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Effectiveness of Coronavirus Disease 2019 Vaccines Against Hospitalization and Death in Canada: A Multiprovincial, Test-Negative Design Study

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Background. A major goal of coronavirus disease 2019 (COVID-19) vaccination is to prevent severe outcomes (hospitalizations and deaths). We estimated the effectiveness of messenger RNA (mRNA) and ChAdOx1 COVID-19 vaccines against severe outcomes in 4 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 participants, with 31 776 COVID-19 hospitalizations and 5842 deaths. Vaccine effectiveness was 83% after a first dose and 98% after a second dose against both hospitalization and death (separately). Against severe outcomes, effectiveness was 87% (95% confidence interval [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 1-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 vaccine provide excellent protection against severe outcomes.

Keywords. SARS-CoV-2; hospitalization; death; vaccine effectiveness; test-negative design.

A major goal of coronavirus disease 2019 (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 (ie, "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 messenger RNA (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.

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METHODS

Study Design, Setting, and Population

Using a common study protocol across 4 Canadian provinces, we conducted a test-negative design study [4] that involved Ontario, Quebec, British Columbia (BC), and Manitoba (total population 30 million, approximately 79% of the Canadian population) among community-dwelling residents who sought severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) testing. We included all residents aged ≥18 years, eligible for provincial health insurance, not living in long-term care, 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 (Janssen/Johnson & Johnson) 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 (formerly the Institute for Clinical Evaluative Sciences; Ontario), Institut National de Santé Publique du Québec, BC Centre for Disease Control, and the University of Manitoba Vaccine and Drug Evaluation Centre (Supplementary Tables 1 and 2).

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 intensive care unit 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 death occurring within 30 days following a positive SARS-CoV-2 test or within 7 days postmortem. Participants 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 that occurred until 30 September 2021 and included only the first positive test. Symptomatic participants who tested negative during the study period were treated as test-negative controls using specimen collection date as the index date. For controls with multiple negative tests, we randomly selected 1 symptomatic test-negative specimen collection date. SARS-CoV-2 lineage was determined using whole-genome sequencing or screening polymerase chain reaction (PCR) tests for various mutations to group test-positive specimens into mutually exclusive categories: Alpha, Beta, Gamma, Beta/Gamma, Delta, non-variant of concern (VOC) SARS-CoV-2 (Supplementary 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 (Supplementary Table 3), 2-week periods of test (to control for temporal changes in virus circulation and vaccine uptake), number of reverse-transcription 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 behaviors), and 4 area-level social determinants of health (median neighborhood income, proportion of the working population employed as nonhealth essential workers [ie, 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 (ORs) comparing the odds of being vaccinated vs 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 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 participant characteristics (age group, sex, presence of any comorbidity), vaccine product, and SARS-CoV-2 lineage. We also estimated ORs for varying dosing intervals among participants 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 (Supplementary

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 1 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 participants (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 (Supplementary Table 4). 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 neighborhoods with lower income/more material deprivation, more people per dwelling, greater proportions of essential workers (Ontario, BC), and greater proportions of visible minorities than controls. Vaccinated participants were more likely to be older, have a comorbidity, have received influenza vaccination, and less likely to be male than unvaccinated participants (Supplementary Table 5). Most vaccinated participants received BNT162b2 (Supplementary Table 6).

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, Supplementary Table 7).

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 2*A*, Supplementary 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 2*B*, Supplementary Table 8).

In subgroup analyses, the pooled aVE was lower for adults aged ≥80 years vs younger adults aged 18–59 years and in participants with comorbidities vs those without comorbidities ≥14 days after a first dose; however, aVE became comparable across all subgroups ≥7 days after a second dose (Figure 3*A*, Supplementary Table 9). 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. The aVE was similar ≥7 days after a second dose of a mixed mRNA or ChAdOx1/mRNA mixed schedule (Figure 3*B*, Supplementary Table 10). The 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 3*C*, Supplementary Table 11).

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% CIs for aVE overlapped (Figure 4, Supplementary Table 12). The 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 (Supplementary Table 13), all province-specific VE estimates suggest that the vaccines were significantly protective with some variation in the magnitude.

In sensitivity analyses that included severe outcomes from administrative data in Ontario, we identified 22 759 severe outcomes; pooled sensitivity analyses yielded VE estimates similar to those from the primary analyses (Supplementary Table 14).

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 1-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 a very high level of protection with both homologous and heterologous schedules. Finally, our findings suggest that lengthening dosing intervals had a minimal impact on VE against severe outcomes.

Our pooled aVE estimates against hospitalization and death ≥14 days after a single dose were higher than reported estimates in a systematic review and meta-analysis of studies

Table 1. Baseline Characteristics of Study Participants 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 d after dose 1	58 315 (10.5)	124 274 (13.0)	101 851 (11.6)	34 622 (28.7)
≥7 d after dose 2	92 771 (16.6)	151 722 (15.9)	138 192 (15.8)	18 061 (15.0)
Interval between 2 doses, median (IQR), d	56 (38, 75)	70 (58, 91)	63 (55, 76)	45 (22, 64)
mRNA-1273 Moderna Spikevax				
≥14 d after dose 1	15 196 (2.7)	32 377 (3.4)	28 452 (3.2)	12 480 (10.4)
≥7 d after dose 2	27 798 (5.0)	41 415 (4.3)	35 915 (4.1)	7832 (6.5)
Interval between 2 doses, median (IQR), d	48 (35, 62)	63 (56, 78)	61 (52, 72)	38 (31, 46)
ChAdOx1 AstraZeneca Vaxzevria[b]				
≥14 d after dose 1	5071 (0.9)	9689 (1.0)	8938 (1.0)	5916 (4.9)
≥7 d after dose 2	1219 (0.2)	3699 (0.4)	4590 (0.5)	275 (0.2)
Interval between 2 doses, median (IQR), d	65 (59, 72)	59 (55, 65)	60 (56, 63)	61 (38, 71)
ChAdOx1 COVISHIELD				
≥14 d after dose 1	2554 (0.5)	3911 (0.4)	3957 (0.5)	…
≥7 d after dose 2	33 (0.0)	10 (0.0)	263 (0.0)	…
Interval between 2 doses, median (IQR), d	76 (38, 81)	71 (57, 77)	66 (57, 71)	…
Age, mean (standard deviation), y	44 (18)	47 (17)	45 (18)	44 (17)
Age group, y				
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)	6931 (5.8)
≥80	22 265 (4.0)	36 493 (3.8)	39 957 (4.6)	3925 (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 mo				
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)	5755 (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)
Neighborhood 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	2535 (0.5)	…	89 645 (10.2)	4749 (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	3857 (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	4017 (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)

Table 1. Continued

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)
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	3848 (0.7)	…	50 222 (5.7)	385 (0.3)
SARS-CoV-2 cases with severe outcomes	17 437 (3.1)	7854 (0.8)	5928 (0.7)	2201 (1.8)
SARS-CoV-2 lineage for those testing positive[h]				
Non-variant of concern	5312 (30.5)	…	519 (8.8)	995 (45.2)
Alpha (B.1.1.7)	7033 (40.3)	1575 (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)	1684 (9.7)	585 (7.4)	1257 (21.2)	107 (4.9)
Unspecified	…	…	…	294 (13.4)

Abbreviations: IQR, interquartile range; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[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]Neighborhood income quintile has variable cutoff 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.

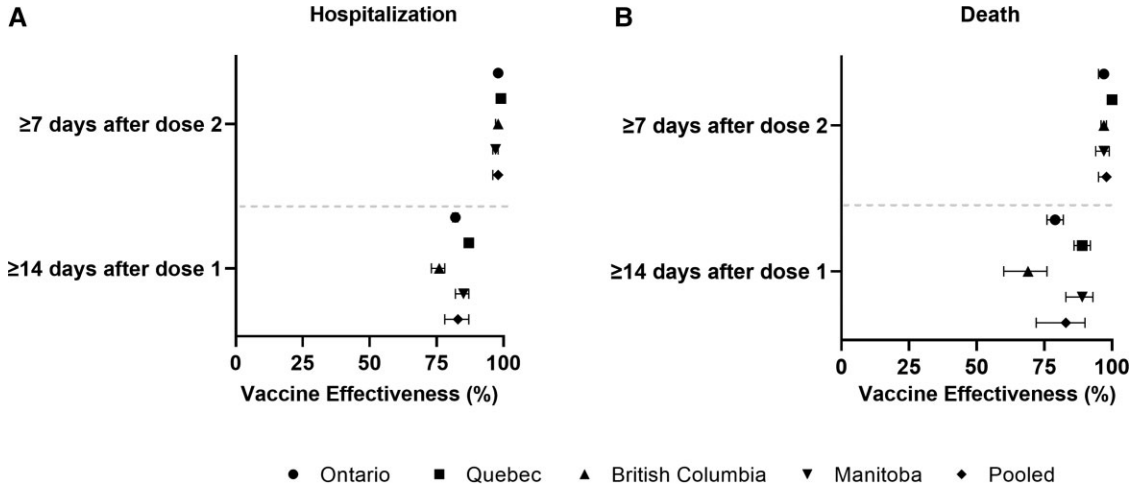

Figure 1. Province-specific and pooled adjusted vaccine effectiveness ≥14 days after a first dose and ≥7 days after a second dose against hospitalization *(A)* and death *(B)* in Ontario, Quebec, British Columbia, and Manitoba.

published up to 22 July 2021 (61%; 95% CI, 41%–81% against hospitalization and 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 (eg, CoronaVac) and different populations (eg, 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

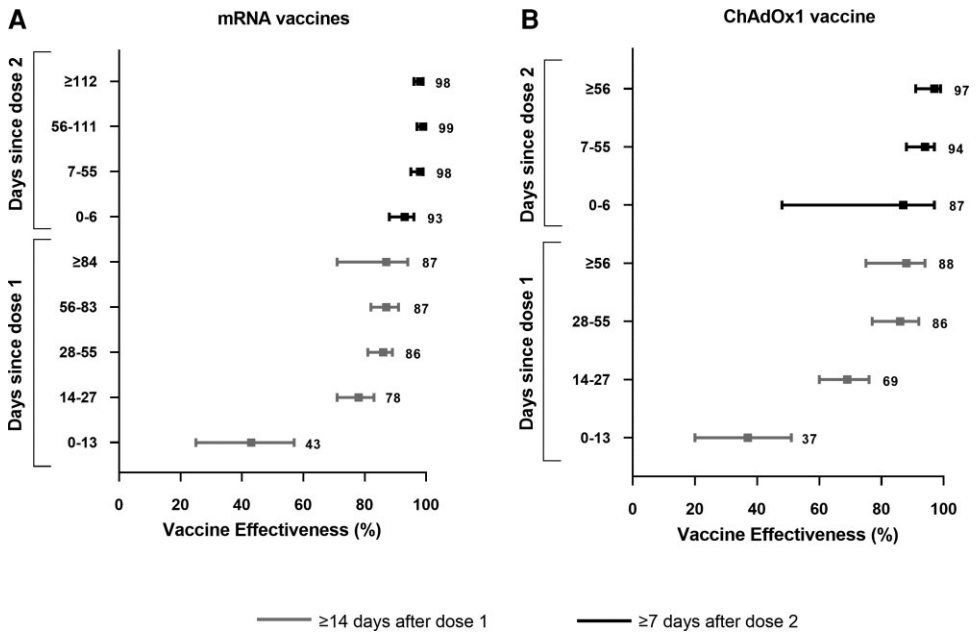

Figure 2. Pooled adjusted vaccine effectiveness against severe outcomes of hospitalization or death for mRNA *(A)* and ChAdOx1 *(B)* vaccines in Ontario, Quebec, British Columbia, and Manitoba. Abbreviation: mRNA, messenger RNA.

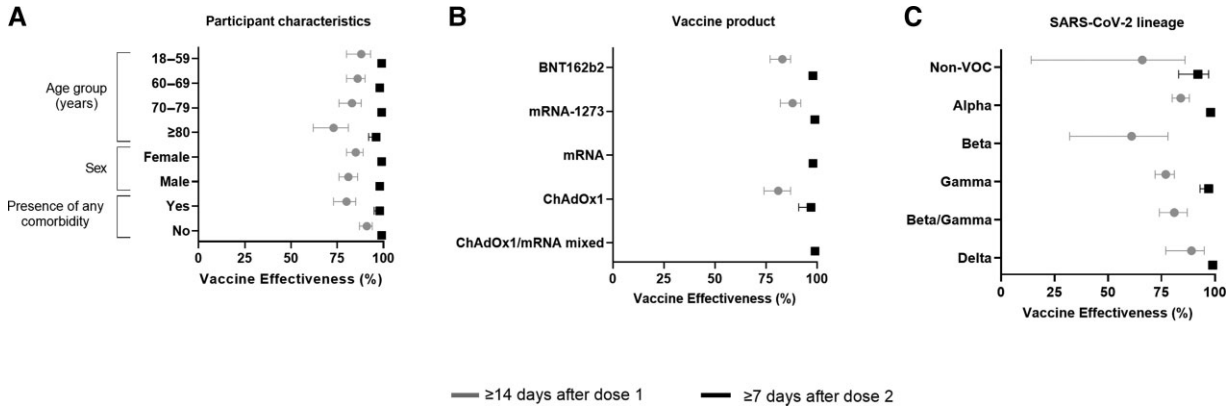

Figure 3. Pooled adjusted vaccine effectiveness against severe outcomes of hospitalization or death ≥14 days after a first dose and ≥7 days after a second dose by participant characteristics *(A)*, vaccine product *(B)*, and SARS-CoV-2 lineage *(C)* in Ontario, Quebec, British Columbia, and Manitoba. Abbreviations: mRNA, messenger RNA; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; VOC, variant of concern.

hospitalization and 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 with shorter follow-up, and very few participants 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 VE of 84%–89% against hospitalizations or hospitalizations and deaths up to

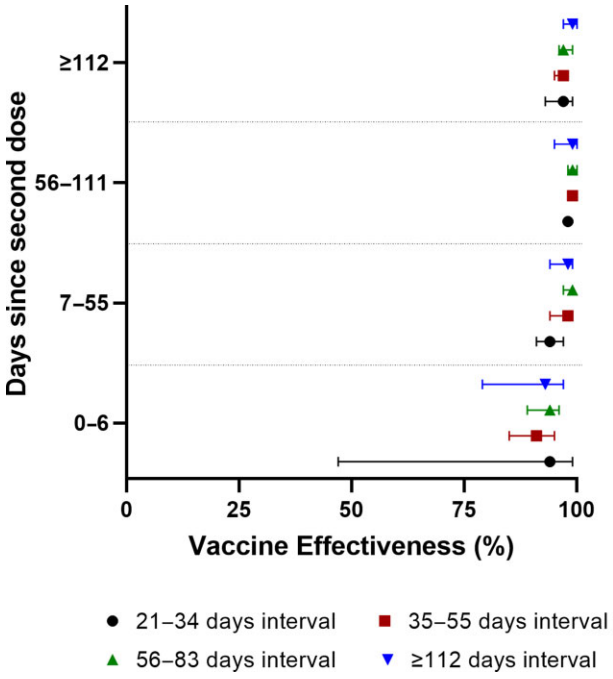

Figure 4. Pooled adjusted vaccine effectiveness against severe outcomes of hospitalization or death for participants who received 2 doses of an messenger RNA vaccine by various intervals between vaccine doses and time since the second dose in Ontario, Quebec, British Columbia, and Manitoba.

24 weeks were observed with 2 doses of mRNA vaccines in the United States [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 a 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 adults aged ≥80 years compared with ≥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 VE against Alpha (84%–97%) and Delta (92%–98%) with a second dose has been reported [23–26].

We observed similar high pooled aVE (≥97%) against severe outcomes ≥7 days after receipt of a second dose of homologous BNT162b2, mRNA-1273, or ChAdOx1 vaccine series; these estimates were similar to our pooled aVE after receipt of 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 with 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 with 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 with 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 behavior, 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 VE against severe outcomes was 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 who required hospitalization, and we do not expect differential under- or overestimation 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 that face limited vaccine supply.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author Contributions. J. C. K., S. N., G. D. S., C. H. R., N. Z., and M. T. designed and oversaw the study. S. N., Y. F., H. A. V. G., and G. Z. conducted province-specific analyses. S. N. 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. Data used in for this study were derived from administrative health and social data as a secondary use. The dataset for Ontario for this study is held securely in coded form at ICES. While legal data-sharing agreements between ICES and data providers (eg, healthcare organizations and government) prohibit ICES from making the dataset publicly available, access may be granted to those who meet prespecified 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 were provided under specific data-sharing agreements only for approved use at the Manitoba Centre for Health Policy (MCHP). The original source data are 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 have been noted in the Acknowledgments section 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.

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