BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-059944
Article Type:	Original research
Date Submitted by the Author:	07-Dec-2021
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Keywords:	COVID-19, HAEMATOLOGY, INFECTIOUS DISEASES, Epidemiology < INFECTIOUS DISEASES

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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: 241

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.

Abstract

Objective: To compare outcomes between O and non-O blood groups, and by mRNA and Ad-V vaccines.

Design: Population-based cohort study.

Setting: All of Ontario, Canada. Linked datasets captured clinical encounters, vaccinations and laboratory testing for SARS-CoV-2.

Participants: Individuals aged 12+ years with known ABO blood group and free of SARS-CoV-2 before January 15, 2021.

Main outcomes measures: The main exposure, first SARS-CoV-2 vaccination, was modeled in a time-varying manner. O and non-O blood group was known prior to vaccination. SARS-CoV-2 infection, and severe COVID-19 (hospitalization or death), were assessed starting 14 days after vaccination, up to June 27, 2021.

Results: 2,472,261 individuals were included. 1,743,916 (70.5%) had at least one vaccination, of which 24.6% were fully vaccinated. Relative to unvaccinated, after receiving their first mRNA (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-2 infection was lower, as was severe COVID-19 (aHR 0.29, 95% CI 0.20-0.43 [mRNA]; 0.29, 95% CI 0.26-0.33 [Ad-V]). Stratifying by blood group produced similar results. For example, after first mRNA vaccination, the aHR of severe COVID-19 was 0.31 (95% CI 0.27-0.36) among non-O, and 0.27 (95% CI 0.22 to 0.32) among O blood groups, relative to unvaccinated. Fully vaccinated individuals had the lowest risk of SARS-CoV-2 and severe COVID-19.

Conclusions SARS-CoV-2 infection and severe COVID-19 are reduced by vaccination. This effect does not vary by vaccine type or blood group, but is more pronounced among fully, than partially, vaccinated individuals.

Keywords: SARS-CoV-2; COVID-19; vaccination; ABO blood group; effectiveness; cohort study.

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.

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 (https://www.ices.on.ca/DAS/AHRQ/COVID-19-Dashboard#vaccinecoverage), 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. Patient-level 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 follow-up 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

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 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,

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-19-related 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 healthcare-seeking 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

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

Funded by a grant from the Ontario Academic Health Sciences Centre AFP Innovation Fund, and the Ontario Ministry of Health (MOH).

This study was also supported by ICES, which is funded by an annual grant from the Ontario MOH and the Ministry of Long-Term Care. Parts of this material are based on data and information compiled and provided by MOH and the Canadian Institute for Health Information. The analyses, conclusions, opinions and statements expressed herein are solely those of the authors and do not reflect those of the funding or data sources; no endorsement is intended or should be inferred.

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.

References

<1> Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. N Engl J Med 2020;383:2603-2615.

<2> Sadoff J, Le Gars M, Shukarev G, Heerwegh D, Truyers C, de Groot AM, et al. Interim Results of a Phase 1-2a Trial of Ad26.COV2.S Covid-19 Vaccine. N Engl J Med. 2021;384:1824-1835. doi: 10.1056/NEJMoa2034201.

<3> Pormohammad A, Zarei M, Ghorbani S, Mohammadi M, Razizadeh MH, Turner DL, Turner RJ. Efficacy and Safety of COVID-19 Vaccines: A Systematic Review and Meta-Analysis of Randomized Clinical Trials. Vaccines (Basel) 2021;9:467. doi: 10.3390/vaccines9050467. PMID: 34066475; PMCID: PMC8148145.

<4> Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, et al. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. N Engl J Med 2021;384:403-416. doi: 10.1056/NEJMoa2035389.

<5> Thompson MG, Burgess JL, Naleway AL, Tyner HL, Yoon SK, Meece J, et al. Interim Estimates of Vaccine Effectiveness of BNT162b2 and mRNA-1273 COVID-19 Vaccines in Preventing SARS-CoV-2 Infection Among Health Care Personnel, First Responders, and Other Essential and Frontline Workers - Eight U.S. Locations, December 2020-March 2021. MMWR Morb Mortal Wkly Rep 2021;70:495-500. doi: 10.15585/mmwr.mm7013e3.

<6> Ray JG, Schull MJ, Vermeulen MJ, Park AL. Association Between ABO and Rh Blood Groups and SARS-CoV-2 Infection or Severe COVID-19 Illness : A Population-Based Cohort Study. Ann Intern Med 2020:M20-4511. doi: 10.7326/M20-4511.

<7> Pendu JL, Breiman A, Rocher J, Dion M, Ruvoën-Clouet N. ABO Blood Types and COVID-19: Spurious, Anecdotal, or Truly Important Relationships? A Reasoned Review of Available Data. Viruses. 2021; 13:160. https://doi.org/10.3390/v13020160.

<8> Chung H, He S, Nasreen S, Sundaram ME, Buchan SA, Wilson SE, et al. Effectiveness of BNT162b2 and mRNA-1273 covid-19 vaccines against symptomatic SARS-CoV-2 infection and severe covid-19 outcomes in Ontario, Canada: test negative design study. BMJ 2021;374:n1943. doi: 10.1136/bmj.n1943.

<9> Suissa S. Immortal time bias in pharmaco-epidemiology. Am J Epidemiol 2008;167:492-9. http://doi: 10.1093/aje/kwm324.

<10> National Advisory Committee on Immunization (NACI): Statements and publications. Recommendations on the use of COVID-19 vaccines. Publication date: July 22, 2021. https://www.canada.ca/en/public-health/services/immunization/national-advisory-committee-on-immunization-naci/recommendations-use-covid-19-vaccines.html#t19 (accessed on August 15, 2021).

<11> Liu N, Zhang T, Ma L, Zhang H, Wang H, Wei W, Pei H, Li H. The impact of ABO blood group on COVID-19 infection risk and mortality: A systematic review and meta-analysis. Blood Rev 2021;48:100785. doi: 10.1016/j.blre.2020.100785.

<12> BOURKE GJ, CLARKE N, THORNTON EH. SMALLPOX VACCINATION: ABO AND RHESUS BLOOD GROUPS. J Med Genet 1965;2:122-5. doi: 10.1136/jmg.2.2.122.

<13> Mackenzie JS, Fimmel PJ. The effect of ABO blood groups on the incidence of epidemic influenza and on the response to live attenuated and detergent split influenza virus vaccines. Journal of Hygiene 1978;80:21-30.

<14> Buchta C, Körmöczi G, Heinze G, Puhr R, Kompatscher M, Jüngling G, et al. Lack of impact of ABO blood group or corresponding isoantibodies on the immune response after rabies vaccination. Wien Klin Wochenschr 2005;117:412-6. doi: 10.1007/s00508-005-0366-3.

<15> Ramamurthy T, Wagener D, Chowdhury G, Majumder PP. A large study on immunological response to a whole-cell killed oral cholera vaccine reveals that there are significant geographical differences in response and that O blood group individuals do not elicit a higher response. Clin Vaccine Immunol 2010;17:1232-7. doi: 10.1128/CVI.00123-10.

<16> Jara A, Undurraga EA, González C, Paredes F, Fontecilla T, Jara G, er al. Effectiveness of an Inactivated SARS-CoV-2 Vaccine in Chile. N Engl J Med 2021;385:875-884. doi: 10.1056/NEJMoa2107715. Epub 2021 Jul 7. PMID: 34233097; PMCID: PMC8279092.

<17> Calip GS, Miksad RA, Sarkar S. Time-Related Biases in Nonrandomized COVID-19-Era Studies Using Real-world Data. JAMA Oncol 2021 Jun 17. doi: 10.1001/jamaoncol.2021.1715.

<18> Dean NE, Hogan JW, Schnitzer ME. Covid-19 Vaccine Effectiveness and the Test-Negative Design. N Engl J Med 2021 Sep 8. doi: 10.1056/NEJMe2113151.

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

Characteristic		Any SARS-Cov-2 vaccination (N = 1,743,916)	No SARS-COV-2 vaccination (N = 728,345)	Standardized 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		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 June 13, 2021 (14 days prior to end of follow-up)		428,503 (24.6)	--	
Vaccine dose 2 same as dose 1	*Same*	424,517 (24.3)	--	
	Different	3,969 (0.2)	--	
	Unknown	17 (0.0)	--	
	No second dose	1,315,413 (75.4)		
Median (IQR) follow-up for assessing the primary study outcome, d		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		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

[a]Missing for 6180 (0.25%) of all persons
[b]Missing for 5247 (0.21%) of all persons
[c]Before January 15, 2021

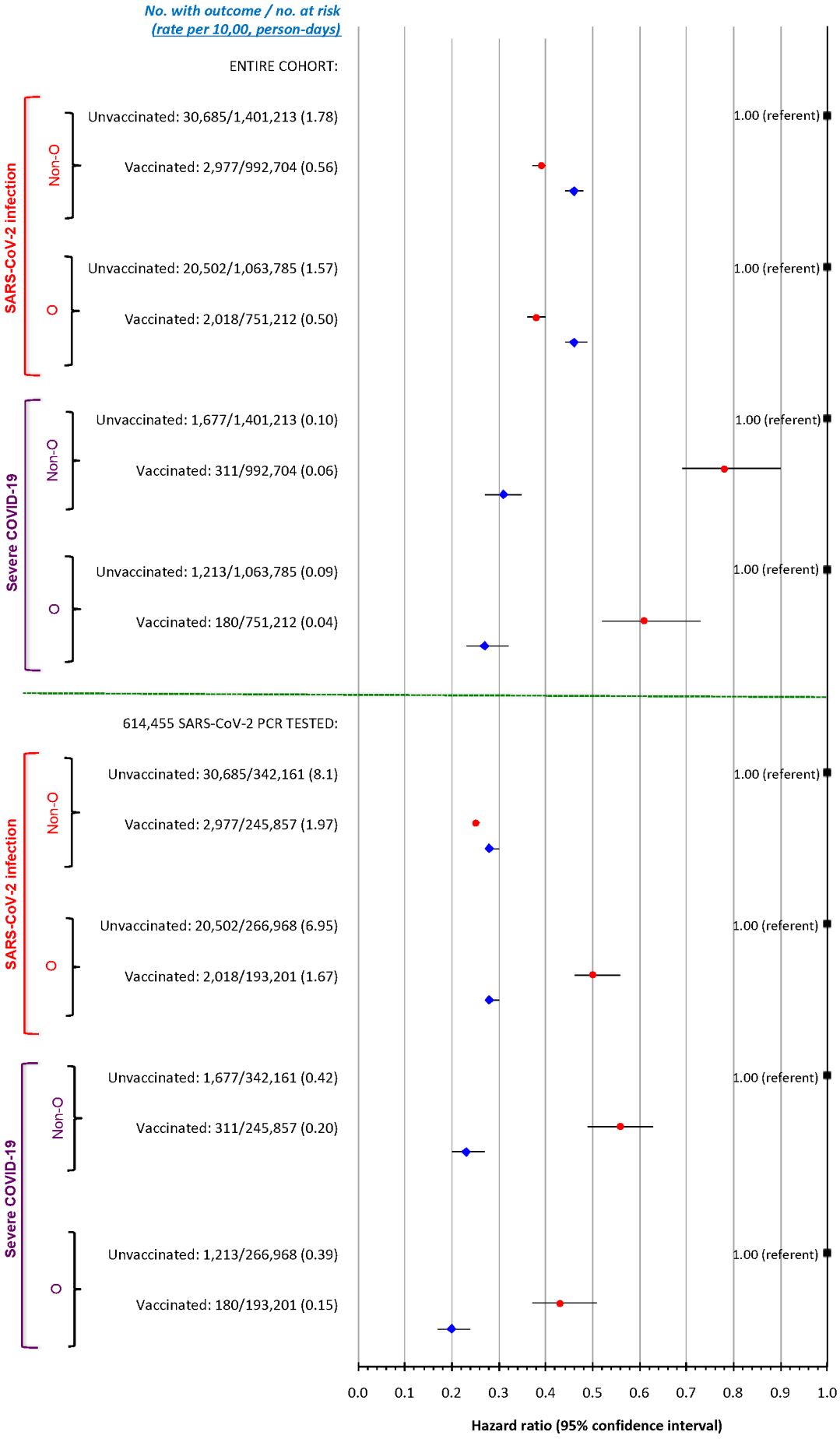
Table 2. SARS-CoV-2 vaccination and associated risk of SARS-CoV-2 infection, or severe COVID-19 (hospitalization or death) – each assessed starting at least 14 days after the first vaccination, among the entire cohort. Data are presented by time-varying exposure after first vaccination vs. unvaccinated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

Study outcome	Exposure state[a]	No. person-days of follow-up[a]	No. with outcome (rate per 10,000 person-days)	Unadjusted hazard ratio (95% CI%)	Adjusted hazard ratio (95% CI%)[b]
SARS-CoV-2 infection	Unvaccinated (N = 2,464,998)	303,209,192	51,187 (1.69)	1.00 (referent)	1.00 (referent)
	Vaccinated (N = 1,743,916)	93,324,805	4995 (0.54)	0.38 (0.37 to 0.39)	0.46 (0.45 to 0.48)
Severe COVID-19[c]	Unvaccinated (N = 2,464,998)	307,438,194	2890 (0.09)	1.00 (referent)	1.00 (referent)
	Vaccinated (N = 1,743,916)	93,575,031	491 (0.05)	0.71 (0.64 to 0.79)	0.29 (0.26 to 0.33)
SARS-CoV-2 infection	Unvaccinated (N = 2,464,998)	303,209,192	51,187 (1.69)	1.00 (referent)	1.00 (referent)
	Adenovirus-vectored (N = 143,358)	8,263,735	434 (0.53)	0.39 (0.36 to 0.43)	0.49 (0.44 to 0.54)
	Modified RNA (N = 1,600,524)	85,059,246	4561 (0.54)	0.38 (0.37 to 0.39)	0.46 (0.44 to 0.47)
Severe COVID-19[c]	Unvaccinated (N = 2,464,998)	307,438,194	2890 (0.09)	1.00 (referent)	1.00 (referent)
	Adenovirus-vectored (N = 143,358)	8,284,162	27 (0.03)	0.46 (0.31 to 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 to 0.82)	0.29 (0.26 to 0.33)

[a]Exposure is time-varying, therefore, some individuals may have contributed time as unvaccinated, and then subsequently, as vaccinated.

[b]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.

[c]In 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 test.



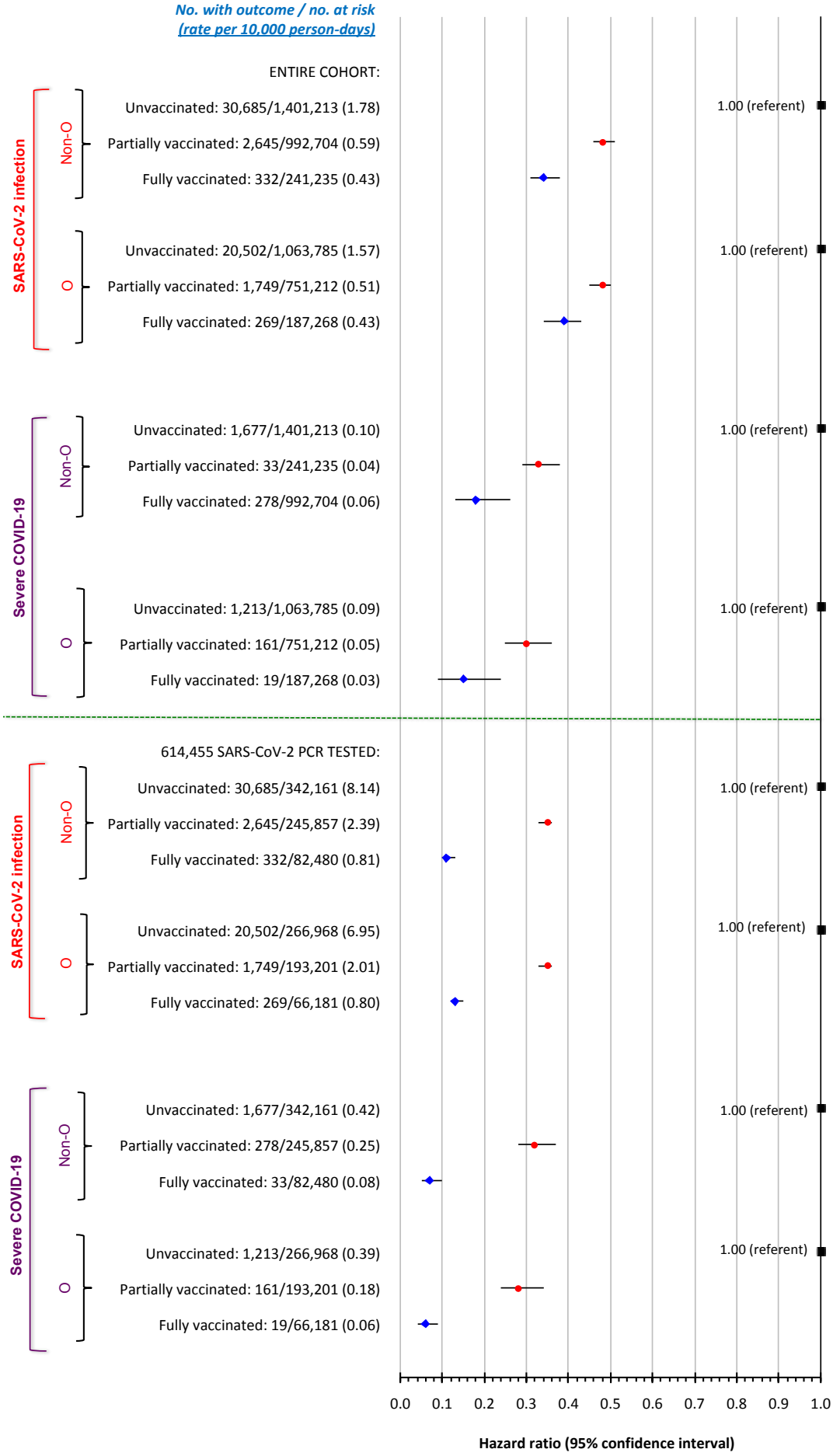


Table S1. Variables used to define cohort entry and exclusion criteria, as well as study exposures, outcomes, adjustment, and stratification.

Assessment	Timing	Disease, procedure or condition	CIHI-DAD, SDS or NACRS ICD-10-CA diagnosis or CCI procedure codes	OHIP ICD-9 diagnostic fee codes; or other data source	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, 883-9, 10331-7 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	--	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, XON13530-1, 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 https://github.com/icescentral/COVID19-Lab-Results
	January 15, 2021 (time zero)	Implausible or missing sex, birth date or death date	--	Registered Persons Database (RPDB) - contains demographic information and encrypted health care 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	--

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
	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 (DAD, NACRS)	RPDB, COVAXON, OLISC19	--
	December 15, 2020 to June 13, 2021	Duplicate vaccination record	--	COVAXON	--
Study exposures	December 15, 2020 to June 13, 2021	COVID-19 partially vaccinated status	--	COVAXON	--
	Same as above	COVID-19 1st dose type (mRNA, viral vector, unknown, none)	--	COVAXON	--
	Same as above	COVID-19 fully-vaccinated status (fully-vaccinated, partially-vaccinated, unvaccinated)	--	COVAXON	--
Stratification variable	January 2007 to December 2020	ABO blood group (O, other)	--	LOINC codes 882-1, 883-9, 10331-7 in OLIS	--
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	--

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 AND 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	--	RPDB	--
	Same as above	Area income quintile	--	Statistics Canada Census	--
	Same as above	Rural residence	--	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, E14	OHIP ICD-9: 250 OHIP fee codes: Q040, K029, K030, K045, K046	https://pubmed.ncbi.nlm.nih.gov/11874939/

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
	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): I500, I501, I509	OHIP ICD-9: 428	https://pubmed.ncbi.nlm.nih.gov/23735455/
	Within 5 years before January 15, 2021 (time zero)	History of malignant neoplasm	ICD-10-CA (DAD, SDS, NACRS): C00-C97	--	--
	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://pubmed.ncbi.nlm.nih.gov/23560464/

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 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 30 days, but < 150 days, in the year before the index date: R849, G082, G083, G085, G090-G096, G294, G322, G323, G325, G326, G330-G332, G860-G866, H540, H740 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	https://pubmed.ncbi.nlm.nih.gov/20613656/
			Exclude kidney transplant CCI (DAD): 1PC85	Exclude kidney transplant OHIP fee codes: S433, S434 CORR treatment code: 171 plus ≥ 1 Transplanted Organ Code [1-3]: 10, 11, 12, 18, 19	https://pubmed.ncbi.nlm.nih.gov/26019887/

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
	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, I24 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	--	https://pubmed.ncbi.nlm.nih.gov/20847972/

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
	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 Flutter: ICD-10-CA: I48 Ventricular Arrhythmia & Tachycardia: ICD-10-CA: I470, I472, I490, I493 Permanent Pacemaker: CCI: 1HZ53GRNM, 1HZ53LANM, 1HZ53GRNK, 1HZ53LANK, 1HZ53GRNL, 1HZ53LANL Implantable Cardioverter-Defibrillator: CCI: 1HZ53GRFS, 1HZ53LAFS, 1HZ53SYFS, 1HZ53HAFS	--	https://pubmed.ncbi.nlm.nih.gov/19433698/ https://www.ices.on.ca/Publications/Atlases-and-Reports/2006/Canadian-Institute-for-Health-Information https://pubmed.ncbi.nlm.nih.gov/17599603/

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
	Same as above	History of pulmonary embolism, deep vein thrombosis, or other venous thromboembolism	ICD-10-CA (DAD, SDS, NACRS): I260, I269, O88201, O88202, O88203, O88204, O88209, I636, I822, I828, I829, I801, I802, I803, I808, I809, O22301, O22303, O22309, O22501, O22503, O22509, O87102, O87104, O87109, O87304, O87309, I676, I81, I820, I823, O228, O229, O878, O879 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, 3GT70KE, 3JY10VA, 3JY10VC, 3JY10VN, 3JY10VX, 3JY12VA , 3JY20WC	OHIP ICD-9: 677, 415, 671, 451, 452 AND one of the following radiological professional fee codes for a VTE diagnostic test billed within 3 days: J198, J498, J499, J493, J202, J502, J206, J506, J182, J482, X406, X407, X125, X188, X403, X405, X408, X126, X410, X231, X233, X127, X413, X421, X425, J655, J660, J859, J860	--

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
Other baseline variables	Any time before January 15, 2021 (time zero)	Asthma	The ICES-derived ASTHMA database was used to identify patients with diagnosed asthma before the index date, based on 2 OHIP diagnostic codes or 1 DAD diagnostic code. ICD-10-CA: J45, J46	OHIP ICD-9: 493	https://pubmed.ncbi.nlm.nih.gov/20011725/
	Same as above	Chronic obstructive pulmonary disease (COPD)	The ICES-derived COPD database was used to identify patients with diagnosed COPD before the index date, based on 1 OHIP diagnostic code or 1 DAD diagnostic code. ICD-10-CA: J41-J44	OHIP ICD-9: 491, 492, 496	https://pubmed.ncbi.nlm.nih.gov/19863368/ *The COPD algorithm was validated in those aged ≥ 35 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-I13, I15	OHIP ICD-9: 401-405	https://pubmed.ncbi.nlm.nih.gov/20101286/

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
	Same as above	Immunocompromised (HIV or organ transplant)	--	The ICES-derived HIV database was used to identify patients with pre-existing HIV, based on 3 physician claims in 3 years. 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.	https://pubmed.ncbi.nlm.nih.gov/21738786/
	Same as above	Dementia	The ICES-derived DEMENTIA 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, 331 ODB 1 prescription for a cholinesterase inhibitor	https://pubmed.ncbi.nlm.nih.gov/27567819/

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, incontinence, nutrition issues, functional performance) and health services utilization (i.e., ≥ 2 hospital stays or ED visits, geriatrician or home care visit).	--	https://pubmed.ncbi.nlm.nih.gov/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, 772	--

Assessment	Timing	Disease, procedure or condition	CIHI-DAD, SDS or NACRS ICD-10-CA diagnosis or CCI procedure codes	OHIP ICD-9 diagnostic fee codes; or other data source	Validation studies or documentation for some codes
	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, H340 Acute Ischemic Stroke: 1 hospitalization with a main diagnosis coded with one of the following codes: ICD-10-CA (DAD): I63 (except I636), I64, H341	--	http://canadianstrokenetwork.ca/en/wp-content/uploads/2014/08/Stroke_Core_ENG.pdf

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; OLISCV9: Ontario Laboratories Information System COVID-19 Laboratory Data; RPDB: Registered Persons Database; SDS: Same Day Surgery

Figure S1. Study cohort creation.

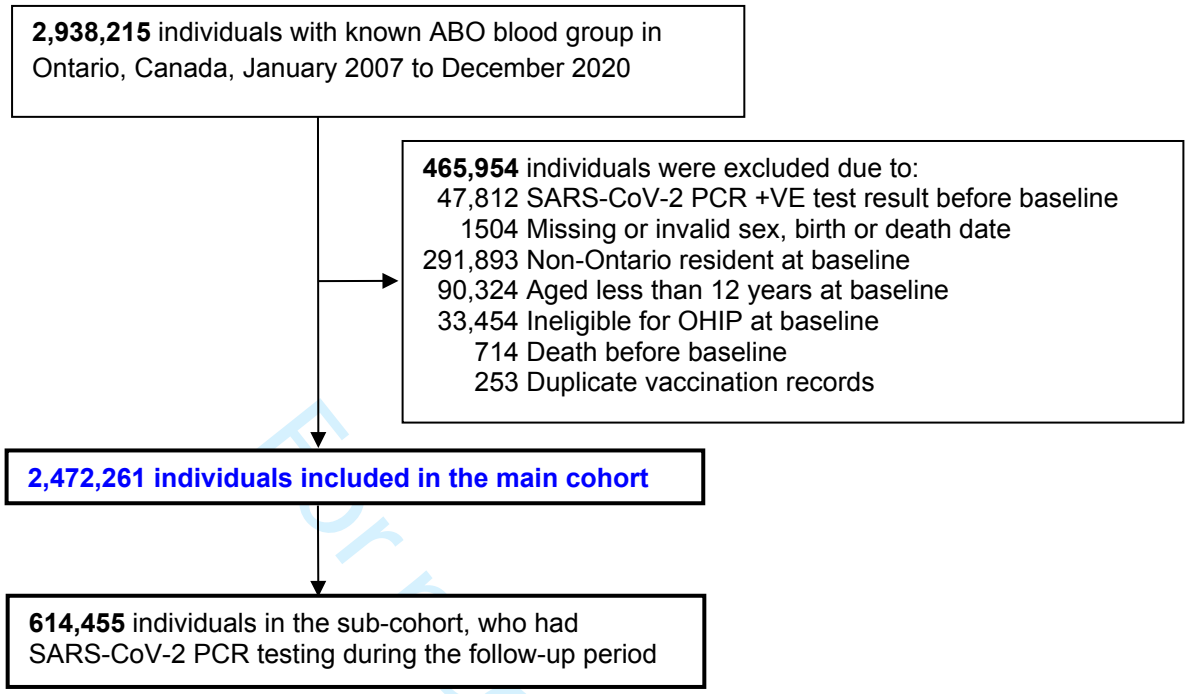


Table S2 (*Additional analysis 1*). SARS-CoV-2 vaccination and associated risk of SARS-CoV-2 infection, or severe COVID-19 (hospitalization or death) – each assessed starting at least 14 days after the first vaccination. *This analysis is limited to 614,455 individuals who had SARS-CoV-2 PCR testing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

Study outcome	Exposure state[a]	No. person-days of follow-up[a]	No. with outcome (rate per 10,000 person-days)	Unadjusted hazard ratio (95% CI%)	Adjusted hazard ratio (95% CI%)[b]
SARS-CoV-2 infection	Unvaccinated (N = 609,129)	67,185,613	51,187 (7.62)	1.00 (referent)	1.00 (referent)
	Vaccinated (N = 439,058)	27,220,438	4995 (1.84)	0.25 (0.24 to 0.26)	0.28 (0.27 to 0.29)
Severe COVID-19	Unvaccinated (N = 609,129)	71,414,615	2890 (0.40)	1.00 (referent)	1.00 (referent)
	Vaccinated (N = 439,058)	27,470,663	491 (0.18)	0.50 (0.45 to 0.56)	0.22 (0.20 to 0.25)

[a]Exposure is time-varying, therefore, some individuals may have contributed time as unvaccinated, and then subsequently as vaccinated.

[b]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 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.

Study outcome	Stratified by blood group	Exposure state[a]	No. person-days of follow-up[a]	No. with outcome (rate per 10,000 person-days)	Adjusted hazard ratio (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)
	O	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)
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)
	O	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)

[a]Exposure is time-varying, therefore, some individuals may have contributed time as unvaccinated, and then subsequently, as vaccinated.

[b]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.

Supplementary file 3. STROBE checklist.

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
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, follow-up, 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 modifiers. 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 groupings were chosen and 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

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined 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 on exposures 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	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	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 time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Figure 2
Discussion			
Key results	18	Summarise key results with reference to study objectives	7
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of 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

BMJ Open

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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-059944.R1
Article Type:	Original research
Date Submitted by the Author:	18-May-2022
Complete List of Authors:	Ray, Joel; ICES, Departments of Medicine, Obstetrics and Gynaecology Park, Alison; Insitute for Clinical Evaluative Sciences
Primary Subject Heading:	Infectious diseases
Secondary Subject Heading:	Epidemiology, Haematology (incl blood transfusion), Immunology (including allergy), Public health
Keywords:	HAEMATOLOGY, INFECTIOUS DISEASES, Epidemiology < INFECTIOUS DISEASES, COVID-19, Blood bank & transfusion medicine < HAEMATOLOGY

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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

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.

Abstract

Objective: To compare outcomes between O and non-O blood groups, and by mRNA and Ad-V vaccines.

Design: Population-based cohort study.

Setting: All of Ontario, Canada. Linked datasets captured clinical encounters, vaccinations and laboratory testing for SARS-CoV-2.

Participants: Individuals aged 12+ years with known ABO blood group and free of SARS-CoV-2 before January 15, 2021.

Main outcomes measures: The main exposure, first SARS-CoV-2 vaccination, was modeled in a time-varying manner. O and non-O blood group was known prior to vaccination. SARS-CoV-2 infection, and severe COVID-19 (hospitalization or death), were assessed starting 14 days after vaccination, up to June 27, 2021.

Results: 2,472,261 individuals were included. 1,743,916 (70.5%) had at least one vaccination, of which 24.6% were fully vaccinated. 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. Relative to unvaccinated, after receiving their first mRNA (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-2 infection was lower, as was severe COVID-19 (aHR 0.29, 95% CI 0.20-0.43 [mRNA]; 0.29, 95% CI 0.26-0.33 [Ad-V]). Stratifying by blood group produced similar results. For example, after first mRNA vaccination, the aHR of severe COVID-19 was 0.31 (95% CI 0.27-0.36) among non-O, and 0.27 (95% CI 0.22 to 0.32) among O blood groups, relative to unvaccinated. Fully vaccinated individuals had the lowest risk of SARS-CoV-2 and severe COVID-19.

Conclusions SARS-CoV-2 infection and severe COVID-19 are reduced by vaccination. This effect does not vary by vaccine type or blood group, but is more pronounced among fully, than partially, vaccinated individuals.

Keywords: SARS-CoV-2; COVID-19; vaccination; ABO blood group; effectiveness; cohort study.

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.

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. Patient-level 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 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 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 follow-up 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.

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-19-related 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 healthcare-seeking 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

Funded by a grant from the Ontario Academic Health Sciences Centre AFP Innovation Fund, and the Ontario Ministry of Health (MOH).

This study was also supported by ICES, which is funded by an annual grant from the Ontario MOH and the Ministry of Long-Term Care. Parts of this material are based on data and information compiled and provided by MOH and the Canadian Institute for Health Information. The analyses, conclusions, opinions and statements expressed herein are solely those of the authors and do not reflect those of the funding or data sources; no endorsement is intended or should be inferred.

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.

References

1. Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. N Engl J Med 2020;383:2603-2615.

2. Sadoff J, Le Gars M, Shukarev G, Heerwegh D, Truyers C, de Groot AM, et al. Interim Results of a Phase 1-2a Trial of Ad26.COV2.S Covid-19 Vaccine. N Engl J Med. 2021;384:1824-1835. doi: 10.1056/NEJMoa2034201.

3. Pormohammad A, Zarei M, Ghorbani S, Mohammadi M, Razizadeh MH, Turner DL, Turner RJ. Efficacy and Safety of COVID-19 Vaccines: A Systematic Review and Meta-Analysis of Randomized Clinical Trials. Vaccines (Basel) 2021;9:467. doi: 10.3390/vaccines9050467. PMID: 34066475; PMCID: PMC8148145.

4. Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, et al. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. N Engl J Med 2021;384:403-416. doi: 10.1056/NEJMoa2035389.

5. Thompson MG, Burgess JL, Naleway AL, Tyner HL, Yoon SK, Meece J, et al. Interim Estimates of Vaccine Effectiveness of BNT162b2 and mRNA-1273 COVID-19 Vaccines in Preventing SARS-CoV-2 Infection Among Health Care Personnel, First Responders, and Other Essential and Frontline Workers - Eight U.S. Locations, December 2020-March 2021. MMWR Morb Mortal Wkly Rep 2021;70:495-500. doi: 10.15585/mmwr.mm7013e3.

6. Ray JG, Schull MJ, Vermeulen MJ, Park AL. Association Between ABO and Rh Blood Groups and SARS-CoV-2 Infection or Severe COVID-19 Illness : A Population-Based Cohort Study. Ann Intern Med 2020:M20-4511. doi: 10.7326/M20-4511.

7. Goel R, Bloch EM, Pirenne F, et al. ABO blood group and COVID-19: a review on behalf of the ISBT COVID-19 Working Group. Vox Sang 2021;116:849-861. doi: 10.1111/vox.13076.

8. ICES. ICES COVID-19 Dashboard. 2022. https://www.ices.on.ca/DAS/AHRQ/COVID-19-Dashboard#vaccinecoverage (accessed 16 May 2022).

9. Ontario Ministry of Health. COVID-19 Vaccine Data in Ontario. 2022. https://data.ontario.ca/dataset/covid-19-vaccine-data-in-ontario (accessed 16 May 2022).

10. Chung H, He S, Nasreen S, Sundaram ME, Buchan SA, Wilson SE, et al. Effectiveness of BNT162b2 and mRNA-1273 covid-19 vaccines against symptomatic SARS-CoV-2 infection and severe covid-19 outcomes in Ontario, Canada: test negative design study. BMJ 2021;374:n1943.

doi: 10.1136/bmj.n1943.

11. Suissa S. Immortal time bias in pharmaco-epidemiology. Am J Epidemiol 2008;167:492-9.

12. National Advisory Committee on Immunization (NACI): Statements and publications. Recommendations on the use of COVID-19 vaccines. Publication date: July 22, 2021. https://www.canada.ca/en/public-health/services/immunization/national-advisory-committee-on-immunization-naci/recommendations-use-covid-19-vaccines.html#t19 (accessed 15 August, 2021).

13. Liu N, Zhang T, Ma L, Zhang H, Wang H, Wei W, Pei H, Li H. The impact of ABO blood group on COVID-19 infection risk and mortality: A systematic review and meta-analysis. Blood Rev 2021;48:100785. doi: 10.1016/j.blre.2020.100785.

14. Bourke GJ, Clarke N, Thornton EH. Smallpox vaccination:: ABO and Rhesus blood groups. J Med Genet 1965;2:122-5. doi: 10.1136/jmg.2.2.122.

15. Mackenzie JS, Fimmel PJ. The effect of ABO blood groups on the incidence of epidemic influenza and on the response to live attenuated and detergent split influenza virus vaccines. Journal of Hygiene 1978;80:21-30.

16. Buchta C, Körmöczi G, Heinze G, Puhr R, Kompatscher M, Jüngling G, et al. Lack of impact of ABO blood group or corresponding isoantibodies on the immune response after rabies vaccination. Wien Klin Wochenschr 2005;117:412-6. doi: 10.1007/s00508-005-0366-3.

17. Ramamurthy T, Wagener D, Chowdhury G, Majumder PP. A large study on immunological response to a whole-cell killed oral cholera vaccine reveals that there are significant geographical differences in response and that O blood group individuals do not elicit a higher response. Clin Vaccine Immunol 2010;17:1232-7. doi: 10.1128/CVI.00123-10.

18. Jara A, Undurraga EA, González C, et al. Effectiveness of an Inactivated SARS-CoV-2 Vaccine in Chile. N Engl J Med 2021;385:875-884. doi: 10.1056/NEJMoa2107715. Epub 2021 Jul 7. PMID: 34233097; PMCID: PMC8279092.

19. Calip GS, Miksad RA, Sarkar S. Time-Related Biases in Nonrandomized COVID-19-Era Studies Using Real-world Data. JAMA Oncol 2021 Jun 17. doi: 10.1001/jamaoncol.2021.1715.

20. Dean NE, Hogan JW, Schnitzer ME. Covid-19 Vaccine Effectiveness and the Test-Negative Design. N Engl J Med 2021 Sep 8. doi: 10.1056/NEJMe2113151.

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

Characteristic		Any SARS-Cov-2 vaccination (N = 1,743,916)	No SARS-COV-2 vaccination (N = 728,345)	Standardized 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		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 June 13, 2021 (14 days prior to end of follow-up)		428,503 (24.6)	--	
Vaccine dose 2 same as dose 1	*Same*	424,517 (24.3)	--	
	Different	3,969 (0.2)	--	
	Unknown	17 (0.0)	--	
	No second dose	1,315,413 (75.4)		
Median (IQR) follow-up for assessing the primary study outcome, d		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		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

[a]Missing for 6180 (0.25%) of all persons
[b]Missing for 5247 (0.21%) of all persons
[c]Before January 15, 2021

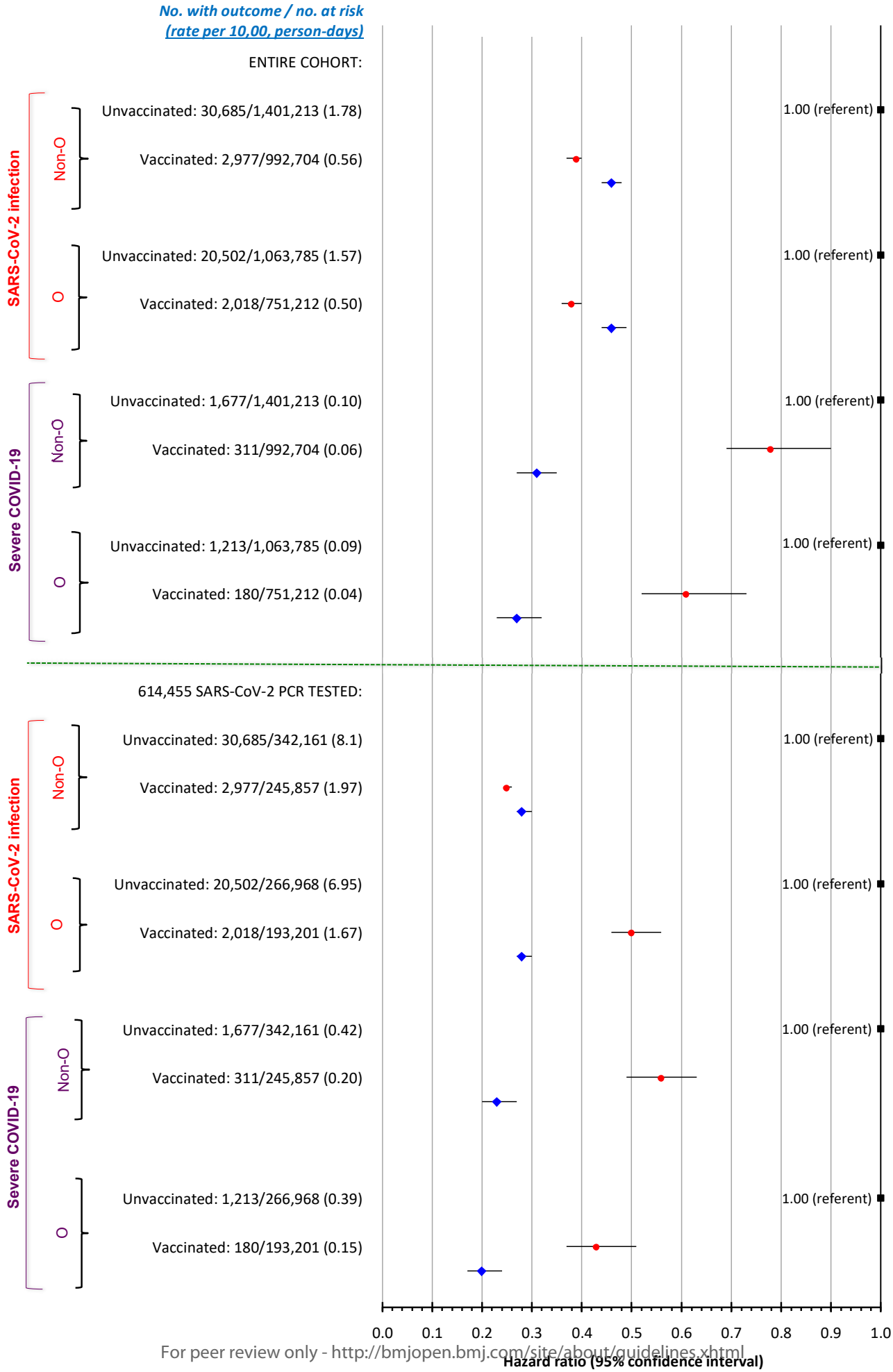
Table 2. SARS-CoV-2 vaccination and associated risk of SARS-CoV-2 infection, or severe COVID-19 (hospitalization or death) – each assessed starting at least 14 days after the first vaccination, among the entire cohort. Data are presented by time-varying exposure after first vaccination vs. unvaccinated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

Study outcome	Exposure state[a]	No. person-days of follow-up[a]	No. with outcome (rate per 10,000 person-days)	Unadjusted hazard ratio (95% CI%)	Adjusted hazard ratio (95% CI%)[b]
SARS-CoV-2 infection	Unvaccinated (N = 2,464,998)	303,209,192	51,187 (1.69)	1.00 (referent)	1.00 (referent)
	Vaccinated (N = 1,743,916)	93,324,805	4995 (0.54)	0.38 (0.37 to 0.39)	0.46 (0.45 to 0.48)
Severe COVID-19[c]	Unvaccinated (N = 2,464,998)	307,438,194	2890 (0.09)	1.00 (referent)	1.00 (referent)
	Vaccinated (N = 1,743,916)	93,575,031	491 (0.05)	0.71 (0.64 to 0.79)	0.29 (0.26 to 0.33)
SARS-CoV-2 infection	Unvaccinated (N = 2,464,998)	303,209,192	51,187 (1.69)	1.00 (referent)	1.00 (referent)
	Adenovirus-vectored (N = 143,358)	8,263,735	434 (0.53)	0.39 (0.36 to 0.43)	0.49 (0.44 to 0.54)
	Modified RNA (N = 1,600,524)	85,059,246	4561 (0.54)	0.38 (0.37 to 0.39)	0.46 (0.44 to 0.47)
Severe COVID-19[c]	Unvaccinated (N = 2,464,998)	307,438,194	2890 (0.09)	1.00 (referent)	1.00 (referent)
	Adenovirus-vectored (N = 143,358)	8,284,162	27 (0.03)	0.46 (0.31 to 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 to 0.82)	0.29 (0.26 to 0.33)

[a]Exposure is time-varying, therefore, some individuals may have contributed time as unvaccinated, and then subsequently, as vaccinated.

[b]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.

[c]In the vaccinated and unvaccinated groups, respectively, there were 21 deaths (0.02 per 100,000 person-days) and 133 deaths (0.04 per 100,000 person-days), from 1 day before, up to 3 days after, a SARS-CoV-2 positive PCR test, with a corresponding adjusted hazard ratio of 0.24 (95% CI 0.14 to 0.41).



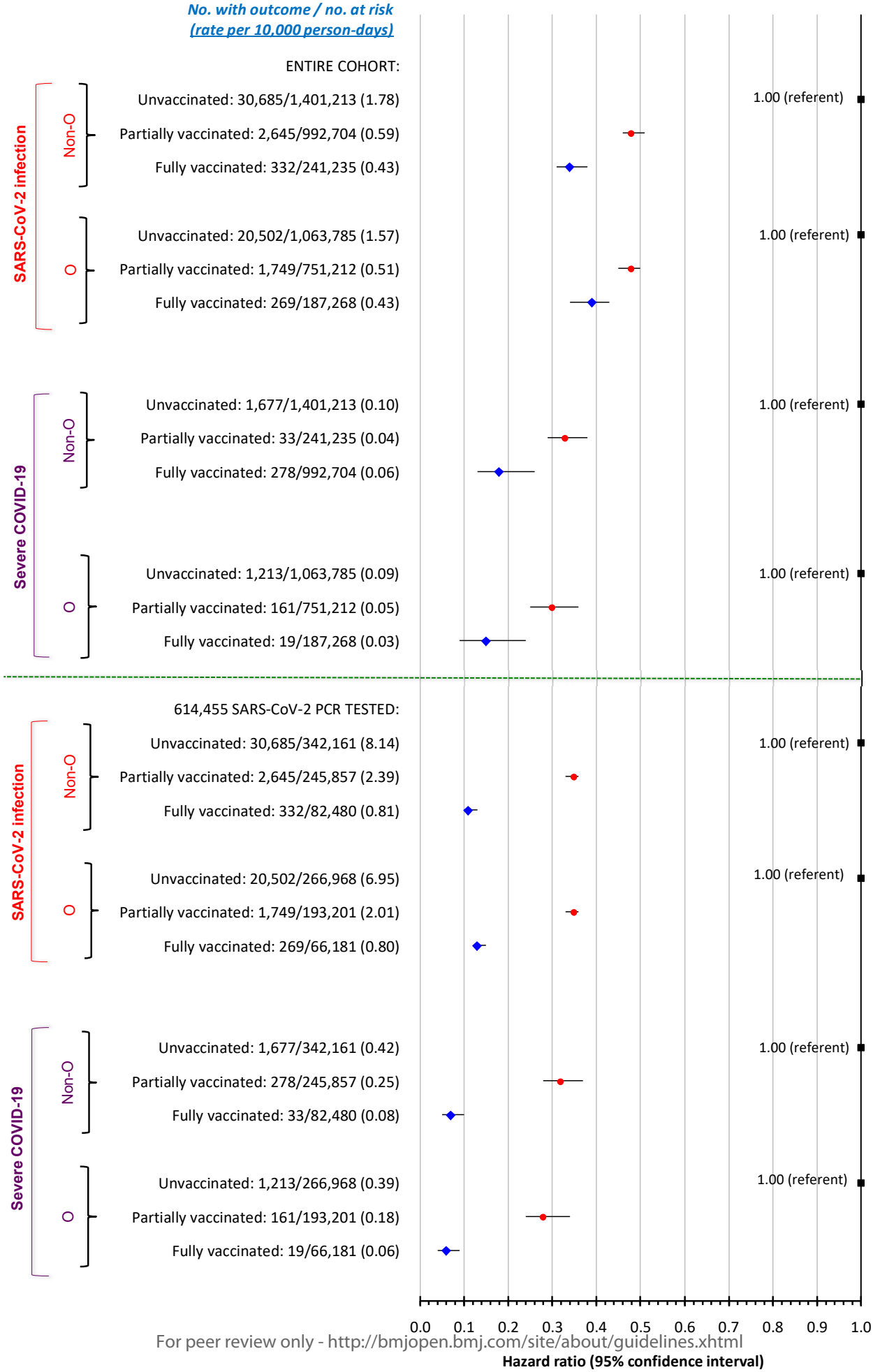


Table S1. Variables used to define cohort entry and exclusion criteria, as well as study exposures, outcomes, adjustment, and stratification.

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
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, 883-9, 10331-7 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	--	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 https://github.com/icescentral/COVID19-Lab-Results
	January 15, 2021 (time zero)	Implausible or missing sex, birth date or death date	--	Registered Persons Database (RPDB) - 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	--

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
	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 (DAD, NACRS)	RPDB, COVAXON, OLISC19	--
	December 15, 2020 to June 13, 2021	Duplicate vaccination record	--	COVAXON	--
Study exposures	December 15, 2020 to June 13, 2021	COVID-19 partially vaccinated status	--	COVAXON	--
	Same as above	COVID-19 1st dose type (mRNA, viral vector, unknown, none)	--	COVAXON	--
	Same as above	COVID-19 fully-vaccinated status (fully-vaccinated, partially-vaccinated, unvaccinated)	--	COVAXON	--
Stratification variable	January 2007 to December 2020	ABO blood group (O, other)	--	LOINC codes 882-1, 883-9, 10331-7 in OLIS	--
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	--

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 AND 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	--	RPDB	--
	Same as above	Area income quintile	--	Statistics Canada Census	--
	Same as above	Rural residence	--	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, E14	OHIP ICD-9: 250 OHIP fee codes: Q040, K029, K030, K045, K046	https://pubmed.ncbi.nlm.nih.gov/11874939/

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
	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): I500, I501, I509	OHIP ICD-9: 428	https://pubmed.ncbi.nlm.nih.gov/23735455/
	Within 5 years before January 15, 2021 (time zero)	History of malignant neoplasm	ICD-10-CA (DAD, SDS, NACRS): C00-C97	--	--
	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://pubmed.ncbi.nlm.nih.gov/23560464/

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 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 90 days, but < 150 days, in the year before the index date: R849, G082, G083, G085, G090-G096, G294, G295, G323, G325, G326, G330-G333, G860-G866, H540, H740 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	https://pubmed.ncbi.nlm.nih.gov/20613656/
			Exclude kidney transplant CCI (DAD): 1PC85	Exclude kidney transplant OHIP fee codes: S435, S434 CORR treatment code: 171 plus ≥ 1 Transplanted Organ Code [1-3]: 10, 11, 12, 18, 19	https://pubmed.ncbi.nlm.nih.gov/26019887/

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
	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, I24 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	--	https://pubmed.ncbi.nlm.nih.gov/20847972/

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
	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 Flutter: ICD-10-CA: I48 Ventricular Arrhythmia & Tachycardia: ICD-10-CA: I470, I472, I490, I493 Permanent Pacemaker: CCI: 1HZ53GRNM, 1HZ53LANM, 1HZ53GRNK, 1HZ53LANK, 1HZ53GRNL, 1HZ53LANL Implantable Cardioverter-Defibrillator: CCI: 1HZ53GRFS, 1HZ53LAFS, 1HZ53SYFS, 1HZ53HAFS	--	https://pubmed.ncbi.nlm.nih.gov/19433698/ https://www.ices.on.ca/Publications/Atlases-and-Reports/2006/Canadian-Institute-for-Health-Information https://pubmed.ncbi.nlm.nih.gov/17599603/

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
	Same as above	History of pulmonary embolism, deep vein thrombosis, or other venous thromboembolism	ICD-10-CA (DAD, SDS, NACRS): I260, I269, O88201, O88202, O88203, O88204, O88209, I636, I822, I828, I829, I801, I802, I803, I808, I809, O22301, O22303, O22309, O22501, O22503, O22509, O87102, O87104, O87109, O87304, O87309, I676, I81, I820, I823, O228, O229, O878, O879 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, 3GT70KE, 3JY10VA, 3JY10VC, 3JY10VN, 3JY10VX, 3JY12VA , 3JY20WC	OHIP ICD-9: 677, 415, 671, 451, 452 AND one of the following OHIP radiological professional fee codes for a VTE diagnostic test billed within 3 days: J198, J498, J193, J493, J202, J502, J206, J506, J182, J482, X406, X407, X125, X188, X401, X405, X408, X126, X410, X231, X232, X233, X127, X413, X421, X425, J659, J660, J859, J860	--

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
Other baseline variables	Any time before January 15, 2021 (time zero)	Asthma	The ICES-derived ASTHMA database was used to identify patients with diagnosed asthma before the index date, based on 2 OHIP diagnostic codes or 1 DAD diagnostic code. ICD-10-CA: J45, J46	OHIP ICD-9: 493	https://pubmed.ncbi.nlm.nih.gov/20011725/
	Same as above	Chronic obstructive pulmonary disease (COPD)	The ICES-derived COPD database was used to identify patients with diagnosed COPD before the index date, based on 1 OHIP diagnostic code or 1 DAD diagnostic code. ICD-10-CA: J41-J44	OHIP ICD-9: 491, 492, 496	https://pubmed.ncbi.nlm.nih.gov/19863368/ *The COPD algorithm was validated in those aged ≥ 35 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-I13, I15	OHIP ICD-9: 401-405	https://pubmed.ncbi.nlm.nih.gov/20101286/

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
	Same as above	Immunocompromised (HIV or organ transplant)	--	The ICES-derived HIV database was used to identify patients with pre-existing HIV, based on 3 physician claims in 3 years. 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.	https://pubmed.ncbi.nlm.nih.gov/21738786/
	Same as above	Dementia	The ICES-derived DEMENTIA 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, 331 ODB 1 prescription for a cholinesterase inhibitor	https://pubmed.ncbi.nlm.nih.gov/27567819/

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, incontinence, nutrition issues, functional performance) and health services utilization (i.e., ≥ 2 hospital stays or ED visits, geriatrician or home care visit).	--	https://pubmed.ncbi.nlm.nih.gov/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, 773	--

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
	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, H340 Acute Ischemic Stroke: 1 hospitalization with a main diagnosis coded with one of the following codes: ICD-10-CA (DAD): I63 (except I636), I64, H341	--	http://canadianstrokenetwork.ca/en/wp-content/uploads/2014/08/Stroke_Core_ENG.pdf

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.

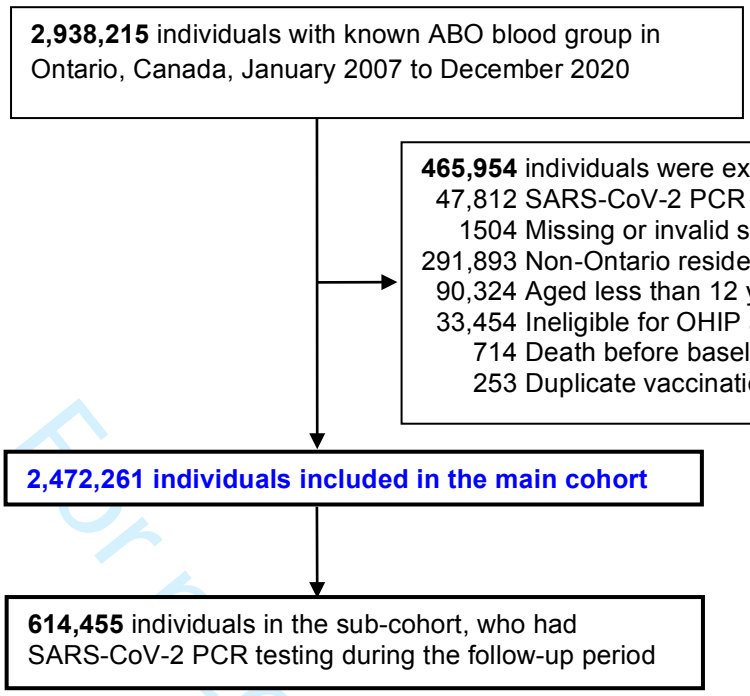


Table S2 (*Additional analysis 1*). SARS-CoV-2 vaccination and associated risk of SARS-CoV-2 infection, or severe COVID-19 (hospitalization or death) – each assessed starting at least 14 days after the first vaccination. *This analysis is limited to 614,455 individuals who had SARS-CoV-2 PCR testing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

Study outcome	Exposure state[a]	No. person-days of follow-up[a]	No. with outcome (rate per 10,000 person-days)	Unadjusted hazard ratio (95% CI%)	Adjusted hazard ratio (95% CI%)[b]
SARS-CoV-2 infection	Unvaccinated (N = 609,129)	67,185,613	51,187 (7.62)	1.00 (referent)	1.00 (referent)
	Vaccinated (N = 439,058)	27,220,438	4995 (1.84)	0.25 (0.25 to 0.26)	0.28 (0.27 to 0.29)
Severe COVID-19	Unvaccinated (N = 609,129)	71,414,615	2890 (0.40)	1.00 (referent)	1.00 (referent)
	Vaccinated (N = 439,058)	27,470,663	491 (0.18)	0.50 (0.46 to 0.56)	0.22 (0.20 to 0.25)

[a]Exposure is time-varying, therefore, some individuals may have contributed time as unvaccinated, and then subsequently, as vaccinated.
[b]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 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.

Study outcome	Stratified by blood group	Exposure state[a]	No. person-days of follow-up[a]	No. with outcome (rate per 10,000 person-days)	Adjusted hazard ratio (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)
	O	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)
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)
	O	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)

[a]Exposure is time-varying, therefore, some individuals may have contributed time as unvaccinated, and then subsequently, as vaccinated.
[b]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.

Supplementary file 3. STROBE checklist.

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
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, follow-up, 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 modifiers. 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 groupings were chosen and 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

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined 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 on exposures 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	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	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 time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Figure 2
Discussion			
Key results	18	Summarise key results with reference to study objectives	7
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of 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