposure was a first SARS-CoV-2 vaccination, handled in a time-varying manner, with a lag of 14 days after vaccination to ensure that the person had a chance to develop immunity. December 15, 2020 was the date when high-risk persons were first vaccinated, and January 15, 2021 the time when Canada began mass vaccinating its citizens. [11] So, for example, a person who was vaccinated on January 1, 2021 or earlier was considered exposed on January 15, 2021, whereas a person who was vaccinated on February 1, 2021 was considered exposed on February 15, 2021 and unexposed before that date.

The main study outcome was *SARS-CoV-2 infection*, defined as a positive SARS-CoV-2 PCR test – regardless of indication, symptoms or illness severity – arising during the follow-up period, from January 15, 2021 to June 27, 2021. The second study outcome was a *severe COVID-19*, defined as a positive SARS-CoV-2 PCR test in conjunction with either a hospitalization within +/- 3 days, or a death within -1 to +3 days, of that positive PCR test. A +/- 3-day margin was to allow for PCR testing antecedent to, or following, the hospital admission. The -1 day window permitted the possibility that a PCR specimen was labeled on the day following a COVID-19 death. Both study outcomes were assessed starting at least 14 days after vaccination, among those vaccinated.[12] (Table S1).

Data analyses

For the overall cohort, study outcomes were based on population-at-risk denominators, which included both those who did and did not necessarily undergo SARS-CoV-2 PCR testing after January 15, 2021. Time-to-event analyses generated incidence rates, and Cox proportional hazard models produced unadjusted and adjusted hazard ratios (HR), comparing firstvaccinated to unvaccinated persons (referent). Censoring occurred if a person lost their Ontario Health Insurance Plan coverage, were outcome-free by June 27, 2021 (the end of study period),

or the day after they died (if a death occurred). HR were adjusted for age, sex, rural residence, area income quintile – each at baseline -- as well as prior diabetes mellitus, malignancy, heart failure, cardiac ischemia or arrhythmia, chronic kidney disease or venous thromboembolism (Table S1). Additional analysis 1 restricted the at-risk denominator those individuals who underwent SARS-CoV-2 PCR testing at least 14 days after their first vaccination.

The main cohort model was repeated, with each study outcome assessed by more specifically comparing first mRNA vaccination or first Ad-V vaccination to unvaccinated persons (referent).

Next, and central to the study, we examined the risk of each study outcome in relation to first-vaccination status, further stratified by O and non-O blood groups. This was done among the entire cohort, as well as restricted to those who underwent SARS-CoV-2 PCR testing at least 14 days after their first vaccination.

Consideration was given to receipt of a second vaccination as a time-dependent variable. Hence, "fully vaccinated" and "partially vaccinated" persons were each compared to unvaccinated individuals, stratified by O and non-O groups – with these analyses conducted among the whole cohort, as well as limited to just those who had SARS-CoV-2 testing in the observation period.

Analyses were planned *a priori*. Statistical analyses were performed using SAS version 9.4 for UNIX (SAS Institute Inc., Cary, NC).

Patient and public involvement

No patient was consulted or involved in this study.

Did we involve patients/service users/carers/lay people in the design of this study? No.

Was the development of outcome measures informed by patients' priorities, experience, and preferences? No.

Were patients/carers/lay people involved in the recruitment to and conduct of the study? No. How will the results be disseminated to study participants? Not applicable.

Are patients/carers/lay people thanked in the contributorship statement/acknowledgements? Not applicable.

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Was the development of the research question and outcome measures informed by patients' priorities, experience, and preferences? No.

Results

Among 2,938,215 individuals, 2,472,261 met the inclusion criteria (Figure S1). Of these, 1,743,916 (70.5%) had at least one vaccination (Table 1). Those vaccinated were more likely to be female, older in age, residing in a higher income area, and have higher rates of certain comorbid conditions, like cancer, diabetes and hypertension (Table 1). Of those vaccinated, 1,600,524 (91.8%) first received an mRNA vaccine, and 143,358 (8.2%) an Ad-V vaccine. A second vaccine was administered to 24.6% of individuals by June 13, 2021 (i.e., by 2 weeks before the end of the study observation period), comprising the mRNA vaccine among 415,632 (23.8%), and the Ad-V among 12,855 (0.7%) (Table 1).

After a median follow-up of 163 days (IQR 163 to 163), the rate of SARS-CoV-2 positivity was 0.54 per 10,000 person-days among first-vaccinated persons, and 1.69 per 10,000 person-days among non-vaccinated persons -- an unadjusted HR of 0.38 (95% CI 0.37 to 0.39) and an adjusted HR of 0.46 (95% CI 0.45 to 0.48). The corresponding HR were equally protective for those receiving a first mRNA vaccine (adjusted HR 0.46, 95% CI 0.44 to 0.47) or first Ad-V vaccine (adjusted HR 0.49, 95% CI 0.44 to 0.54), each relative to being unvaccinated (Table 2). The adjusted HR for severe COVID-19 was 0.29 (95% CI 0.26 to 0.33) comparing vaccinated to unvaccinated persons, with similar estimates by vaccine type (Table 2).

There were 439,058 (25.2%) vaccinated people who had SARS-CoV-2 PCR testing during followup period, from January 15, 2021 onward, compared to 175,397 (24.1%) unvaccinated individuals – a small standardized difference of 0.03. Restricting the at-risk denominator to 614,455 individuals, and comparing the vaccinated to the unvaccinated, the adjusted HR were 0.28 (95% CI 0.27 to 0.29) for SARS-CoV-2 positivity, and 0.22 (95% CI 0.20 to 0.25) for severe COVID-19, albeit, at much higher event rates than seen in the entire cohort (Additional analysis 1, Table S2)

Among the entire cohort, the protective effect associated with a first mRNA or Ad-V vaccine against SARS-CoV-2 infection or severe COVID-19 was equally seen among those with O and non-O blood groups (Figure 1, upper). This pattern was also seen by vaccine type (Table S3),

and among the 614,455 individuals who had SARS-CoV-2 PCR testing (Figure 1, lower). In the entire cohort, relative to the unvaccinated, fully vaccinated individuals had the lowest risk of SARS-CoV-2 infection, followed by partially vaccinated persons (Figure 2, upper). For example, among those with blood group O, the corresponding adjusted HR were 0.39 (95% CI 0.34 to 0.43) and 0.48 (95% CI 0.45 to 0.50). Moreover, the HRs did not differ by blood group. The same was evident for severe COVID-19 (Figure 2, upper). Restricting to the sub-cohort who had SARS-CoV-2 testing, the protective effect conferred by full and partial vaccination was similar by blood groups (Figure 2, lower)

Discussion

Main findings

This population-based cohort study observed a lower risk of SARS-CoV-2 infection, as well as severe COVID-19 hospitalization or death, in association with SARS-CoV-2 vaccination. This conferred protective effect did not vary by vaccine type or blood group, but was more pronounced among fully, than partially, vaccinated individuals.

Comparison with other studies

A 2021 meta-analysis of 54,218 persons showed a lower risk of SARS-CoV-2 infection comparing O vs. non-O blood group (odds ratio 0.71, 95% CI 0.60 to 0.84).[13] In a cohort study of 225,556 adults and children in Ontario, before SARS-CoV-2 vaccination, we previously observed a lower relative risk of SARS-CoV-2 infection (0.88, 95% CI 0.84 to 0.92) and severe COVID-19 illness or death (0.87, 0.78 to 0.97) among those with O vs. non-O blood group.[6] The current study is the first to explore effect modification of O blood group on vaccine effectiveness against SARS-CoV-2 infection or related illness. Just as we found no effect modification, prior research on the smallpox vaccine suggested no differences in "vaccine success" by ABO blood group,[14] nor for influenza A,[15] rabies [16] and cholera [17] vaccines. Thus, if O blood group is somehow protective against SARS-CoV-2 infection or illness, it is unlikely to generate any additive benefit to that conferred by available mRNA and Ad-V vaccines.

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The current study observed a relative risk reduction against severe COVID-19 of between 82-85% after full vaccination, and between 67-70% following partial vaccination (Figure 2). In Chile, among those aged 60+ years and fully vaccinated, vaccine effectiveness was 67% against infection, 85% for the prevention of hospitalization, and 87% for the prevention of Covid-19related death, with corresponding estimates of 16%, 37% and 46% after partial vaccination.[18] Our findings about vaccine effectiveness are similar to those of randomized clinical trials of SARS-CoV-2 vaccination,[1-4] or another observational study from Ontario.[10] Taken together, SARS-CoV-2 vaccination by mRNA or Ad-V is effective at preventing serious disease.

Limitations

This study was limited to persons who had ABO blood group testing, and who are more likely to have required blood transfusion or to have been pregnant in the past.[6] As a study strength, identification of blood group status preceded SARS-CoV-2 vaccination or index PCR testing. While we excluded those with SARS-CoV-2 infection prior January 15, 2021, we did not know who had acquired natural immunity. While vaccination and study outcomes were fully ascertained within a universal healthcare system, a minority of individuals may have been vaccinated outside of Ontario, and not identified herein. The potential for immortal time bias – the influence of misclassified follow-up time for individuals who were vaccinated, which could differentially favour their survival – was mitigated by treating vaccine exposure as time varying, and by setting follow-up time to a common starting date of January 15, 2021.[19] All study covariates, including demographic and clinical variables, were captured prior to time zero. A protective effect of vaccination was seen in the additional analyses restricted to those who underwent PCR testing. This was akin to using a test-negative design, in which common access to, and uptake of, medical care can reduces unmeasured confounding related to healthcareseeking behaviours.[20] While the current study was largely completed prior to the emergence of the SARS-CoV-2 Delta/B.1.617 variant, it is unlikely that ABO blood group would be expected to modify vaccine effectiveness within the subsequent period. Last, adverse events following immunization were not studied herein, nor the tendency for such adverse events related to ABO blood group.

Conclusions

The protective benefit offered by mRNA or Ad-V SARS-CoV-2 vaccination – especially full vaccination — is not further modulated by ABO blood group status. Large-scale population or targeted vaccination programs should continue, with ongoing research about how to mitigate emerging viral variants.

Contributions to authorship

JGR, AP: Study concept, analysis and interpretation of the data, drafting of manuscript, manuscript revision, approval of final version.

Data sharing statement

No additional data available.

Ethics approval

The use of data in this project was authorized under section 45 of Ontario's Personal Health Information Protection Act, which does not require review by a Research Ethics Board.

Funding

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No grant number is assigned to either funding source.

Competing interests

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None.

Figure legends

Figure 1. SARS-CoV-2 vaccination and associated risk of SARS-CoV-2 infection, or severe COVID-19 (hospitalization or death), stratified by O and non-O blood groups. Data are presented for the entire cohort (upper panel), and 614,455 individuals who had SARS-CoV-2 PCR testing during the follow-up period (lower panel). Analyses are by time-varying exposure after first vaccination. Unadjusted hazard ratios are in red, and adjusted hazard ratios in blue, adjusted for age, sex, rural residence, area income quintile – each at baseline -- as well as prior diabetes mellitus, malignancy, heart failure, cardiac ischemia or arrhythmia, chronic kidney disease or venous thromboembolism.

Figure 2. Full or partial SARS-CoV-2 vaccination and associated risk of SARS-CoV-2 infection, or severe COVID-19 (hospitalization or death), stratified by O and non-O blood groups. Data are presented for the entire cohort (upper panel), and 614,455 individuals who had SARS-CoV-2 PCR testing during the follow-up period (lower panel). Analyses are by time-varying exposure after first vaccination. Unadjusted hazard ratios are in red, and adjusted hazard ratios in blue, adjusted for age, sex, rural residence, area income quintile – each at baseline -- as well as prior diabetes mellitus, malignancy, heart failure, cardiac ischemia or arrhythmia, chronic kidney disease or venous thromboembolism.

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Table 1. Characteristics of 2,472,261 individuals in Ontario, Canada aged 12 years and older, with known ABOblood group, and without evidence of SARS-CoV-2 infection before January 15, 2021. All data are presented as anumber (%) unless otherwise indicated.

Characteristic		Any SARS-Cov-2 vaccination (N = 1.743.916)	No SARS-COV-2 vaccination (N = 728.345)	Standardize difference
On January 15, 2021 (time zero)			(
Mean (SD) age, y		50.8 (18.4)	40.6 (15.4)	0.60
12-17		13,009 (0.7)	11,509 (1.6)	0.08
18-39		589,158 (33.8)	415,983 (57.1)	0.48
40-59		568,693 (32.6)	208,310 (28.6)	0.09
60-69		218,653 (12.5)	42,386 (5.8)	0.23
70-79		209,118 (12.0)	29,116 (4.0)	0.30
80+		145,285 (8.3)	21,041 (2.9)	0.24
Female		1,200,499 (68.8)	548,647 (75.3)	0.15
Area income quintile (Q) ^a	Q1 (lowest)	298,360 (17.1)	182,483 (25.1)	0.20
	Q2	332,128 (19.0)	153,526 (21.1)	0.05
	Q3	360,666 (20.7)	147,174 (20.2)	0.01
	Q4	375,199 (21.5)	134,421 (18.5)	0.08
	Q5 (highest)	373,655 (21.4)	108,469 (14.9)	0.17
Rural residence ^b	Rural	164,607 (9.4)	76,733 (10.5)	0.04
Pregnant		23,137 (1.3)	19,410 (2.7)	0.10
O blood group	6	315,903 (43.4)	751,212 (43.1)	0.01
Pre-existing conditions			· · · ·	
Diabetes mellitus		292,661 (16.8)	70,062 (9.6)	0.21
Malignancy		405,034 (23.2)	104,741 (14.4)	0.23
Heart failure		89,604 (5.1)	18,085 (2.5)	0.14
Cardiac ischemia or arrhythmia		144,692 (8.3)	27,106 (3.7)	0.19
Chronic kidney disease		90,732 (5.2)	19,760 (2.7)	0.13
Venous thromboembolism		41,006 (2.4)	13,342 (1.8)	0.04
Stroke or transient ischemic attack		31,638 (1.8)	6,763 (0.9)	0.08
Chronic hypertension		571,167 (32.8)	116,201 (16.0)	0.40
Asthma		300,546 (17.2)	126,172 (17.3)	0.00
Dementia, or frailty		264,694 (15.2)	107,972 (14.8)	0.01
Anemia		265,861 (15.2)	96,060 (13.2)	0.06
Chronic obstructive pulmonary disease		89,413 (5.1)	20,352 (2.8)	0.12
HIV or organ transplant		9,754 (0.6)	2,770 (0.4)	0.03
At time of first vaccination				
Vaccine type	Modified RNA	1,600,524 (91.8)		
	Adenovirus-vectored	143,358 (8.2)		
	Unspecified	34 (0.0)		
Vaccine name	Astrazeneca	117,100 (6.7)		
	Covishield	26,086 (1.5)		
	Janssen	172 (0.0)		
	Moderna	315,370 (18.1)		
	Pfizer	1,285,154 (73.7)		
	Unspecified	34 (0.0)		

Characteristic		Any SARS-Cov-2 vaccination (N = 1,743,916)	No SARS-COV-2 vaccination (N = 728,345)	Standardized difference
At time of second vaccination				
Vaccine type	Modified RNA	415,632 (23.8)		
	Adenovirus-vectored	12,855 (0.7)		
	Unspecified	16 (0.0)		
	No second dose	1,315,413 (75.4)		
Vaccine name	Astrazeneca	12,692 (0.7)		
	Covishield	157 (0.0)		
	Janssen	6 (0.0)		
	Moderna	86,791 (5.0)		
	Pfizer	328,841 (18.9)		
	Unspecified	16 (0.0)		
	No second dose	1,315,413 (75.4)		
Received two vaccine doses by		428,503 (24.6)		
of follow-up)				
Vaccine dose 2 same as dose 1	Same	121 517 (21 3)		
	Different	3 969 (0 2)		
	Unknown	17 (0 0)		
	No second dose	1 315 <i>J</i> 13 (75 <i>J</i>)		
Median (IQR) follow-up for assessing the primary study outcome, d	10	163.0 (163.0-163.0)	163.0 (163.0-163.0)	0.39
Median (IQR) follow-up for assessing the secondary study outcome, d	2	163.0 (163.0-163.0)	163.0 (163.0-163.0)	0.16
Had SARS-CoV-2 PCR testing during follow-up period, from January 15, 2021 onward		439,058 (25.2)	175,397 (24.1)	0.03
Missing for 6180 (0.25%) of all person Missing for 5247 (0.21%) of all person Before January 15, 2021	ns ns			

7 of 35 Table 2. SARS-CoV-2 vaccination and associated risk of SARS-CoV-2 infection, or severe COVID-19 (hospitalization or death) – eacling assessed starting at least 14 days after the first vaccination, among the entire cohort. Data are presented by time-varying exposure after first vaccination vs. unvaccination vs. unvaccination, as well as by first includi)59944 vaccination type vs. unvaccinated (lower maroon).

			No. with outcome (rate	Unadjusted	Adjusted
		No. person-days of	per 10,000 person-	hazardratio	hazard ratio
Study outcome	Exposure state ^a	follow-up ^a	days)	(9 5 % آي (90)	(95% CI%) ^ь
CARC Cold 2 infection	Unvaccinated (N = 2,464,998)	303,209,192	51,187 (1.69)	1.00 kg kg rent)	1.00 (referent)
SARS-COV-2 INJECTION	Vaccinated (N = 1,743,916)	93,324,805	4995 (0.54)	0.38 (9 , 3 7 0 0.39)	0.46 (0.45 to 0.48)
	Up			ont S	
	Unvaccinated (N = 2,464,998)	307,438,194	2890 (0.09)	1.00 () () () () () () () () () (1.00 (referent)
Severe COVID-19	Vaccinated (N = 1,743,916)	93,575,031	491 (0.05)	0.71 (0 .044 0 0.79)	0.29 (0.26 to 0.33)
				ata ata	
				mini MES	
	Unvaccinated (N = 2,464,998)	303,209,192	51,187 (1.69)	1.0@(reprent)	1.00 (referent)
SARS-CoV-2 infection	Adenovirus-vectored (N = 143,358)	8,263,735	434 (0.53)	0.39 (6 .36 5 o 0.43)	0.49 (0.44 to 0.54)
	Modified RNA (N = 1,600,524)	85,059,246	4561 (0.54)	0.38 (9 .37 9 o 0.39)	0.46 (0.44 to 0.47)
				ng,	
	Unvaccinated (N = 2,464,998)	307,438,194	2890 (0.09)	1.00 (regerent)	1.00 (referent)
Severe COVID-19 ^c	Adenovirus-vectored (N = 143,358)	8,284,162	27 (0.03)	0.46 (🛱:31 do 0.68)	0.29 (0.20 to 0.43)
	Modified RNA (N = 1,600,524)	85,289,045	464 (0.05)	∕0.73 (0 .66 ± 0 0.82)	0.29 (0.26 to 0.33)

^aExposure is time-varying, therefore, some individuals may have contributed time as unvaccinated, and then subsequen $\mathbf{\overline{d}}$ y, $\mathbf{\overline{a}}$ s vaccinated. ^bAdjusted for age, sex, rural residence, area income quintile – each at baseline -- as well as prior diabetes mellitus, maligandy, heart failure, cardiac ischemia or arrhythmia, chronic kidney disease or venous thromboembolism.

^cIn the vaccinated and unvaccinated groups, respectively, there were 21 deaths (0.02 per 100,000 person-days) and 133 de the second persondays), from 1 day before, up to 3 days after, a SARS-CoV-2 positive PCR test, with a corresponding adjusted hazard ratio of 024 (95% CI 0.14 to 0.41).

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review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml Hazard ratio (95% confidence interval)

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Table S1. Variables used to define cohort entry and exclusion criteria, as well as study exposures, outcomes, adjustment, and stratification.

Assessment	Timing	Disease, procedure or condition	CIHI-DAD, SDS or NACRS ICD-10-CA diagnosis or CCI procedure codes	OHIP ICD-9 diagnosis or fee codes; or other data source	Validation studies or documentation for some codes
criteria	date January 2007 to December 2020	blood group test result in Ontario, Canada		in the Ontario Laboratory Information System (OLIS) - includes most outpatient laboratory information in Ontario	
Exclusion criteria	SARS-CoV-2 specimen date January 15, 2020 to January 14, 2021	Individuals with a SARS-CoV- 2 RNA PCR positive laboratory result in Ontario, Canada prior to time zero	 Telieu	OLISC19 - includes Test Request (TR)/LOINC codes for SARS-CoV-2 and other respiratory virus testing: TR12936-1, TR12937-9, 94315-9, 94314-2, 94316-7, XON13512-9, XON13529-3, XON13528-5, XON13531-9, XON13527-7. These codes, plus keywords such as "COVID", "SARS-CoV-2", "Novel coronavirus" or "nCOV" or microorganism SNOMED codes (840533007 [SARS-CoV-2], 168209000 [No Virus Identified]), were used to define the data pull from OLIS.	For the ICES methodology and Python script for cleaning and parsing OLIS lab results for SARS- CoV-2 and other respiratory viruses, see <u>https://github.co</u> <u>m/icescentral/C</u> <u>OVID19-Lab- Results</u>
	January 15, 2021 (time zero)	Implausible or missing sex, birth date or death date		Registered Persons Database (<u>RPDB</u>) - contains demographic information and encrypted healthcare numbers for all individuals eligible for OHIP	
	Same as above	Non-Ontario resident or not eligible for OHIP at time zero		RPDB	
	Same as above	Aged less < 12 years at time zero		RPDB	

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	condition	ICD-10-CA diagnosis or CCI procedure codes	or other data source	studies or documentatio for some code
Same as above	Death occurred before baseline, before the vaccination date, or > 1 day before the SARS-CoV-2 specimen date	Discharge disposition is not alive (<u>DAD</u> , <u>NACRS</u>)	RPDB, COVAXON, OLISC19	
December 15, 2020 to June 13, 2021	Duplicate vaccination record		COVAXON	
December 15, 2020 to June 13, 2021	COVID-19 partially vaccinated status		COVAXON	
Same as above	COVID-19 1 st dose type (mRNA, viral vector, unknown, none)		COVAXON	
Same as above	COVID-19 fully-vaccinated status (fully-vaccinated, partially-vaccinated, unvaccinated)		COVAXON	
January 2007 to December 2020	ABO blood group (O, other)	- 0	LOINC codes 882-1, 883-9, 10331-7 in OLIS	
SARS-CoV-2 specimen date January 15, 2021 (time zero) to June 27, 2021, censored at loss OHIP eligibility or the day	Earliest SARS-CoV-2 positive test.		OLISC19	
	Same as above December 15, 2020 to June 13, 2021 December 15, 2020 to June 13, 2021 Same as above Same as above January 2007 to December 2020 SARS-CoV-2 specimen date January 15, 2021 (time zero) to June 27, 2021, censored at loss OHIP eligibility or the day after death.	Same as aboveDeath occurred before baseline, before the vaccination date, or > 1 day before the SARS-CoV-2 specimen dateDecember 15, 2020 to June 13, 2021Duplicate vaccination record vaccinated statusDecember 15, 2020 to June 13, 2021COVID-19 partially vaccinated statusSame as aboveCOVID-19 1st dose type (mRNA, viral vector, unknown, none)Same as aboveCOVID-19 fully-vaccinated status (fully-vaccinated, partially-vaccinated, unvaccinated)January 2007 to December 2020ABO blood group (O, other) east.SARS-CoV-2 specimen date January 15, 2021 (time zero) to June 27, 2021, censored at loss OHIP eligibility or the day after death.Earliest SARS-CoV-2 partially vaccinated status (fully vaccinated status (fully vaccinated, unvaccinated)	Same as aboveDeath occurred before baseline, before the vaccination date, or > 1 day before the SARS-CoV-2 specimen dateDischarge disposition is not alive (DAD, NACRS)December 15, 2020 to June 13, 2021Duplicate vaccination record vaccinated statusDecember 15, 2020 to June 13, 2021COVID-19 partially vaccinated statusSame as aboveCOVID-19 partially vaccinated statusSame as aboveCOVID-19 1st dose type (mRNA, viral vector, unknown, none)Same as aboveCOVID-19 fully-vaccinated, partially-vaccinated, unvaccinated)January 2007 to December 2020ABO blood group (O, other) testSARS-CoV-2 specimen date January 15, 2021 (time zero) to June 27, 2021, censored at loss OHIP eligibility or the day after death	Same as aboveDeath occurred before baseline, before the vaccination date, or > 1 day before the SARS-COV-2 specimen dateDischarge disposition is not alive (DAD, NACRS)RPDB, COVAXON, OLISC19December 15, 2020 to June 13, 2021Duplicate vaccination record vaccinated statusCOVAXONDecember 15, 2020 to June 13, 2021COVID-19 partially vaccinated statusCOVAXONSame as aboveCOVID-19 partially vaccinated statusCOVAXONSame as aboveCOVID-19 14th dose type (mRNA, viral vector, unknown, none)COVAXONSame as aboveCOVID-19 fully-vaccinated, partially-vaccinated, unvaccinated, unvaccinated, unvaccinated, unvaccinated, unvaccinated, unvaccinated, unvaccinated, unvaccinated, unvaccinated, unvaccinated, unvaccinated, unvaccinated, unvaccinated, unvaccinated, unvaccinated, unvaccinated, unvaccinated, unvaccinated, unvaccinated, unvaccinated, unvaccinated, unvaccinated, unvaccinated, unvaccinated, unvaccinated, unvaccinated, unvaccinated, unvaccinated, unvaccinated, unvaccinated, unvaccinated, unvaccinated, unvaccinated, unvaccinated, unvaccinated, unvaccinated, unvaccinated, unvaccinated, unvaccinated, unvaccinated, unvaccinated, unvaccinated, unvaccinated, unvaccinated, unvaccinated, unvaccinated, unvaccinated, unvaccinated, unvaccinated, unvaccinated, unvaccinated, unvaccinated, unvaccinated, unvaccinated, unvaccinated, unvaccinated, unvaccinated, unvaccinated, unvaccinated, unvaccinated, unvaccinated, unvaccinated, unvaccinated, unvaccinated, unvaccinated, unvaccinated

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Assessment	Timing	Disease, procedure or condition	CIHI-DAD, SDS or NACRS ICD-10-CA diagnosis or CCI procedure codes	OHIP ICD-9 diagnosis or fee codes; or other data source	Validation studies or documentation for some codes
Secondary study outcome	SARS-CoV-2 specimen date January 15, 2021 (time zero) to June 30, 2021, censored at loss OHIP eligibility or the day after death.	Earliest SARS-CoV-2 positive test <u>AND</u> a hospital admission within -/+ 3 days or death within -1 to +3 days of the SARS-CoV-2 specimen date.	DAD (hospital admission, not alive at discharge), NACRS (hospital admission, not alive at discharge), SDS (not alive at discharge)	OLISC19 (SARS-CoV-2 test), RPDB (death)	
Covariates	January 15, 2021 (time zero)	Age	-	RPDB	
	Same as above	Sex	01	RPDB	
	Same as above	Area income quintile		Statistics Canada Census	
	Same as above	Rural residence	- 0.	Statistics Canada Census	
	Any time before January 15, 2021 (time zero)	Diabetes mellitus	The ICES-derived ODD database was used to identify patients with diagnosed diabetes before the index date, based on 2 OHIP diagnostic codes or 1 OHIP fee code or 1 DAD/SDS diagnostic code, within 2 years. ICD-10-CA: E10, E11, E13,	OHIP ICD-9: 250 OHIP fee codes: Q040, K029, K030, K045, K046	https://pubmed. ncbi.nlm.nih.gov /11874939/

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S	Same as above	History of heart failure	The ICES-derived CHF	OHIP ICD-9: 428	https://pubr
		For pee	database was used to identify patients with CHF, based on 1 ED, hospitalization or outpatient claim, and a second claim in 1 year. The CHF database is limited to those 40 years of age or older. ICD-10-CA (DAD, SDS): 1500, 1501, 1509		ncbi.nlm.nih /23735455/
W b 2	Within 5 years before January 15, 2021 (time zero)	History of malignant neoplasm	ICD-10-CA (DAD, SDS, NACRS): C00-C97		
Si	Same as above	Chronic kidney disease (CKD)	CKD diagnosis ICD-10-CA (DAD, NACRS): E102, E112, E132, E142, I12, I13, N08, N18, N19	CKD diagnosis ICD-9 (OHIP): 403, 585	https://pubr ncbi.nlm.nih /23560464/

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Assessment	Timing	Disease, procedure or condition	CIHI-DAD, SDS or NACRS ICD-10-CA diagnosis or CCI procedure codes	OHIP ICD-9 diagnosis or fee codes; or other data source	Validation studies or documentation for some codes
			Chronic dialysis	Chronic dialysis	https://pubmed.
			At least 2 of the following	At least 2 of the following OHIP fee	ncbi.nlm.nih.gov
			CCI (DAD, SDS) codes	codes separated by 90 days, but <	<u>/20613656/</u>
			separated by 90 days, but	150 days, in the year before the	
			< 150 days, in the year	index date: R849, G082, G083, G085,	
			before the index date:	G090-G096, G294, G295, G323,	
			1PZ21	G325, G326, G330-G333, G860-	
				G866, H540, H740	
		, pee	rro,	Treatment codes (CORR): 060, 111, 112, 113, 121, 122, 123, 131, 132, 133, 141, 151, 152, 211, 221, 231, 241, 242, 251, 252, 311, 312, 313, 321, 322, 323, 331, 332, 333, 413, 423, 433, 443, 453	
			Exclude kidney transplant	Exclude kidney transplant	https://pubmed.
			CCI (DAD): 1PC85	OHIP fee codes: S435, S434	ncbi.nlm.nih.gov
					/26019887/
				CORR treatment code: 171 plus ≥ 1	
				Transplanted Organ Code [1-3]: 10,	
				11, 12, 18, 19	

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Assessment	It Timing Disease, procedure or CIHI-DAD, SDS or NACRS OHI condition ICD-10-CA diagnosis or CCI procedure codes		OHIP ICD-9 diagnosis or fee codes; or other data source	Validation studies or documentation for some codes	
	Same as above	History of cardiac ischemia	At least 1 hospitalization		https://pubmed.
			(DAD) or ED (NACRS) visit		ncbi.nlm.nih.gov
			with a diagnosis or		/20847972/
			procedure coded with 1 of		
			the following codes:		
			Angina:		
			ICD-10-CA: I20, I2382, I24		
		6			
			Chronic Ischemic Heart		
			Disease:		
			ICD-10-CA: I25		
			Myocardial infarction:		
			ICD-10-CA: I21, I22		
			· · ·		
			Coronary Artery Bypass		
			Grafting:		
			CCI: 1IJ76, 1IJ80		
			Percutaneous Coronary		
			Intervention:		
			CCI: 1IJ26, 1IJ50, 1IJ55,		
			1IJ57		

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Assessment	Timing	Disease, procedure or condition	CIHI-DAD, SDS or NACRS ICD-10-CA diagnosis or CCI procedure codes	OHIP ICD-9 diagnosis or fee codes; or other data source	Validation studies or documentation
	Samo as abovo	History of cardiac arrhythmia	At least 1 bespitalization		https://pubmod
	Same as above		(DAD) or ED (NACPS) visit	-	nchi nlm nih gov
			(DAD) OF ED (NACKS) VISIC		/10/22609/
			with a diagnosis of		/19455090/
			the fellowing coded with 1 of		
			the following codes:		nttps://www.ice
					.on.ca/Publicatio
			Atrial Fibriliation/Atrial		ns/Atlases-and-
			Flutter:		Reports/2006/Ca
			ICD-10-CA: 148		nadian-Institute-
					tor-Health-
			Ventricular Arrhythmia &		Information
			Tachycardia:		
			ICD-10-CA: I470, I472,		https://pubmed.
			1490, 1493		ncbi.nlm.nih.gov
					/17599603/
			Permanent Pacemaker:		
			CCI: 1HZ53GRNM,		
			1HZ53LANM, 1HZ53GRNK,		
			1HZ53LANK, 1HZ53GRNL,		
			1HZ53LANL		
				U _b	
			Implantable Cardioverter-		
			Defibrillator:		
			CCI: 1HZ53GRFS,		
			1HZ53LAFS, 1HZ53SYFS.		
			1HZ53HAFS		

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Assessment	Timing	Disease, procedure or condition	CIHI-DAD, SDS or NACRS ICD-10-CA diagnosis or CCI procedure codes	OHIP ICD-9 diagnosis or fee codes; or other data source	Validation studies or documentatior for some codes
	Same as above	History of pulmonary	ICD-10-CA (DAD, SDS,	OHIP ICD-9: 677, 415, 671, 451, 452	
		embolism, deep vein	NACRS): 1260, 1269,		
		thrombosis, or other venous	088201, 088202, 088203,	AND	
		thromboembolism	088204, 088209, 1636,		
			1822, 1828, 1829, 1801,	one of the following OHIP	
			1802, 1803, 1808, 1809,	radiological professional fee codes	
			022301, 022303, 022309,	for a VTE diagnostic test billed within	
		U L	022501, 022503, 022509,	3 days: J198, J498, J193, J493, J202,	
			087102, 087104, 087109,	J502, J206, J506, J182, J482, X406,	
			087304, 087309, 1676,	X407, X125, X188, X401, X405, X408,	
			181, 1820, 1823, 0228,	X126, X410, X231, X232, X233, X127,	
			0229, 0878, 0879	X413, X421, X425, J659, J660, J859,	
				J860	
			AND		
			one of the following CCI		
			codes for diagnostic		
			imaging during the same		
			admission: 3KX30DA,		
			3KX30DB, 3KX30DC,		
			3KX30DD, 3KR10VC.		
			3KR10VN, 3KR12VA.		
			3KX10VA. 3KX10VC.		
			3KX10VN. 3KX10VX.		
			3KX12VA, 3IM10VC.		
			3IM10VX. 3IM10VY.		
			3IM12VA. 3GT70CA.		
			3GT70CC. 3GT70CE.		
			3GT70KC. 3GT70KD.		
			3GT70KF, 3JY10VA.		
			3JY10VC. 3JY10VN		
			3JY10VX, 3JY12VA		
			31Y20WC		
	L	1	33.20110	1	I

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Assessment	Timing	Disease, procedure or condition	CIHI-DAD, SDS or NACRS ICD-10-CA diagnosis or CCI procedure codes	OHIP ICD-9 diagnosis or fee codes; or other data source	Validation studies or documentati for some cod
Other baseline variables	Any time before January 15, 2021 (time zero)	Asthma	The ICES-derived <u>ASTHMA</u> database was used to identify patients with diagnosed asthma before the index date, based on 2 OHIP diagnostic codes or 1 DAD diagnostic code.	OHIP ICD-9: 493	https://pubn ncbi.nlm.nih /20011725/
	Same as above	Chronic obstructive pulmonary disease (COPD)	The ICES-derived <u>COPD</u> database was used to identify patients with diagnosed COPD before the index date, based on 1 OHIP diagnostic code or 1 DAD diagnostic code.	OHIP ICD-9: 491, 492, 496	https://pubr ncbi.nlm.nih /19863368/ COPD algorit was validate those aged ≥ years.
	Same as above	Chronic hypertension	The ICES-derived HYPER database was used to identify patients with: a) 1 hospital admission with a hypertension diagnosis, or b) an OHIP claim with a hypertension diagnosis followed within 2 years by either an OHIP claim or a hospital admission with a hypertension diagnosis. ICD-10-CA (DAD, SDS): I10- 113, 115	OHIP ICD-9: 401-405	https://pubr ncbi.nlm.nih /20101286/

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Assessment	Timing	Disease, procedure or condition	CIHI-DAD, SDS or NACRS ICD-10-CA diagnosis or CCI procedure codes	OHIP ICD-9 diagnosis or fee codes; or other data source	Validation studies or documenta for some co
	Same as above	Immunocompromised (HIV		The ICES-derived <u>HIV</u> database was	https://pub
		or organ transplant)		avisting LIV based on 2 physician	/2172979C
				claims in 3 years.	/21/38/86/
		A.		OHIP ICD-9: 042-044	
				CORRLINK links CORR and DAD data	
				and includes patients who received	
				an organ transplant, and does not	
				include dialysis patients.	
	Same as above	Dementia	The ICES-derived	OHIP ICD-9: 290, 331	https://pub
			DEMENTIA database was		<u>ncbi.nlm.ni</u> ł
			used to identify individuals	ODB	/27567819/
			with 1 hospitalization for	1 prescription for a cholinesterase	
			dementia and/or 3	inhibitor	
			outpatient visits for		
			dementia, each separated		
			by 30 days, within 2 years,		
			or 1 prescription from		
			ODB.		
			ICD-10-CA (DAD, SDS):		
			F00-F03, G30		

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Assessment	Timing	Disease, procedure or condition	CIHI-DAD, SDS or NACRS ICD-10-CA diagnosis or CCI procedure codes	OHIP ICD-9 diagnosis or fee codes; or other data source	Validation studies or documentation for some codes
	Within 1 year before January 15, 2021 (time zero)	Frailty	 Identified based on the following rules, using DAD and OHIP databases: 1. Long-term care residence (i.e., admitted from/discharged to, a nursing home after hospital stay, or location of physician billing claim was long- term care facility); 2. Receipt of palliative care; 3. Two or more domains derived from frailty scales (i.e., cognitive impairment, falls, general health status, 		https://pubmed. ncbi.nlm.nih.gov /28974280/
	Within Eugars	Anomia	incontinence, nutrition issues, functional performance) and health services utilization (i.e., ≥ 2 hospital stays or ED visits, geriatrician or home care visit).		
	Within 5 years before January 15, 2021 (time zero)	Anemia	ICD-10-CA (DAD, SDS, NACRS): D50-D53, D55, D56, D572-D574, D58- D61, D63, P55, P560, P570	ОНІР ІСД-9: 280-285, 773	

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Assessment	Timing	Disease, procedure or condition	CIHI-DAD, SDS or NACRS ICD-10-CA diagnosis or	OHIP ICD-9 diagnosis or fee codes; or other data source	Validation studies or
			CCI procedure codes		documentation
	Same as above	History of transient ischemic	Transient Ischemic Attack		http://canadia
	Sume as above	attack or acute ischemic	At least 1 hospitalization		trokenetwork
		stroke	or ED visit with 1 of the		en/wp-
			following diagnosis codes:		content/uploa
			0 0		/2014/08/Stro
			ICD-10-CA (DAD, NACRS):		_Core_ENG.pd
			G450-G453, G458, G459,		
		U k	H340		
		6			
			Acute Ischemic Stroke:		
			1 hospitalization with a		
			main diagnosis coded with		
			one of the following		
			codes:		
			ICD-10-CA (DAD): 163		
			(except I636), I64, H341		

ASTHMA: Ontario Asthma dataset; CCI: Canadian Classification of Interventions; CHF: Ontario Congestive Heart Failure dataset; CIHI: Canadian Institute for Health Information; CORR: Canadian Organ Replacement Registry; COVAXON: Ontario COVID-19 Vaccine Data; DAD: Discharge Abstract Database; DEMENTIA: Ontario Dementia dataset; ED: Emergency Department; HIV: Ontario HIV dataset; HYPER: Ontario Hypertension dataset; ICD-9: International Classification of Diseases, 9th Revision; ICD-10-CA: International Classification of Diseases, 10th Revision, Canada; ICU: Intensive Care Unit; LHIN: Local Health Integration Network; LOINC: Logical Observation Identifiers Names and Codes; NACRS: National Ambulatory Care Reporting System; ODB: Ontario Drug Benefit; ODD: Ontario Diabetes Dataset; OHIP: Ontario Health Insurance Plan; OLIS: Ontario Laboratories Information System; OLISC19: Ontario Laboratories Information System COVID-19 Laboratory Data; RPDB: Registered Persons Database; SDS: Same Day Surgery

Figure S1. Study cohort creation.



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 Table S2 (Additional analysis 1). SARS-CoV-2 vaccination and associated risk of SARS-CoV-2 infection, or severe COVID-19 (hospitalization or death) – each assessed starting at least 14 days after the first vaccination. This analysis is limited to 614,455 individuals who had SARS-CoV-2 PCR testing during the follow-up period, from January 15, 2021 onward.

			No. with outcome	Unadjusted	Adjusted
		No. person-days of	(rate per 10,000	hazard ratio	hazard ratio
Study outcome	Exposure state ^a	follow-up ^a	person-days)	(95% CI%)	(95% CI%) ^b
CARC Cold 2 infantion	Unvaccinated (N = 609,129)	67,185,613	51,187 (7.62)	1.00 (referent)	1.00 (referent)
SANS-COV-2 INJECTION	Vaccinated (N = 439,058)	27,220,438	4995 (1.84)	0.25 (0.25 to 0.26)	0.28 (0.27 to 0.29)
		0			
Soucra COVID 10	Unvaccinated (N = 609,129)	71,414,615	2890 (0.40)	1.00 (referent)	1.00 (referent)
Severe COVID-13	Vaccinated (N = 439,058)	27,470,663	491 (0.18)	0.50 (0.46 to 0.56)	0.22 (0.20 to 0.25)

^aExposure is time-varying, therefore, some individuals may have contributed time as unvaccinated, and then subsequently, as vaccinated.

^bAdjusted for age, sex, rural residence, area income quintile – each at baseline -- as well as prior diabetes mellitus, malignancy, heart failure, cardiac

ischemia or arrhythmia, chronic kidney disease or venous thromboembolism.
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Table S3. SARS-CoV-2 vaccination and associated risk of SARS-CoV-2 infection, or severe COVID-19 (hospitalization or death), stratified by O and non-O blood groups, among the entire cohort. Data are presented by time-varying exposure after first vaccination type vs. unvaccinated, with study outcomes assessed starting at least 14 days after the first vaccination.

				No. with outcome	Adjusted
	Stratified by		No. person-days of	(rate per 10,000	hazard ratio
Study outcome	blood group	Exposure state ^a	follow-up ^a	person-days)	(95% CI%) ^b
SARS-CoV-2 infection	Non-O	Unvaccinated (N = 1,401,213)	172,490,490	30,685 (1.78)	1.00 (referent)
		Adenovirus-vectored (N = 80,411)	4,637,314	260 (0.56)	0.49 (0.43 to 0.55)
		Modified RNA (N = 912,274)	48,108,108	2717 (0.56)	0.46 (0.44 to 0.48)
		6			
	0	Unvaccinated (N = 1,063,785)	130,718,702	20,502 (1.57)	1.00 (referent)
		Adenovirus-vectored (N = 62,947)	3,626,421	174 (0.48)	0.49 (0.42 to 0.57)
		Modified RNA (N = 688,250)	36,951,138	1844 (0.50)	0.46 (0.44 to 0.48)
		9			
Severe COVID-19	Non-O	Unvaccinated (N = 1,401,213)	175,034,046	1677 (0.10)	1.00 (referent)
		Adenovirus-vectored (N = 80,411)	4,649,419	15 (0.03)	0.27 (0.16 to 0.45)
		Modified RNA (N = 912,274)	48,242,495	296 (0.06)	0.31 (0.27 to 0.36)
	0	Unvaccinated (N = 1,063,785)	132,404,148	1213 (0.09)	1.00 (referent)
		Adenovirus-vectored (N = 62,947)	3,634,743	12 (0.03)	0.33 (0.18 to 0.58)
		Modified RNA (N = 688,250)	37,046,550	168 (0.05)	0.27 (0.22 to 0.32)

^aExposure is time-varying, therefore, some individuals may have contributed time as unvaccinated, and then subsequently, as vaccinated.

^bAdjusted for age, sex, rural residence, area income quintile – each at baseline -- as well as prior diabetes mellitus, malignancy, heart failure, cardiac ischemia or arrhythmia, chronic kidney disease or venous thromboembolism.

Supplementary file 3.	STROBE	E checklist.	
Section/Topic	Item #	Recommendation	Reported or
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract 두 주 프	3
		لله من ح (b) Provide in the abstract an informative and balanced summary of what was done and what wag figund	3
Introduction		ate	
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported 6	4
Objectives	3	State specific objectives, including any prespecified hypotheses 폭읍 බ	4
Methods	1	and a serie d	
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, and data	
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	
		(b) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifier Give diagnostic criteria, if applicable	
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	NA
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which good by the second second why	5,6
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	5,6
		(b) Describe any methods used to examine subgroups and interactions	5,6
		(c) Explain how missing data were addressed	NA
		(d) If applicable, explain how loss to follow-up was addressed	
		(e) Describe any sensitivity analyses	NA

		BMJ Open by copyrig	Page
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, example for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6, eFig 1
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	eFig 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information and be and potential confounders	Table 1
		(b) Indicate number of participants with missing data for each variable of interest	Table 1
		(c) Summarise follow-up time (eg, average and total amount)	6
Outcome data	15*	Report numbers of outcome events or summary measures over time	Figure 1
Main results	16	(<i>a</i>) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision degrees, 95% confidence interval). Make clear which confounders were adjusted for and why they were included a a b a	6, Figure 1
		(b) Report category boundaries when continuous variables were categorized	NA
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses and sensitivity analyses	Figure 2
Discussion		ning	
Key results	18	Summarise key results with reference to study objectives	7
Limitations		Si Si	
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity and arealyses, results from similar studies, and other relevant evidence	7,8
Generalisability	21	Discuss the generalisability (external validity) of the study results	8
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	9