Effectiveness of COVID-19 vaccines against hospitalization and death in Canada: A multiprovincial test-negative design study

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ABSTRACT

Background: A major goal of COVID-19 vaccination is to prevent severe outcomes (hospitalizations and deaths). We estimated the effectiveness of mRNA and ChAdOx1 COVID-19 vaccines against severe outcomes in four Canadian provinces between December 2020 and September 2021.

Methods: We conducted this multiprovincial retrospective test-negative study among community-dwelling adults aged ≥18 years in Ontario, Quebec, British Columbia, and Manitoba using linked provincial databases and a common study protocol. Multivariable logistic regression was used to estimate province-specific vaccine effectiveness against COVID-19 hospitalization and/or death. Estimates were pooled using random effects models.

Results: We included 2,508,296 tested subjects, with 31,776 COVID-19 hospitalizations and 5,842 deaths. Vaccine effectiveness was 83% after a first dose, and 98% after a second dose, against both hospitalization and death (separately). Against severe outcomes (hospitalization or death), effectiveness was 87% (95%CI: 71%–94%) ≥84 days after a first dose of mRNA vaccine, increasing to 98% (95%CI: 96%–99%) ≥112 days after a second dose. Vaccine effectiveness against severe outcomes for ChAdOx1 was 88% (95%CI: 75%–94%) ≥56 days after a first dose, increasing to 97% (95%CI: 91%–99%) ≥56 days after a second dose. Lower one-dose effectiveness was observed for adults aged ≥80 years and those with comorbidities, but effectiveness became comparable after a second dose. Two doses of vaccines provided very high protection for both homologous and heterologous schedules, and against Alpha, Gamma, and Delta variants.

Conclusions: Two doses of mRNA or ChAdOx1 vaccines provide excellent protection against severe outcomes of hospitalization and death.

Key words: SARS-CoV-2; hospitalization; death; vaccine effectiveness; test-negative design; Canada

INTRODUCTION

A major goal of COVID-19 vaccination is to prevent hospitalizations and deaths. Provincial COVID-19 vaccination programs in Canada have involved extended intervals between first and second doses due to vaccine supply constraints, and use of heterologous (i.e., 'mix-and-match') vaccine schedules due to concerns regarding vaccine-induced immune thrombotic thrombocytopenia associated with ChAdOx1 (AstraZeneca Vaxzevria, COVISHIELD) and variable supplies of specific vaccine products [1, 2].

Assessing COVID-19 vaccine effectiveness (VE) against severe outcomes with longer follow-up after each dose will inform our understanding of the duration of protection. Real-world effectiveness data on heterologous vaccine schedules and extended dosing intervals against severe outcomes are limited [3]. We estimated the effectiveness of mRNA (BNT162b2 [Pfizer-BioNTech Comirnaty] and mRNA-1273 [Moderna Spikevax]) and ChAdOx1 vaccines against hospitalizations and deaths, including longer follow-up periods, heterologous vaccine schedules, and extended dosing intervals.

METHODS

Study design, setting, and population

Using a common study protocol across 4 Canadian provinces, we conducted a test-negative design study [4] involving Ontario, Quebec, British Columbia (BC), and Manitoba (total population 30 million, ~79% of the Canadian population) among community-dwelling residents who sought SARS-CoV-2 testing. We included all residents aged ≥18 years, eligible for provincial health insurance, not living in long-term care, and tested for SARS-CoV-2 between

the start of vaccine availability in a province (Ontario, Quebec: 14 December 2020; BC: 15 December; Manitoba: 16 December) and 30 September 2021 and met our case or control definitions. We excluded recipients of non-Health Canada-authorized vaccines or Ad26.COV2.S (Johnson & Johnson Janssen) vaccine.

Data sources and definitions

We linked data from provincial SARS-CoV-2 laboratory testing, COVID-19 public health surveillance, COVID-19 vaccination, and health administrative datasets using unique encoded identifiers in each province at: ICES (Ontario), Institut National de Santé Publique du Québec, BC Centre for Disease Control, and the University of Manitoba Vaccine and Drug Evaluation Centre (Supplemental Tables S1 and S2).

Outcomes

Our primary outcome was COVID-19 hospitalization or death identified from notifiable disease reporting systems and/or other administrative databases. COVID-19 hospitalization was defined as hospitalization or ICU admission with a positive SARS-CoV-2 test within 14 days prior to or 3 days after hospitalization. We excluded nosocomial cases flagged in notifiable disease reporting systems and SARS-CoV-2-positive cases with specimen collection >3 days after hospital admission. COVID-19 death was defined as death with a positive SARS-CoV-2 test identified from notifiable disease reporting systems or deaths occurring within 30 days following a positive SARS-CoV-2 test or within 7 days post-mortem. Subjects with COVID-19 hospitalizations and deaths were treated as test-positive cases using the earliest of the specimen collection date, hospitalization date, or death date as the index date. We included outcomes

occurring until 30 September 2021, and included only the first positive test. Symptomatic subjects who tested negative during the study period were treated as test-negative controls using specimen collection date as index date. For controls with multiple negative tests, we randomly selected one symptomatic test-negative specimen collection date. SARS-CoV-2 lineage was determined using whole genome sequencing or screening PCR tests for various mutations to group test-positive specimens into mutually exclusive categories: Alpha, Beta, Gamma, Beta/Gamma, Delta, non-VOC SARS-CoV-2 (Supplemental methods).

COVID-19 vaccination

Information on vaccine product, date of administration, and dose number were collected from provincial COVID-19 vaccination information systems.

Covariates

Information on the following covariates were obtained from relevant data sources [5-7]: age group, sex, geographic region (Supplemental Table S3), 2-week periods of test (to control for temporal changes in virus circulation and vaccine uptake), number of RT-PCR tests during the 3 months prior to the start of the study (as a proxy for frequently tested at-risk individuals), comorbidities that increase the risk of severe COVID-19 [8], receipt of 2019–2020 and/or 2020–2021 influenza vaccination (as a proxy for health behaviours), and 4 area-level social determinants of health (median neighbourhood income, proportion of the working population employed as non-health essential workers [i.e., those unable to work from home], average number of persons per dwelling, and proportion of the population who self-identify as a visible

minority) [5]. All covariates except week of SARS-CoV-2 test were measured as of the start of the study period.

Statistical analyses

Baseline characteristics were summarized as means (standard deviation) for continuous variables and frequencies and percentages for categorical variables. Logistic regression models were used to estimate crude and adjusted odds ratios (OR) comparing the odds of being vaccinated versus unvaccinated between test-positive cases and test-negative controls separately in each province. Adjusted models accounted for all covariates listed above.

We estimated overall ORs separately for hospitalization and death but for all vaccines combined ≥14 days after a first dose (among those who had received only 1 dose at the time of testing) and ≥7 days after a second dose. We also estimated ORs by time since the most recent dose for mRNA vaccines and ChAdOx1 separately; follow-up periods were shorter after ChAdOx1 than mRNA vaccines because of fewer ChAdOx1 recipients. We conducted subgroup analysis by subject characteristics (age group, sex, presence of any comorbidity), vaccine product, and SARS-CoV-2 lineage. We also estimated ORs for varying dosing intervals among subjects who received 2 doses of mRNA vaccines.

Each province conducted analyses independently to estimate province-specific ORs. There were some variations in data sources and analyses among the provinces (Supplemental methods). We conducted a sensitivity analysis by also including hospitalizations and deaths from administrative databases in Ontario.

Meta-analyses

We pooled the log OR estimates from each province using random-effects models with inverse variance weighting [9]. We used random-effects models because provinces differed slightly in population demographics and vaccination programs. We converted ORs to VE using the formula: VE=(1–OR)*100. We assessed between-province heterogeneity using the I^2 statistic. Pooled VE estimates were not presented if based on just one province. Meta-analyses were conducted using the meta package in R version 4.1.2 [10].

RESULTS

Overall, we included 2,508,296 community-dwelling SARS-CoV-2-tested subjects (Table 1). We identified 33,420 COVID-19-associated severe outcomes; receipt of ≥1 dose of a COVID-19 vaccine ranged from 13% to 20% among test-positive severe outcome cases, and from 40% to 46% among symptomatic test-negative controls (Supplemental Table S4). Cases were more likely to be older, male, have had no SARS-CoV-2 tests during the 3 months before the vaccination program, have a comorbidity, have received an influenza vaccine (Ontario, Quebec), and more likely to reside in neighbourhoods with lower income/more material deprivation, more people per dwelling, and greater proportions of essential workers (Ontario, BC), and greater proportions of visible minorities than controls. Vaccinated subjects were more likely to be older, have a comorbidity, have received influenza vaccination, and less likely to be male than unvaccinated subjects (Supplemental Table S5). Most vaccinated subjects received BNT162b2 (Supplemental Table S6).

Vaccine effectiveness

In pooled analyses, the adjusted VE (aVE) was 83% (95% confidence interval [CI]: 78–87%) against hospitalization and 83% (95%CI: 72–90%) against death after a first dose, increasing to 98% against both hospitalization (95%CI: 96–99%) and death (95%CI: 95–99%) after a second dose (Figure 1, Supplemental Table S7).

Against hospitalization or death, the pooled aVE for mRNA vaccines increased over time from 43% (95%CI: 25–57%) 0–13 days after a first dose to 87% (95%CI: 71–94%) ≥84 days after a first dose; after receiving a second dose, pooled aVE increased from 93% (95%CI: 88–96%) at 0–6 days to 98% (95%CI: 96–99%) at ≥112 days (Figure 2A, Supplemental Table 7). The pooled aVE for ChAdOx1 increased from 37% (95%CI: 20–51%) 0–13 days after a first dose to 88% (95%CI: 75–94%) ≥56 days after a first dose; aVE was 97% (95%CI: 91–99%) ≥56 days after a second dose (Figure 2B, Supplemental Table S8).

In subgroup analyses, the pooled aVE was lower for adults aged ≥80 years versus younger adults aged 18–59 years, and in subjects with comorbidities versus those without comorbidities ≥14 days after a first dose; however, aVE became comparable across all subgroups ≥7 days after a second dose (Figure 3A, Supplemental Table S9). The pooled aVE against severe outcomes was >80% ≥14 days after a first dose for all 3 vaccines, which increased to ≥97% ≥7 days after a second dose. aVE was similar ≥7 days after a second dose of a mixed mRNA or ChAdOx1/mRNA mixed schedule (Figure 3B, Supplemental Table S10). aVE against severe outcomes caused by VOCs was lowest against Beta at 61% and highest against Delta at 89% ≥14

days after a first dose, and increased to ≥97% against Alpha, Gamma, and Delta ≥7 days after a second dose (Figure 3C, Supplemental Table S11).

The pooled aVE for mRNA vaccines 7–55 days after a second dose increased from 94% with a dosing interval of 21–34 days to ≥98% with a longer dosing interval, although 95% confidence intervals for aVE overlapped (Figure 4, Supplemental Table S12). aVE was maintained at ≥97% with longer dosing intervals from 56 days through ≥112 days after a second dose.

Although we observed heterogeneity between provinces, as reflected by I^2 statistics for most models (Supplemental Table S13), all province-specific VE estimates suggest the vaccines were significantly protective with some variation in the magnitude.

In sensitivity analyses including severe outcomes from administrative data in Ontario, we identified 22,759 severe outcomes; pooled sensitivity analyses yielded VE estimates similar to the primary analyses (Supplemental Table S14).

DISCUSSION

We found high and very high effectiveness against hospitalization and death with 1 (83%) and 2 (98%) doses of COVID-19 vaccines, respectively. mRNA and ChAdOx1 vaccines had comparable effectiveness after first and second doses; protection increased or remained relatively stable over time after each dose without noticeable waning over this relatively short period of observation. In subgroup analyses, we observed lower one-dose VE for adults aged ≥80 years and those with comorbidities, but VE became comparable after a second dose. Two doses

provided very high protection against Alpha, Gamma, and Delta variants. We observed very high level of protection with both homologous and heterologous schedules. Finally, our findings suggest that lengthening dosing intervals minimally impacted on VE against severe outcomes.

Our pooled aVE estimates against hospitalization and against death ≥14 days after a single dose were higher than reported estimates in a systematic review and meta-analysis of studies published up to 22 July 2021 (61% [95%CI: 41–81%] against hospitalization, 44% [95%CI: 23–64%] against death) [11]. Our 1-dose VE estimates may have been higher due to a longer period of observation before second dose receipt, as VE may still be rising in the initial weeks post first dose receipt. Also, their VE estimates included other COVID-19 vaccines (e.g., CoronaVac) and different populations (e.g., general population, healthcare workers, older adults, nursing home residents) without stratification by subgroup. VE estimates ≥7 days after a second dose in that study (93% [95%CI: 84–100%] against hospitalization, 97% [95%CI: 95–98%] against death) were comparable to our estimates. Another systematic review and meta-analysis that included published literature up to 25 August 2021 reported a pooled VE of 91% (95%CI: 85%–95%) and 94% (95%CI: 83%–98%) against hospitalization and a composite of severe outcomes due to Delta, respectively, after a second dose [12].

Against hospitalization or death, we observed sustained pooled aVE of 87% for mRNA vaccines at ≥12 weeks, and 88% for ChAdOx1 at ≥8 weeks with wider 95%CIs over time after a first dose. Similarly, pooled aVE of 98% at ≥16 weeks for mRNA vaccines and 97% at ≥8 weeks for ChAdOx1 vaccine after a second dose was observed. However, there were fewer vaccinated cases with longer follow-up compared to shorter follow-up, and very few subjects had an

excessively long follow-up. Similar high VE was also reported against hospitalization and death caused by Delta in England: 95% VE 15–19 weeks after a second dose of BNT162b2 and 2–9 weeks after a second dose of ChAdOx1 [13]. Sustained VEs of 84–89% against hospitalizations, or hospitalizations and deaths up to 24 weeks were observed with 2 doses of mRNA vaccines in the USA [14, 15] and Qatar [16]. A high VE of ≥90% for 28 weeks for mRNA vaccines and ChAdOx1 was also maintained against hospitalizations in Quebec and BC [3]. However, some waning of protection against hospitalizations and deaths after a second dose has been reported. In England, VE against Delta variant-related hospitalization and death decreased from 99% at 2–9 weeks to 92% at ≥20 weeks for BNT162b2, with more pronounced decline for ChAdOx1 from 95% at 2–9 weeks to 80–85% at ≥20 weeks [13]. Protection against hospitalizations and deaths for BNT162b2 was maintained for 6 months with possible decline at ≥7 months in Qatar [16]. In Sweden, VE against hospitalization or mortality for mRNA or ChAdOx1 vaccines declined from 89% (95%CI: 82–93%) at 15–30 days to 64% (95%CI: 44–77%) ≥121 days after a second dose [17]. In Italy, VE against hospitalizations and deaths declined from 87% and 84%, respectively, within 6 months of receiving 2 doses (mainly mRNA and ChAdOx1) to 52% and 34% after 6 months [18]. Confounding by indication resulting from averaging VE across subgroups with different exposure and infection risk, vaccination priority, clinical risk, and increased transmission and/or shorter interval of 3 weeks between doses with longer follow-up and rapid uptake of vaccines may explain the waning of VE observed in these studies [13, 19].

Our finding of comparable VE against severe outcomes in older and younger adults and in people with and without comorbidities after a second dose aligns with findings from previous studies [5, 20-22]. However, a lower overall VE of 88% (95%CI: 82–92%) was also reported

previously in older adults aged ≥80 years compared to ≥94% VE in adults aged <80 years [3]. We found good overall protection against hospitalizations or deaths caused by Alpha and Delta (≥84%) ≥14 days after a first dose, and excellent protection (≥98%) ≥7 days after a second dose. Similar high VEs against Alpha (84–97%) and Delta (92–98%) with a second dose have been reported [23-26].

We observed similar high pooled aVE (≥97%) against severe outcomes ≥7 days after receiving a second dose of homologous BNT162b2, mRNA-1273, or ChAdOx1 vaccine series; these estimates were similar to our pooled aVE after receiving mixed mRNA (98%) or ChAdOx1/mRNA mixed schedule (99%), adding to the evidence of real-world effectiveness of heterologous dosing schedules. Our findings corroborate previously reported VE estimates against hospitalization using homologous and heterologous vaccine schedules from Quebec and BC [3]. Countries and jurisdictions with low 2-dose vaccine coverage and/or facing limited supplies of specific vaccine products could benefit from implementing heterologous vaccine schedules to increase population protection against severe outcomes.

We observed only a slight difference in VE between short and extended dosing intervals for mRNA vaccines as reflected by only 4–5% higher VE with a dosing interval of ≥35 days compared to 21–34 days, and 95%CIs overlapped. Persistently high VE was observed with longer follow-up across different dosing interval categories without evidence of considerable waning. Contrary to our findings, a previous study using data from Quebec and BC observed higher VE against hospitalizations ≥14 days after 2 doses of mRNA vaccines with a dosing interval of 7–8 weeks (98% [95%CI: 97–99%] and 99% [95%CI: 98–99%], respectively)

compared to a dosing interval of 3–4 weeks (87% [95%CI: 79–92%] and 93% [95%CI: 87–96%], respectively) [3]. This likely resulted from differences in methods and follow-up time between the studies. A higher VE was also observed with >6 weeks dosing interval compared to the manufacturer-specified 3- to 4-week interval for mRNA vaccines against SARS-CoV-2 infection [3, 27, 28]. Deciding on the optimal interval between doses must weigh the benefits of delaying second doses against the risks of SARS-CoV-2-related outcomes in the context of local incidence, vaccine coverage, and vaccine supply.

This study has some limitations. First, while the test-negative design accounts for differences in healthcare-seeking behaviour, indications for testing and risks of exposure to SARS-CoV-2 infection between test-positive cases and test-negative controls may differ. Testing indications also varied between the provinces and over the study period. We adjusted for biweekly period of test and number of prior tests to account for these. Our observed pooled aVE of 43% 0–13 days after a first dose of mRNA vaccine might suggest a positively-biased estimate that may result from testing vaccinated individuals for vaccine-associated COVID-19-like adverse events; similar positively-biased VEs against severe outcomes were observed previously [5, 29, 30]. However, it is also possible that while a first dose does not prevent infection during this time, it may provide some protection against severe outcomes due to the 1-3 weeks it takes to develop severe outcomes following infection. Second, although healthcare utilization and thresholds for hospitalization may vary between and within jurisdictions, hospital capacity was maintained to admit patients requiring hospitalization and we do not expect differential under- or over-estimation of severe outcomes, particularly death, with respect to COVID-19 vaccination status. Third, despite a common study protocol, there is likely heterogeneity among provinces in terms

of differences in populations, vaccination programs (rollout logistics and priority groups), SARS-CoV-2 testing criteria, data capture, and covariates adjusted; we used random-effects models to account for statistical heterogeneity. Fourth, given the observational nature of the study, residual confounding remains possible despite adjustment for a number of potential confounders. Fifth, we were unable to differentiate hospitalizations *due to* COVID-19 from hospitalizations *with* COVID-19 in all participating provinces; the latter is more common with Omicron and tends to lower VE against severe outcomes [31]. We believe this bias was minimal in our VE estimates from the pre-Omicron period. Finally, our VE estimates may not apply to Omicron-related severe outcomes.

Our results provide strong evidence of excellent protection against hospitalizations and deaths with 2 doses of mRNA or ChAdOx1 vaccines during the pre-Omicron period. We found relatively stable protection through ≥16 weeks for mRNA vaccines and ≥8 weeks for ChAdOx1. Our findings further support the interchangeability of COVID-19 vaccines. Likewise, the sustained protection from extended dosing intervals lends evidence to delay administration of second doses in settings facing limited vaccine supply.

NOTES

Contributors

JCK, SN, GDS, CHR, NZ, MT designed and oversaw the study. SN, YF, HAVG, and GZ conducted province-specific analyses. SN conducted the meta-analyses and drafted the manuscript. All authors contributed to the analysis plan, interpreted the results, critically reviewed and edited the manuscript, approved the final version, and agreed to be accountable for all aspects of the work.

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Ethics approval

ICES is a prescribed entity under Ontario's Personal Health Information Protection Act (PHIPA). Section 45 of PHIPA authorizes ICES to collect personal health information, without consent, for the purpose of analysis or compiling statistical information with respect to the management of, evaluation or monitoring of, the allocation of resources to or planning for all or

part of the health system. Projects that use data collected by ICES under section 45 of PHIPA, and use no other data, are exempt from REB review. The use of the data in this project is authorized under section 45 and approved by ICES' Privacy and Legal Office.

Data sharing

Data used in this study are from the Manitoba Population Research Data Repository housed at the Manitoba Centre for Health Policy, University of Manitoba and were derived from data provided by Manitoba Health. The authors acknowledge the Manitoba Centre for Health Policy for use of data contained in the Manitoba Population Research Data Repository under project # 2020-037 (HIPC # 2020/2021–04, REB # HS23859 (H2020:181)). Data used in this article was derived from administrative health and social data as a secondary use. The dataset for Ontario from this study is held securely in coded form at ICES. While legal data sharing agreements between ICES and data providers (e.g., healthcare organizations and government) prohibit ICES from making the dataset publicly available, access may be granted to those who meet pre-specified criteria for confidential access, available at www.ices.on.ca/DAS (email: das@ices.on.ca). The full dataset creation plan and underlying analytic code are available from the authors upon request, understanding that the computer programs may rely upon coding templates or macros that are unique to ICES and are therefore either inaccessible or may require modification. The data was provided under specific data sharing agreements only for approved use at the Manitoba Centre for Health Policy (MCHP). The original source data is not owned by the researchers or MCHP and as such cannot be provided to a public repository. The original data source and approval for use has been noted in the acknowledgments of the article. Where necessary, source data specific to this article or project may be reviewed at MCHP with the consent of the original data providers, along with the required privacy and ethical review bodies.

Disclaimers

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Declaration of interests

CHR has received an unrestricted research grant from Pfizer for an unrelated study. SMM received research funding from Assurex, GSK, Merck, Pfizer, Roche and Sanofi for unrelated studies and is/was a member of advisory boards for GSK, Merck, Sanofi and Seqirus and reports consulting fees from these companies. MK received contracts to identify SARS-CoV-2 infected blood donors from Abcellera and to evaluate SARS-CoV-2 serology tests from Siemens; both unrelated to this study. GDS received a grant from Pfizer for an anti-meningococcal immunogenicity study not related to this study. MT reports grants or contracts from CIHR and Ontario Ministry of Health unrelated to this work; and consulting fees from CADTH and Green Shield Canada. NZD reports payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Abbvie and participation on a Data Safety Monitoring Board or Advisory Board for Abbvie. The other authors declare no conflicts of interest.

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Tables and figures:

Table 1: Baseline characteristics of study subjects in Ontario, Quebec, British Columbia, and Manitoba

Characteristic	Ontario, n (%)[a] (N=557,220)	Quebec, n (%)[a] (N=954,208)	British Columbia, n (%)[a] (N=876,397)	Manitoba, n (%)[a] (N=120,471)
BNT162b2 Pfizer-BioNTech Comirnaty				
≥14 days after dose 1	58,315 (10.5)	124,274 (13.0)	101,851 (11.6)	34,622 (28.7)
≥7 days after dose 2	92,771 (16.6)	151,722 (15.9)	138,192 (15.8)	18,061 (15.0)
Interval between 2 doses (days), median (IQR)	56 (38, 75)	70 (58, 91)	63 (55, 76)	45 (22, 64)
mRNA-1273 Moderna Spikevax				
≥14 days after dose 1	15,196 (2.7)	32,377 (3.4)	28,452 (3.2)	12,480 (10.4)
≥7 days after dose 2	27,798 (5.0)	41,415 (4.3)	35,915 (4.1)	7,832 (6.5)
Interval between 2 doses(days), median (IQR)	48 (35, 62)	63 (56, 78)	61 (52, 72)	38 (31, 46)
ChAdOx1 AstraZeneca Vaxzevria[b]				
≥14 days after dose 1	5,071 (0.9)	9689 (1.0)	8,938 (1.0)	5,916 (4.9)
≥7 days after dose 2	1,219 (0.2)	3699 (0.4)	4,590 (0.5)	275 (0.2)
Interval between 2 doses(days), median (IQR)	65 (59, 72)	59 (55, 65)	60 (56, 63)	61 (38, 71)
ChAdOx1 COVISHIELD				
≥14 days after dose 1	2,554 (0.5)	3,911 (0.4)	3,957 (0.5)	-

≥7 days after dose 2	33 (0.0)	10 (0.0)	263 (0.0)	-
Interval between 2 doses(days), median (IQR)	76 (38, 81)	71 (57, 77)	66 (57, 71)	-
Age (years), mean (standard deviation)	44 (18)	47 (17)	45 (18)	44 (17)
Age group (years)				
18–29	141,488 (25.4)	175,744 (18.4)	210,248 (24.0)	30,711 (25.5)
30–39	128,416 (23.0)	217,384 (22.8)	197,183 (22.5)	28,476 (23.6)
40–49	92,740 (16.6)	185,032 (19.4)	143,403 (16.4)	20,902 (17.4)
50–59	80,799 (14.5)	138,724 (14.5)	123,970 (14.1)	16,635 (13.8)
60–69	58,508 (10.5)	126,632 (13.3)	99,396 (11.3)	12,891 (10.7)
70–79	33,004 (5.9)	74,199 (7.8)	62,240 (7.1)	6,931 (5.8)
≥80	22,265 (4.0)	36,493 (3.8)	39,957 (4.6)	3,925 (3.3)
Male sex	237,038 (42.5)	383,234 (40.2)	394,672 (45.0)	51,780 (43.0)
Number of tests in previous 3 months				
0	406,271 (72.9)	714,551 (74.9)	740,569 (84.5)	89,782 (74.5)
1	105,529 (18.9)	171,300 (18.0)	102,832 (11.7)	24,934 (20.7)
≥2	45,420 (8.2)	68,357 (7.2)	32,996 (3.8)	5,755 (4.8)
Any comorbidity[c]	262,241 (47.1)	307,907 (32.3)	330,599 (37.7)	47,103 (39.1)
Receipt of 2019-2020 and/or 2020-2021 influenza vaccination	185,440 (33.3)	260,925 (27.3)	N/A	56,247 (46.7)

Neighbourhood income quintile[d]				
1 (lowest)	100,810 (18.1)	166,800 (17.5)	111,788 (12.8)	21,938 (18.2)
2	108,090 (19.4)	185,658 (19.5)	151,657 (17.3)	23,308 (19.3)
3	111,753 (20.1)	196,837 (20.6)	165,278 (18.9)	23,230 (19.3)
4	114,904 (20.6)	203,589 (21.3)	187,753 (21.4)	23,117 (19.2)
5 (highest)	119,128 (21.4)	201,324 (21.1)	170,276 (19.4)	24,129 (20.0)
Unknown/missing	2,535 (0.5)	-	89,645 (10.2)	4,749 (3.9)
Essential workers quintile[e]				
1 (0%–32.5%)	103,249 (18.5)	220,241 (23.1)	95,159 (10.9)	25,333 (21.0)
2 (32.5%–42.3%)	126,153 (22.6)	218,661 (22.9)	161,535 (18.4)	27,984 (23.2)
3 (42.3%–49.8%)	115,880 (20.8)	195,285 (20.5)	152,624 (17.4)	23,107 (19.2)
4 (50.0%–57.5%)	108,902 (19.5)	171,272 (17.9)	137,267 (15.7)	22,571 (18.7)
5 (57.5%–100%)	99,179 (17.8)	148,749 (15.6)	124,483 (14.2)	19,598 (16.3)
Unknown/missing	3,857 (0.7)	-	205,329 (23.4)	385 (0.3)
Persons per dwelling quintile[f]				
1 (0–2.1)	101,530 (18.2)	192,060 (20.1)	181,303 (20.7)	30,301 (25.2)
2 (2.2–2.4)	100,405 (18.0)	143,369 (15.0)	147,314 (16.8)	19,583 (16.3)
3 (2.5–2.6)	71,933 (12.9)	165,670 (17.4)	152,321 (17.4)	20,084 (16.7)
4 (2.7–3.0)	133,095 (23.9)	239,881 (25.1)	158,033 (18.0)	25,418 (21.1)

5 (3.1–5.7)	146,240 (26.2)	213,228 (22.3)	186,204 (21.2)	23,207 (19.3)
Unknown/missing	4,017 (0.7)	-	51,222 (5.8)	385 (0.3)
Self-identified visible minority quintile[g]				
1 (0.0%–2.2%)	93,149 (16.7)	223,858 (23.5)	100,472 (11.5)	18,289 (15.2)
2 (2.2%–7.5%)	102,423 (18.4)	148,256 (15.5)	147,284 (16.8)	23,194 (19.3)
3 (7.5%–18.7%)	101,805 (18.3)	218,744 (22.9)	178,848 (20.4)	24,346 (20.2)
4 (18.7%–43.5%)	114,781 (20.6)	199,297 (20.9)	204,378 (23.3)	26,293 (21.8)
5 (43.5%–100%)	141,214 (25.3)	164,053 (17.2)	195,193 (22.3)	26,471 (22.0)
Unknown/missing	3,848 (0.7)	-	50,222 (5.7)	385 (0.3)
SARS-CoV-2 cases with severe outcomes	17,437 (3.1)	7,854 (0.8)	5,928 (0.7)	2,201 (1.8)
SARS-CoV-2 lineage for those testing positive[h]				
Non-VOC	5,312 (30.5)	-	519 (8.8)	995 (45.2)
Alpha (B.1.1.7)	7,033 (40.3)	1,575 (20.1)	869 (14.7)	783 (35.6)
Beta/Gamma (B.1.351 or P.1)	226 (1.3)	-	227 (3.8)	22 (1.0)
Beta (B.1.351)	166 (1.0)	-	5 (0.1)	8 (0.4)
Gamma (P.1)	382 (2.2)	-	678 (11.4)	14 (0.6)
Delta (B.1.617.2)	1,684 (9.7)	585 (7.4)	1,257 (21.2)	107 (4.9)
Unspecified	-	-	-	294 (13.4)

[a]Proportion reported, unless stated otherwise.

[b]AstraZeneca Vaxzevria and COVISHIELD vaccines reported only as ChAdOx1 in Manitoba.

[c]Comorbidities include chronic respiratory diseases, chronic heart diseases, hypertension, diabetes, immunocompromising conditions due to underlying diseases or therapy, autoimmune diseases, chronic kidney disease, advanced liver disease, dementia/frailty and history of stroke or transient ischemic attack.

[d]Neighbourhood income quintile has variable cut-off values in each city/Census area to account for cost of living. A dissemination area (DA) being in quintile 1 means it is among the lowest 20% of DAs in its city by income. Material deprivation index quintile used in British Columbia; quintile 1 represents 'most deprived' and quintile 5 represents 'least deprived'.

[e]Percentage of people in the area working in the following occupations: sales and service occupations; trades, transport and equipment operators and related occupations; natural resources, agriculture, and related production occupations; and occupations in manufacturing and utilities. Census counts for people are randomly rounded up or down to the nearest number divisible by 5, which causes some minor imprecision.

[f]Range of persons per dwelling.

[g]Percentage of people in the area who self-identified as a visible minority. Census counts for people are randomly rounded up or down to the nearest number divisible by 5, which causes some minor imprecision.

[h]Proportions calculated using the total number of SARS-CoV-2 cases with severe outcomes as the denominator.

Figure legends:

Figure 1: Province-specific and pooled adjusted vaccine effectiveness ≥14 days after a first dose and ≥7 days after receiving a second dose against hospitalization (panel A) and death (panel B) in Ontario, Quebec, British Columbia, and Manitoba.

Figure 2: Pooled adjusted vaccine effectiveness against severe outcomes of hospitalization or death for mRNA (panel A) and ChAdOx1 (panel B) vaccines in Ontario, Quebec, British Columbia, and Manitoba.

Figure 3: Pooled adjusted vaccine effectiveness against severe outcomes of hospitalization or death ≥14 days after a first dose and ≥7 days after receiving a second dose by subject characteristics (panel A), vaccine product (panel B) and SARS-CoV-2 lineage (panel C) in Ontario, Quebec, British Columbia, and Manitoba.

Figure 4: Pooled adjusted vaccine effectiveness against severe outcomes of hospitalization or death for subjects who received two doses of an mRNA vaccine by various intervals between vaccine doses and time since the second dose in Ontario, Quebec, British Columbia, and Manitoba.

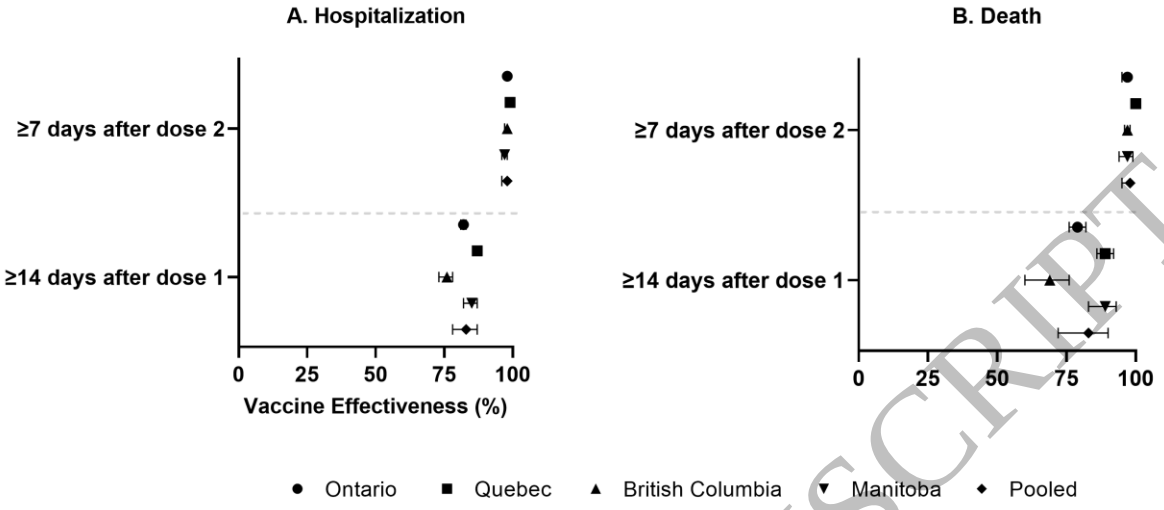

Figure 1
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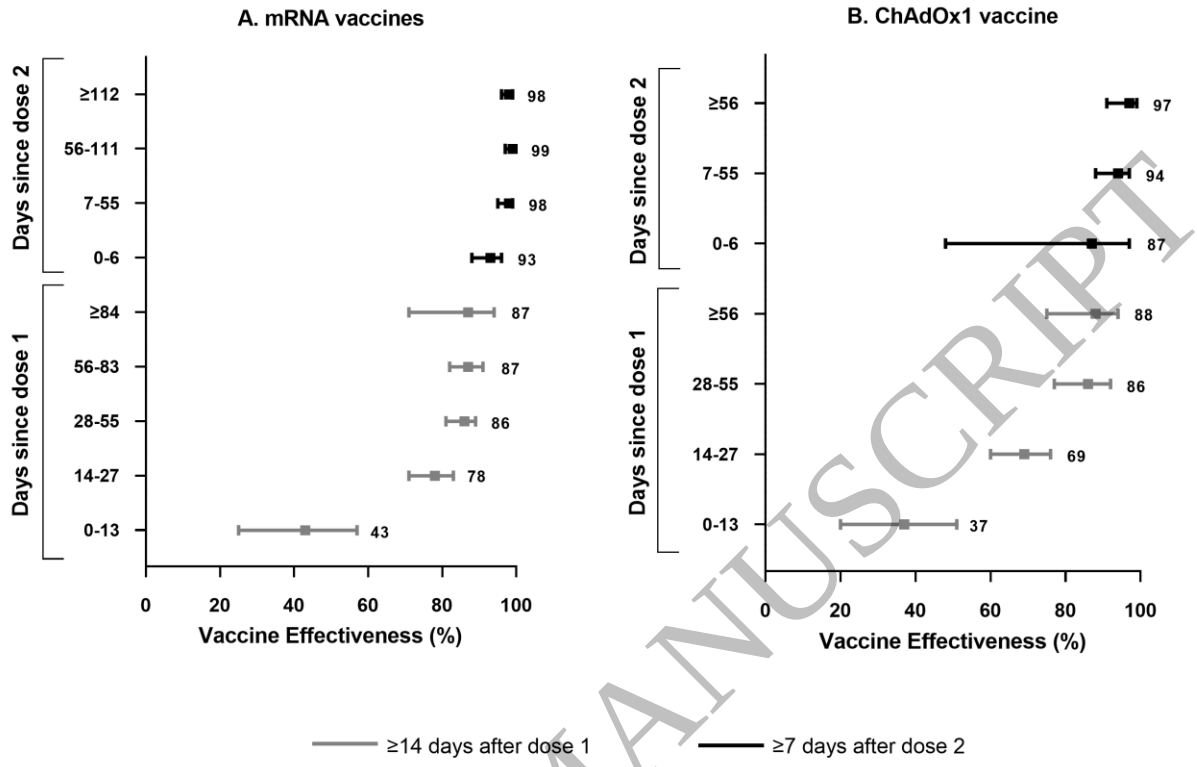

Figure 2
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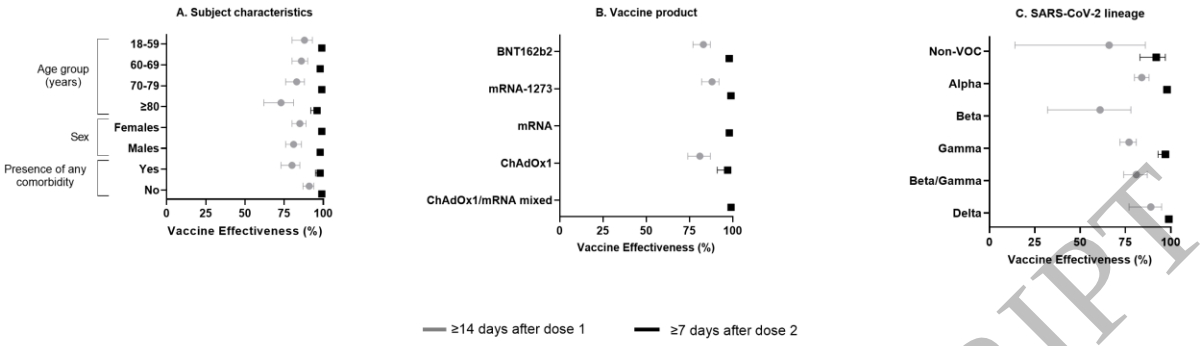

Figure 3
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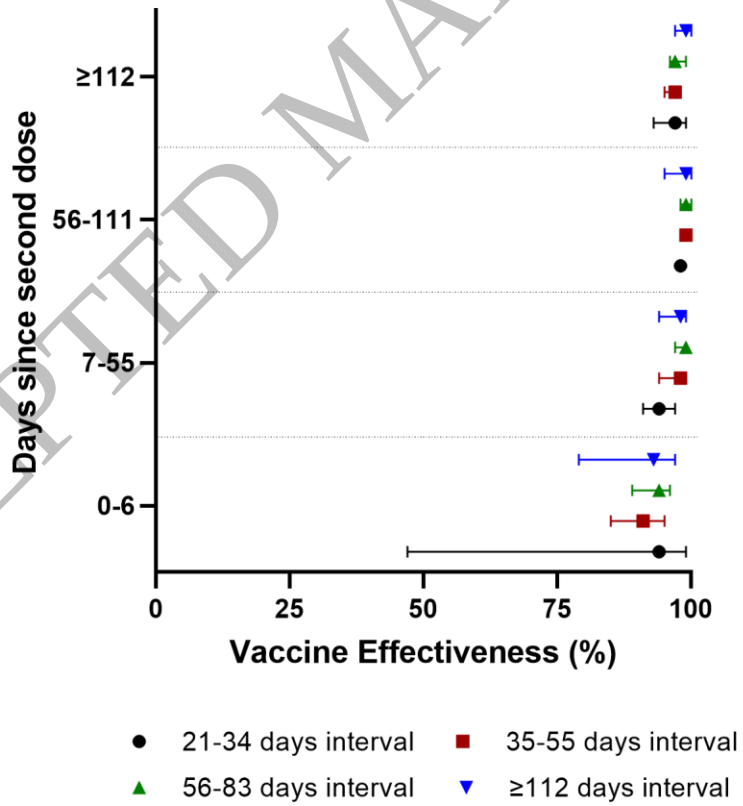

Figure 4
106x115 mm (x DPI)