

# Two-Dose Severe Acute Respiratory Syndrome Coronavirus 2 Vaccine Effectiveness With Mixed Schedules and Extended Dosing Intervals: Test-Negative Design Studies From British Columbia and Quebec, Canada

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**Background.** The Canadian coronavirus disease 2019 (COVID-19) immunization strategy deferred second doses and allowed mixed schedules. We compared 2-dose vaccine effectiveness (VE) by vaccine type (mRNA and/or ChAdOx1), interval between doses, and time since second dose in 2 of Canada's larger provinces.

**Methods.** Two-dose VE against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection or hospitalization among adults  $\geq 18$  years, including due to Alpha, Gamma, and Delta variants of concern (VOCs), was assessed  $\geq 14$  days postvaccination by test-negative design studies separately conducted in British Columbia and Quebec, Canada, between 30 May and 27 November (epi-weeks 22–47) 2021.

**Results.** In both provinces, all homologous or heterologous mRNA and/or ChAdOx1 2-dose schedules were associated with  $\geq 90\%$  reduction in SARS-CoV-2 hospitalization risk for  $\geq 7$  months. With slight decline from a peak of  $>90\%$ , VE against infection was  $\geq 80\%$  for  $\geq 6$  months following homologous mRNA vaccination, lower by  $\sim 10\%$  when both doses were ChAdOx1 but comparably high following heterologous ChAdOx1 + mRNA receipt. Findings were similar by age group, sex, and VOC. VE was significantly higher with longer 7–8-week versus manufacturer-specified 3–4-week intervals between mRNA doses.

**Conclusions.** Two doses of any mRNA and/or ChAdOx1 combination gave substantial and sustained protection against SARS-CoV-2 hospitalization, spanning Delta-dominant circulation. ChAdOx1 VE against infection was improved by heterologous mRNA series completion. A 7–8-week interval between first and second doses improved mRNA VE and may be the optimal schedule outside periods of intense epidemic surge. Findings support interchangeability and extended intervals between SARS-CoV-2 vaccine doses, with potential global implications for low-coverage areas and, going forward, for children.

**Keywords.** SARS-CoV-2; vaccine effectiveness; test-negative design; heterologous; waning.

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The first severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines in Canada were messenger RNA (mRNA) formulations, including BNT162b2 (Pfizer-BioNTech) authorized on 9 December (epi-week 50) 2020 and mRNA-1273 (Moderna) on 23 December (epi-week 52) 2020, both as 2-dose schedules, 3–4 weeks apart. Soon after authorization and given constrained vaccine supplies, experts in the provinces of British Columbia (BC) and Quebec simultaneously (epi-week 51) recommended deferral of second doses until as many prioritized individuals as possible could benefit from

substantial single-dose protection [1] (Supplementary Material 1). To facilitate subsequent completion of the 2-dose schedule, both provinces also highlighted the likely interchangeability of available vaccines. Through January 2021, health authorities in BC and Quebec extended the dosing interval (to 5–6 weeks and 6–12 weeks, respectively), in keeping with recommendations elsewhere [2, 3]. On 3 March (epi-week 9), Canada's National Advisory Committee on Immunization (NACI) endorsed second-dose deferral, recommending an even longer dosing interval of 16 weeks that was immediately adopted by BC and Quebec. A timeline of provincial and national vaccine recommendations and program modifications, with references, is provided in Supplementary Table 1.

On 26 February (epi-week 8) 2021, a chimpanzee adenoviral vectored (ChAdOx1) vaccine (AstraZeneca) was also authorized in Canada as a 2-dose schedule, 4–12 weeks apart. On 29 March (epi-week 13), NACI recommended that ChAdOx1 be restricted to adults aged 55 years and older due to vaccine safety concerns (thrombosis with thrombocytopenia), lowering to 30 years or older on 23 April (epi-week 16). On 1 June (epi-week 22), NACI also recognized the interchangeability of vaccines, recommending that first-dose recipients of ChAdOx1 or mRNA vaccines could (modified in epi-week 24 to *should*) complete the series with either mRNA product (Supplementary Table 1).

In BC and Quebec, vaccination started with long-term-care-facility residents and healthcare workers. Community-dwelling adults were next sequenced by age with single-dose coverage gradually increasing through spring 2021. In late-May/early-June (epi-weeks 21–22), as vaccine supply improved, BC and Quebec reduced the dosing interval from 16 to 8 weeks (Supplementary Table 1), by which time 70% or more of adults aged 18 years or older had received at least 1 dose and less than 10% had received 2 doses. To maximize 2-dose coverage by autumn, both provinces reduced the dosing interval to 4 weeks, such that by early September (epi-week 35), 80% of adults were considered fully vaccinated. The timeline of 1- and 2-dose vaccine coverage in BC and Quebec is provided in Supplementary Figure 1.

We report 2-dose vaccine effectiveness (VE) against infection and hospitalization among adults 18 years and older in BC and Quebec, spanning 30 May–27 November (epi-weeks 22–47) 2021, including early Alpha/Gamma and later Delta variant of concern (VOC) circulation. Mixed vaccine schedules and modified dosing intervals enabled VE comparison by vaccine type (homologous and heterologous), interval between doses, and time since the second dose.

## METHODS

### Study Design and Analysis

Two-dose VE was estimated by a test-negative design (TND), using multivariable logistic regression to derive the adjusted

odds ratio (aOR) for vaccination among SARS-CoV-2 test-positive cases versus test-negative controls. Vaccine effectiveness and 95% confidence intervals (CIs) were computed as  $(1 - \text{aOR}) \times 100\%$ . Adjusted models included age group (18–49, 50–69, 70–79,  $\geq 80$  years), sex (men, women), epi-week (categorical), and region. The latter includes the 5 health authorities in BC, with 18 administrative regions of Quebec also regrouped into 5 categories (Greater Montreal, Greater Quebec City, Central Quebec, Northern Quebec, Other).

### Case and Control Selection

Specimens collected from adults aged 18 years and older between epi-weeks 22 and 47 and assessed for SARS-CoV-2 by publicly funded nucleic acid amplification test (NAAT) were eligible. In both provinces, publicly funded, foremost symptom-based SARS-CoV-2 NAAT testing was broadly accessible through community-based assessment centers, emergency rooms, hospitals, and other sites. Rapid antigen tests were not broadly deployed in Canada during the analysis period.

Case specimens were SARS-CoV-2 NAAT positive; controls were NAAT negative. Both were sampled from laboratory databases capturing such tests province-wide. Individuals could contribute the first test-positive specimen and were censored thereafter. A single test-negative specimen was randomly selected per individual across the analysis period with the same controls used for VE estimation against infection and hospitalization.

Because symptoms and onset dates were not consistently captured, VE was primarily assessed against any infection timed on specimen collection date. In sensitivity analysis, VE estimates in Quebec were derived with restriction to specimens with the “M7” code indicating collection at designated outpatient screening centers for symptomatic individuals only (not possible in BC). Hospitalized cases were admitted on or within 30 days after specimen collection, identified through linkage with notifiable disease lists, supplemented in Quebec by administrative databases. In variant-specific analyses, cases were categorized as Alpha, Gamma, or Delta as per Supplementary Material 2.

### Vaccination Definition

SARS-CoV-2 vaccines were delivered through publicly funded programs primarily at public health clinics and retail pharmacies. Vaccine information was obtained from provincial immunization registries (PIRs). All vaccine providers in both provinces were required to enter SARS-CoV-2 vaccination information into the PIR. Resident vaccinations received outside the province were also entered.

Based upon PIR record on or before the specimen collection date, those who had received 2 doses of BNT162b2, mRNA-1273, or ChAdOx1 were considered vaccinated; those who had received just 1 dose of any vaccine were excluded;

**Table 1. Profile of Participants ≥18 Years Old, by Case and Vaccine Status (Regardless of Time Since Vaccination): British Columbia and Quebec, Canada**

	British Columbia						Quebec					
	Overall (N = 513 877), n (column %)			Vaccinated (n = 409 195), n (row %) <sup>a</sup>			Overall (N = 1 017 359), n (column %)			Vaccinated (n = 852 594), n (row %) <sup>a</sup>		
	Cases	Hosp	Controls	Cases	Hosp	Controls	Cases	Hosp	Controls	Cases	Hosp	Controls
Total	44 964 (9)	3131 (7) <sup>b</sup>	468 913 (91)	17 835 (40)	537 (17)	391 360 (83)	31 718 (3)	1452 (5) <sup>b</sup>	985 641 (97)	15 096 (48)	386 (27)	837 498 (85)
Age group (years)												
18–49	31 031 (69)	1043 (33)	294 946 (63)	10 984 (35)	77 (7)	236 104 (60)	22 923 (72)	527 (36)	581 213 (59)	9435 (41)	65 (12)	463 887 (80)
50–69	10 817 (24)	1228 (39)	119 581 (26)	5111 (47)	187 (15)	105 464 (88)	6802 (21)	502 (35)	272 785 (28)	4123 (61)	99 (20)	249 170 (91)
70–79	2201 (5)	511 (16)	35 608 (8)	1197 (54)	128 (25)	32 817 (92)	1371 (4)	222 (15)	88 922 (9)	1041 (76)	93 (42)	84 744 (95)
80+	915 (2)	349 (11)	18 778 (4)	543 (59)	145 (42)	16 975 (90)	622 (2)	201 (14)	42 721 (4)	497 (80)	129 (64)	39 697 (93)
Median (IQR) years	39 (29–54)	59 (43–71)	42 (31–58)	43 (33–58)	70 (59–80)	43 (32–60)	40 (29–52)	58 (43–72)	44 (32–61)	44 (35–58)	73 (60–82)	46 (34–63)
Sex												
Female	22 218 (49)	1302 (42)	263 608 (56)	9520 (43)	216 (17)	224 240 (85)	16 480 (52)	639 (44)	574 263 (58)	8209 (50)	169 (26)	490 303 (85)
Male	22 746 (51)	1829 (58)	205 305 (44)	8315 (37)	321 (18)	167 120 (81)	15 238 (48)	813 (56)	411 378 (42)	6887 (45)	217 (27)	347 195 (84)
Epidemiological week, 2021												
22–26 (30 May–3 July)	1603 (4)	137 (4)	24 989 (5)	106 (7)	5 (4)	9993 (40)	1383 (4)	74 (5)	78 552 (8)	108 (8)	8 (11)	38 666 (49)
27–30 (4–31 July)	1490 (3)	79 (3)	30 236 (6)	337 (23)	12 (13)	21 443 (71)	966 (3)	39 (3)	83 187 (8)	211 (22)	6 (15)	63 379 (76)
31–34 (1–28 August)	9515 (21)	526 (17)	74 181 (16)	2556 (27)	64 (9)	59 702 (80)	4513 (14)	212 (15)	120 864 (12)	1376 (30)	42 (20)	100 335 (83)
35–39 (29 August–2 October)	14 827 (33)	1036 (33)	133 760 (29)	5702 (38)	171 (20)	115 241 (86)	10 613 (33)	599 (41)	251 348 (26)	4368 (41)	134 (22)	222 203 (88)
40–43 (3–30 October)	10 227 (23)	808 (26)	114 252 (24)	5022 (49)	153 (19)	102 338 (90)	5958 (19)	290 (20)	221 372 (22)	3316 (56)	102 (35)	201 376 (91)
44–47 (31 Oct–27 Nov)	7302 (16)	545 (17)	91 495 (20)	4112 (56)	132 (24)	82 643 (90)	8285 (26)	238 (16)	230 318 (23)	5717 (69)	94 (39)	211 539 (92)
Two-dose vaccine status: <sup>c,d</sup>												
Unvaccinated	27 129 (60)	2594 (83)	77 553 (17)	NA	NA	NA	16 622 (52)	1066 (73)	148 143 (15)	NA	NA	NA
Twice vaccinated, any vaccine	17 835 (40)	537 (17)	391 360 (83)	17 835 (100)	537 (100)	391 360 (100)	15 096 (48)	386 (27)	837 498 (85)	15 096 (100)	386 (100)	837 498 (100)
Two any mRNA vaccines	15 625 (35)	497 (16)	356 578 (76)	15 625 (88)	497 (93)	356 578 (91)	13 854 (44)	344 (24)	771 821 (78)	13 854 (92)	344 (89)	771 821 (92)
Two BNT162b2	11 411 (25)	347 (11)	256 357 (55)	11 411 (64)	347 (65)	256 357 (66)	10 943 (35)	275 (19)	580 186 (59)	10 943 (72)	275 (71)	580 186 (69)
Two mRNA–1273	3007 (7)	100 (3)	71 406 (15)	3007 (17)	100 (19)	71 406 (18)	2554 (8)	61 (4)	170 714 (17)	2554 (17)	61 (16)	170 714 (20)
Two mixed mRNA	1207 (3)	50 (2)	28 815 (6)	1207 (7)	50 (9)	28 815 (7)	357 (1)	8 (1)	20 921 (2)	357 (2)	8 (2)	20 921 (2)
Two ChAdOx1	1246 (3)	33 (1)	12 682 (3)	1246 (7)	33 (6)	12 682 (3)	597 (2)	30 (2)	22 740 (2)	597 (4)	30 (8)	22 740 (3)
Two mixed ChAdOx1/mRNA	962 (2)	6 (<1)	22 094 (5)	962 (5)	6 (<1)	22 094 (6)	645 (2)	12 (1)	42 937 (4)	645 (4)	12 (3)	42 937 (5)
Interval between doses <sup>e</sup>												
21–34 days (3–4 weeks)	NA	NA	NA	659 (4)	24 (5)	11 738 (3)	NA	NA	NA	1151 (8)	38 (10)	40 264 (5)
35–48 days (5–6 weeks)	NA	NA	NA	1611 (9)	46 (9)	25 028 (6)	NA	NA	NA	1158 (8)	14 (4)	50 667 (6)
49–62 days (7–8 weeks)	NA	NA	NA	6473 (36)	88 (16)	151 324 (39)	NA	NA	NA	4346 (29)	53 (14)	220 589 (26)
63–83 days (9–11 weeks)	NA	NA	NA	5787 (32)	180 (34)	138 467 (35)	NA	NA	NA	4926 (33)	108 (28)	289 152 (35)
84–111 days (12–15 weeks)	NA	NA	NA	2805 (16)	161 (30)	55 546 (14)	NA	NA	NA	2242 (15)	99 (26)	154 183 (18)
112+ days (16+ weeks)	NA	NA	NA	500 (3)	38 (7)	9257 (2)	NA	NA	NA	1273 (8)	74 (19)	82 643 (10)
Median (IQR) days	NA	NA	NA	63 (55–77)	76 (60–91)	63 (56–75)	NA	NA	NA	65 (56–82)	80 (69–100)	69 (57–87)
Time since second dose <sup>c</sup>												
0–13 days (0–1 weeks)	NA	NA	NA	1206 (7)	29 (5)	19 806 (5)	NA	NA	NA	917 (6)	17 (4)	51 377 (6)

**Table 1. Continued**

	British Columbia						Quebec					
	Overall (N = 513 877), n (column %)			Vaccinated (n = 409 195), n (row %) <sup>a</sup>			Overall (N = 1 017 359), n (column %)			Vaccinated (n = 862 594), n (row %) <sup>a</sup>		
	Cases	Hosp	Controls	Cases	Hosp	Controls	Cases	Hosp	Controls	Cases	Hosp	Controls
14–27 days (2–3 weeks)	NA	NA	NA	498 (3)	14 (3)	24 902 (6)	NA	NA	NA	425 (3)	21 (5)	58 734 (7)
28–55 days (4–7 weeks)	NA	NA	NA	2016 (11)	45 (8)	63 850 (16)	NA	NA	NA	1640 (11)	35 (9)	137 333 (16)
56–83 days (8–11 weeks)	NA	NA	NA	3361 (19)	95 (18)	83 821 (21)	NA	NA	NA	2821 (19)	59 (15)	167 477 (20)
84–111 days (12–15 weeks)	NA	NA	NA	4051 (23)	121 (23)	87 149 (22)	NA	NA	NA	3300 (22)	98 (25)	175 612 (21)
112–139 days (16–19 weeks)	NA	NA	NA	3750 (21)	114 (21)	67 778 (17)	NA	NA	NA	3428 (23)	87 (23)	148 369 (18)
140–167 days (20–23 weeks)	NA	NA	NA	1739 (10)	87 (16)	29 354 (8)	NA	NA	NA	1847 (12)	55 (14)	71 597 (9)
168–195 days (24–27 weeks)	NA	NA	NA	381 (2)	12 (2)	5815 (1)	NA	NA	NA	455 (3)	9 (2)	18 520 (2)
196+ days (28+ weeks)	NA	NA	NA	833 (5)	20 (4)	8885 (2)	NA	NA	NA	263 (2)	5 (1)	8179 (1)
Median (IQR), days	NA	NA	NA	96 (63–127)	103 (71–133)	85 (51–116)	NA	NA	NA	98 (64–129)	102 (72–127)	84 (48–118)

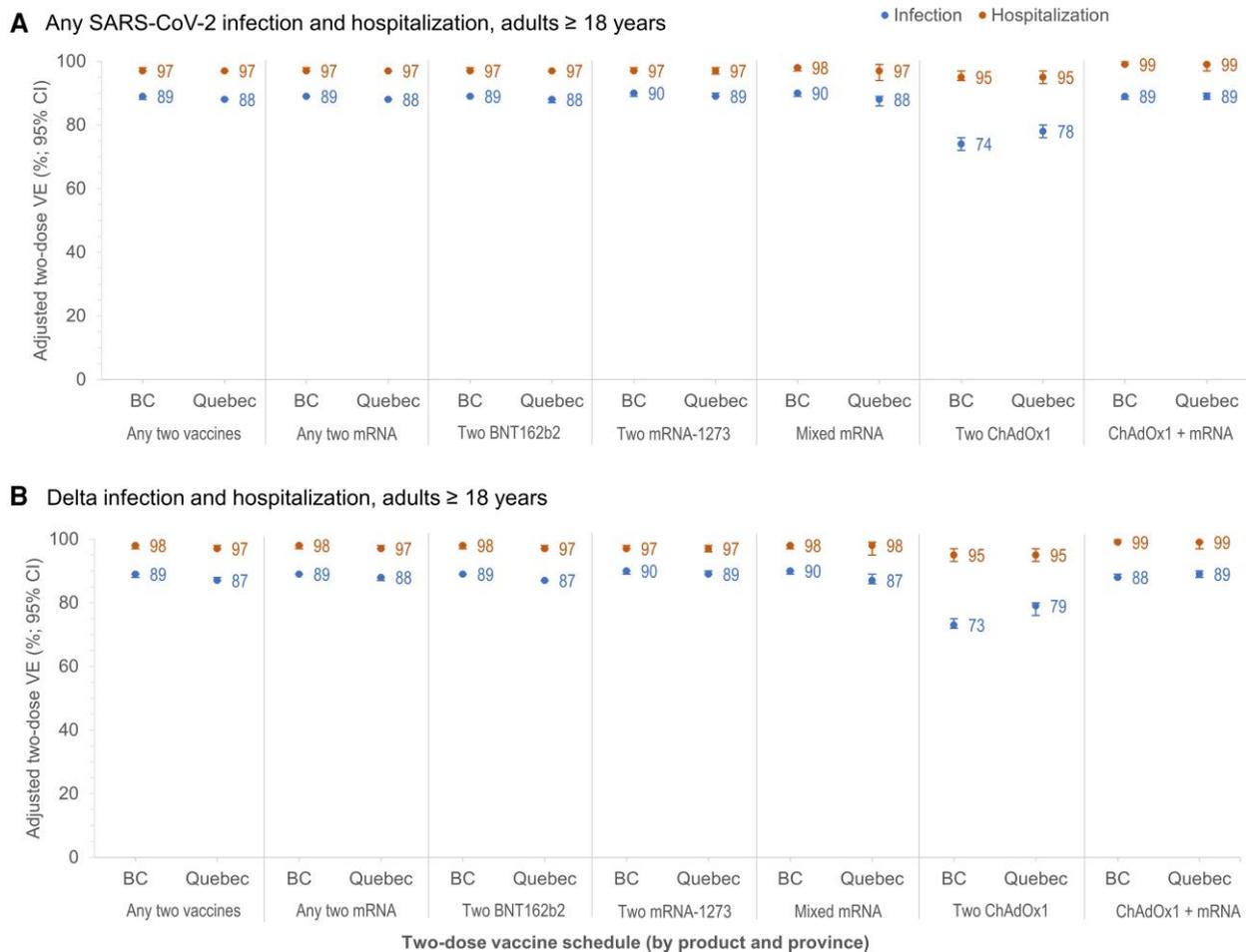
Abbreviations: ChAdOx1, chimpanzee adenoviral vectored vaccine; Hosp, hospitalized cases; IQR, interquartile range; NA, not applicable.

<sup>a</sup>Unless otherwise specified, percentages are cases, hospitalized cases, or controls who received a second vaccine dose on/before specimen collection, by row category, regardless of time since second dose. Excludes specimens from once or more than twice vaccinated on/before specimen collection.

<sup>b</sup>Displayed is the percentage of cases who were hospitalized.

<sup>c</sup>Vaccinated tallies are specimens from individuals twice vaccinated on or before specimen collection, regardless of time since second dose. Unvaccinated received no vaccine doses on or before specimen collection. Excludes specimens from single-dose recipients or those thrice vaccinated on or before specimen collection. All percentages displayed below this row are column %.

<sup>d</sup>In British Columbia, 2 cases (1 hospitalized) and 6 controls from vaccinated individuals had an unspecified vaccine type for the first or second dose.



**Figure 1.** Adjusted 2-dose VE against infection and hospitalization (overall and Delta-specific), by vaccine type, in adults  $\geq 18$  years old: British Columbia and Quebec, Canada, epi-weeks 22–47 (30 May–27 November) of 2021. Shown are adjusted VE and 95% CIs against infection (blue) and hospitalization (orange)  $\geq 14$  days after the second dose by vaccine type, overall (A) and for the Delta variant of concern (B) among adults  $\geq 18$  years old in the provinces of BC and Quebec, Canada. In Quebec, VE against Delta hospitalization was assessed only between epi-weeks 31 and 47 because no hospitalized Delta variant cases were identified prior to that period. For additional details, including corresponding sample sizes and precise unadjusted and adjusted estimates with 95% CIs (and adjustment covariates specified), see [Supplementary Table 5](#) (overall) and [Supplementary Tables 9 and 10](#) (Alpha, Gamma, and Delta variants of concern). Abbreviations: BC, British Columbia; ChAdOx1, chimpanzee adenoviral vectored vaccine; CI, confidence interval; mRNA, messenger RNA; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; VE, vaccine effectiveness.

and those who received no doses were considered unvaccinated. In overall VE analysis, vaccination was defined by second-dose receipt 14 days or more before specimen collection, excluding those vaccinated 0–13 days prior; however, a range of time since the second dose was explored. Individual-level linkage across databases was achieved through unique personal identifiers.

#### Exclusions

Specimens with invalid or missing information were excluded as were specimens collected from individuals identified as cases before the analysis period; residents of long-term-care, assisted-living, or independent-living facilities; and those vaccinated with a product other than BNT162b2, mRNA-1273, or ChAdOx1.

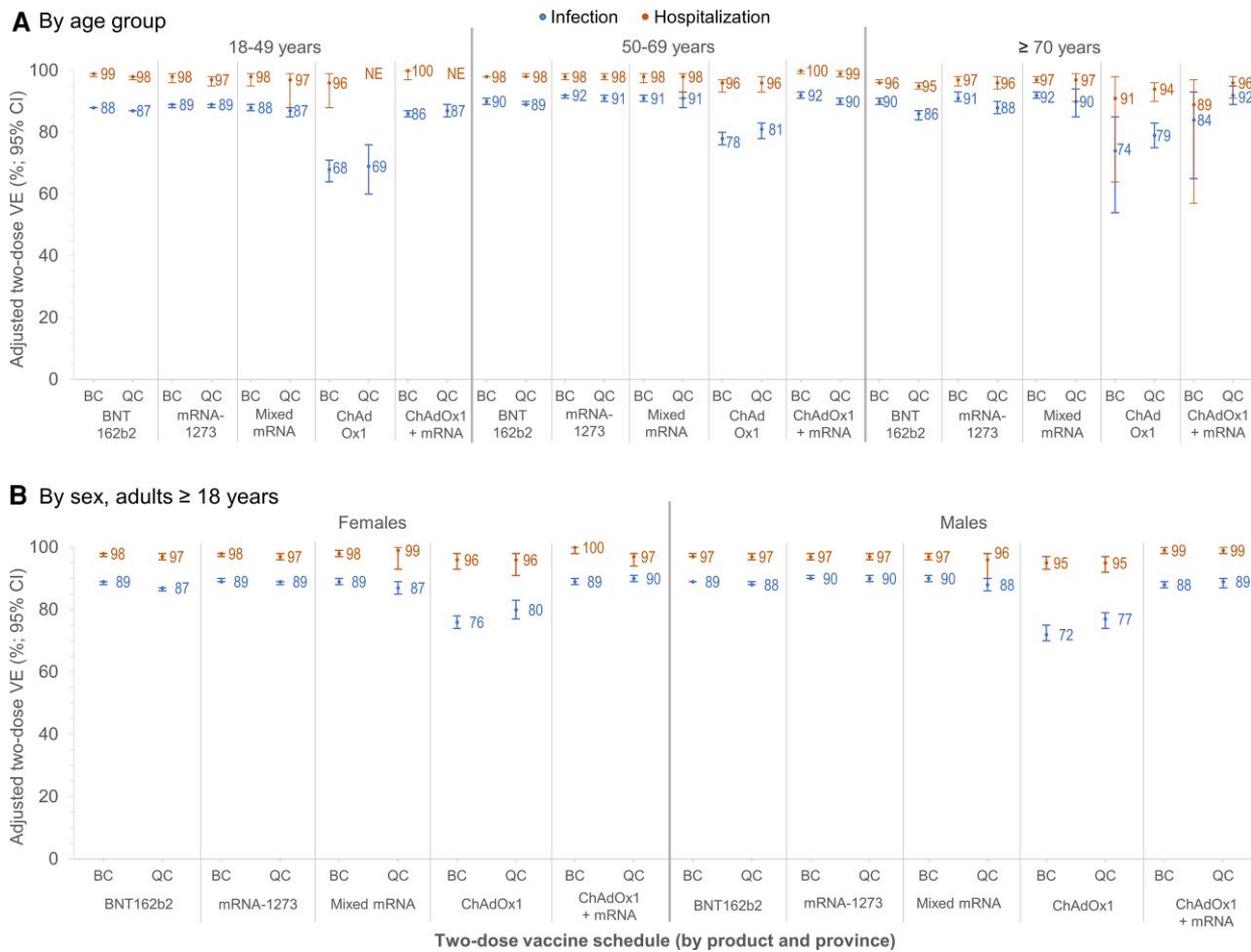
#### Ethics Statement

Data linkages and analyses were authorized by the Provincial Health Officer (BC) and National Director of Public Health (Quebec) under the respective provincial public health legislation without requirement for research ethics board review.

## RESULTS

#### Case and Control Contribution

The total number of specimens collected from adults aged 18 years and older between epi-weeks 22 and 47 and tested for SARS-CoV-2 by publicly funded NAAT was 872 440 in BC and 1 973 637 in Quebec, including 59 590 (7%) and 40 145 (2%) test-positive specimens, respectively (data not shown). Of the latter, 44 964 (75%) and 31 718 (79%) cases, respectively, were eligible for VE analyses, among whom 3173 (7%) and



**Figure 2.** Adjusted 2-dose VE against infection and hospitalization, by age group, sex, and vaccine type in adults  $\geq 18$  years old: British Columbia and Quebec, Canada, epi-weeks 22–47 (30 May–27 November) of 2021. Shown are adjusted VE estimates and 95% CIs against infection (blue) and hospitalization (orange)  $\geq 14$  days after the second dose by age group (A) and sex (B) and by vaccine type in BC and Quebec, Canada. In Quebec, adjusted VE against hospitalization in  $\geq 70$ -year-old adults required collapse of epi-week categories (triweekly) owing to sample-size considerations. For additional details, including corresponding sample sizes and precise unadjusted and adjusted estimates with 95% CIs (and adjustment covariates specified), see [Supplementary Tables 6–8](#). Abbreviations: BC, British Columbia; ChAdOx1, chimpanzee adenoviral vectored vaccine; CI, confidence interval; mRNA, messenger RNA; NE, not estimable or total span of CI is  $\geq 100\%$ ; QC, Quebec; VE, vaccine effectiveness.

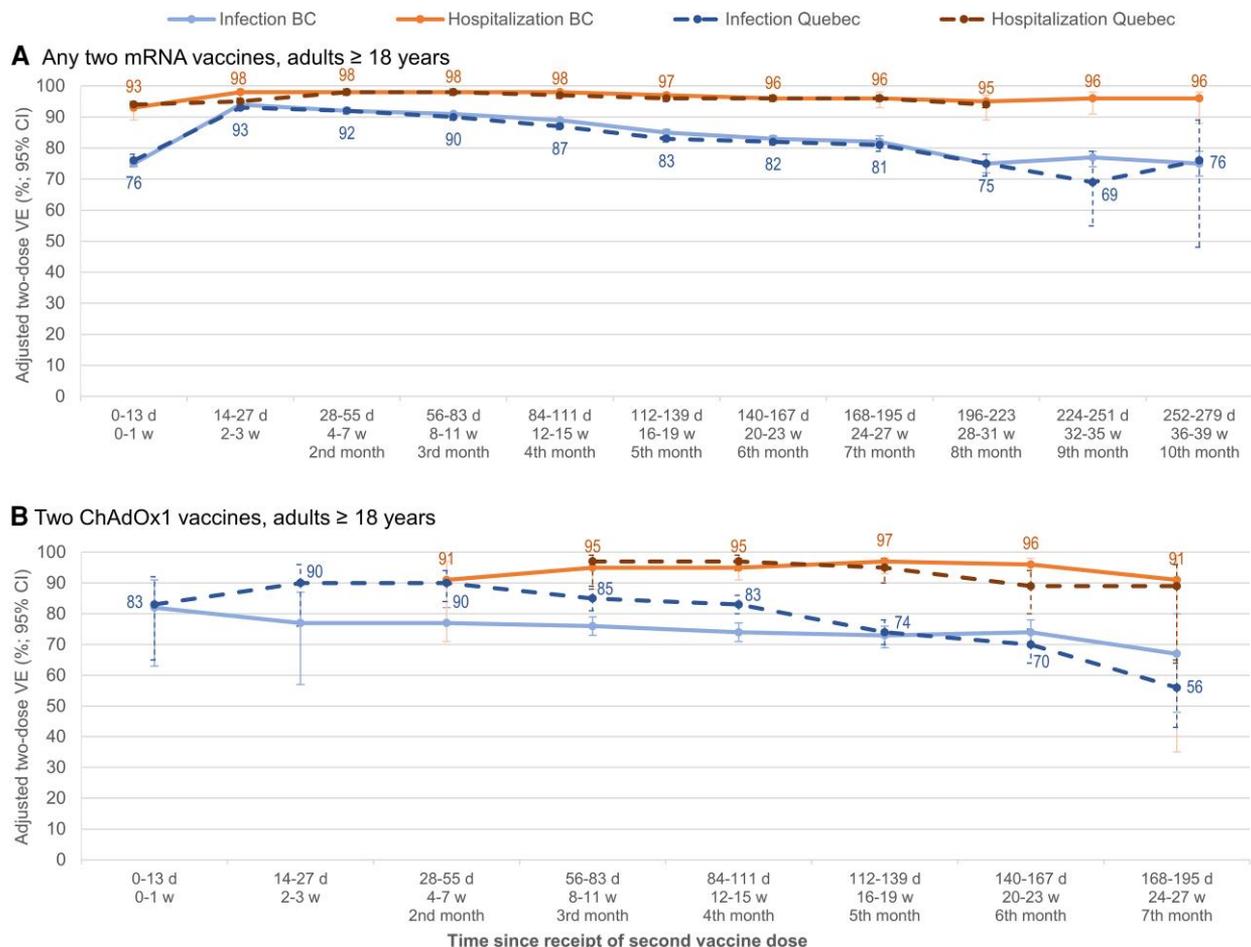
1452 (5%), respectively, were hospitalized (Table 1). Of 812 850 and 1 933 492 test-negative specimens in total, 622 602 (77%) and 1 501 548 (78%), respectively, were eligible for VE analyses. Among contributing adults, 96% in BC and 90% in Quebec provided up to 2 test-negative specimens each. After randomly selecting 1 test-negative specimen per individual, 468 913 (75%) controls in BC and 985 641 (66%) in Quebec were included in VE analyses.

During epi-weeks 22–34, 90% of case viruses in BC and 59% in Quebec were genetically characterized: Alpha, Gamma, and Delta comprised 7%, 7%, and 86%, respectively, in BC and 41%, 0%, and 59% in Quebec (Supplementary Table 2). In both provinces, more than 70% of cases accrued during the second half of the analysis period. From epi-weeks 35–47, 65% and 42% of BC and Quebec case viruses, respectively, were genetically characterized, of which 99% or more were Delta. Assuming full Delta attribution from epi-week 35 in BC and epi-week 36 in Quebec,

94% (42 143/44 964) and 84% (26 520/31 718), respectively, of case viruses across the analysis period were Delta.

#### Vaccination Profiles

Compared with provincial coverage estimates, the weekly percentage who were twice-vaccinated among study controls was higher in the early analysis period (as expected given the exclusion of remaining single-dose recipients), becoming similar (within 5%) from epi-week 30 in BC and epi-week 33 in Quebec (Supplementary Figure 1). Among twice-vaccinated controls in both provinces, approximately 90% received 2 mRNA doses: 66–69% BNT162b2 and 18–20% mRNA-1273 (Table 1). ChAdOx1 recipients comprised 3% and were generally older and more often male (Supplementary Tables 3 and 4). Mixed mRNA recipients comprised 7% in BC and 2% in Quebec, with approximately 5% in both provinces receiving mixed ChAdOx1 + mRNA doses.



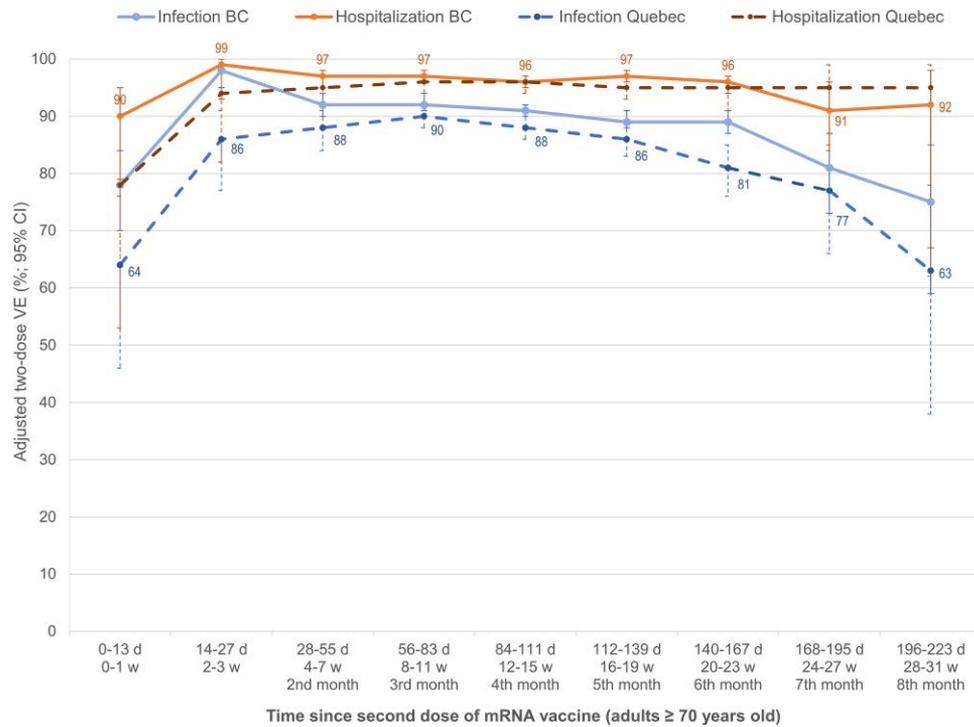
**Figure 3.** Adjusted 2-dose mRNA and ChAdOx1 VE against infection and hospitalization by time since vaccination, in adults ≥ 18 years old: British Columbia and Quebec, Canada, epi-weeks 22–47 (30 May–27 November) of 2021. Shown are adjusted VE estimates and 95% CIs against infection (blue) and hospitalization (orange) by time between receipt of the second dose and specimen collection, among adults ≥ 18 years old in BC (solid lines) and Quebec (dashed lines). Panel A displays estimates for those who received any 2 mRNA vaccines and panel B displays estimates for those who received 2 ChAdOx1 vaccines. Due to sparse data, mRNA estimates are not displayed beyond the eighth month postvaccination against hospitalization in Quebec or beyond the seventh month postvaccination for ChAdOx1 in either province. Displayed are the point estimates against hospitalization for BC and against infection for Quebec. For additional details including all corresponding sample sizes and precise unadjusted and adjusted estimates with 95% CIs (and adjustment covariates specified), see [Supplementary Table 12](#) (including details by mRNA vaccine type and for mixed product schedules). The corresponding information by age subgroups is displayed in [Supplementary Table 13](#) and for Delta-specific VE in [Supplementary Table 14](#) (also by mRNA vaccine type and for mixed products). Abbreviations: BC, British Columbia; ChAdOx1, chimpanzee adenoviral vectored vaccine; CI, confidence interval; d, days; mRNA, messenger RNA; VE, vaccine effectiveness; w, weeks.

Among twice-vaccinated controls, the median interval between first and second doses of mRNA or ChAdOx1 vaccines was 63 and 62 days, respectively, in BC, and longer at 69 and 73 days in Quebec. In both provinces, few mRNA or ChAdOx1 recipients were revaccinated less than 7 weeks apart (~10% and 5%, respectively). More ChAdOx1 recipients in Quebec were revaccinated at 9–11-week interval, also with more in Quebec who were revaccinated at 12 weeks or later among recipients of both kinds of vaccine ([Supplementary Tables 3 and 4](#)). Among twice-vaccinated controls in both provinces, median follow-up post-second dose was approximately 12 weeks, and slightly longer for ChAdOx1 recipients at approximately 14–15 weeks ([Supplementary Tables 3 and 4](#)).

### Vaccine Effectiveness

#### Overall

At 14 days or more post-second dose, all schedules of homologous or heterologous mRNA and/or ChAdOx1 vaccines were associated with 95% or greater reduction in SARS-CoV-2 hospitalization risk ([Figure 1](#)). Vaccine effectiveness against infection was 88–90% for 2 homologous or heterologous mRNA doses ([Figure 1](#), [Supplementary Table 5](#)), significantly lower for 2 homologous ChAdOx1 doses at 74% (95% CI: 72–76%) in BC and 78% (95% CI: 76–80%) in Quebec, but improved significantly with heterologous ChAdOx1 + mRNA vaccination at 89% (95% CI: 88–90%). Findings were similar by age group, sex ([Figure 2](#), [Supplementary Table 8](#)), and VOC ([Figure 1](#), [Supplementary Tables 9 and 10](#)).



**Figure 4.** Adjusted 2-dose VE against infection and hospitalization, by time since mRNA vaccination, in adults  $\geq 70$  years old: British Columbia and Quebec, Canada. Shown are adjusted VE estimates and 95% CIs against infection (blue) and hospitalization (orange) by time between receipt of the second dose of any mRNA vaccine and specimen collection, among adults  $\geq 70$  years old in BC (solid lines) and Quebec (dashed lines). In Quebec, adjusted VE against hospitalization required collapse of epi-week categories (triweekly) owing to sample size considerations. Displayed are the point estimates against hospitalization for BC and against infection for Quebec. For additional details including all corresponding sample sizes and precise unadjusted and adjusted estimates with 95% CIs (and adjustment covariates specified), see [Supplementary Table 13](#) (including details by type of mRNA vaccine). Abbreviations: BC, British Columbia; CI, confidence interval; d, days; mRNA, messenger RNA; VE, vaccine effectiveness; w, weeks.

With restriction to outpatient symptom-based testing in Quebec, findings were similar to overall estimates against any infection in both provinces, notably for mRNA recipients overall (within 5% absolute) and by epi-period (within 10% absolute) ([Supplementary Table 11](#)). Two-dose ChAdOx1 estimates were more variable, due to reduced sample size and other differences by province (eg, dosing intervals).

#### By Time Since Vaccination

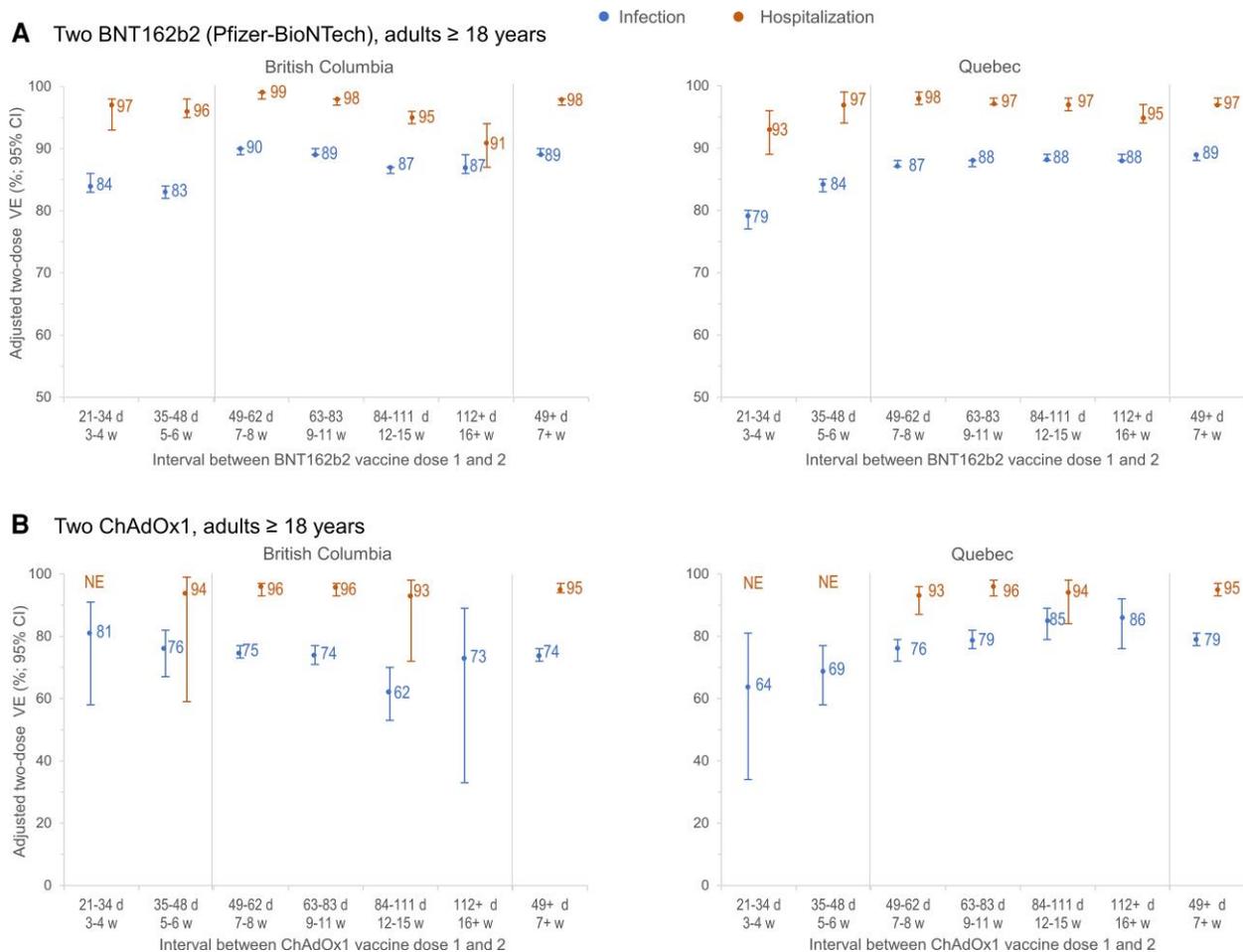
Two-dose VE of 95% or greater against hospitalization lasted at least 8 months for mRNA recipients and 5 months for ChAdOx1, remaining at 90% or greater for at least 7 months for both products ([Figure 3](#), [Supplementary Table 12](#)). Against infection, 2-dose mRNA VE was more than 90% through at least the third month, declining slightly but still 80% or higher through 6–7 months postvaccination, including in adults aged 70 years and older ([Figures 3 and 4](#), [Supplementary Tables 12 and 13](#)). Findings were similar for schedules including at least 1 mRNA dose ([Supplementary Table 12](#)), by age group ([Supplementary Table 13](#)), and for Delta-specific outcomes ([Supplementary Table 14](#)). In Quebec, 2-dose ChAdOx1 VE against infection was 80% or higher through 4 months postvaccination, while ranging

from 74 to 77% in BC and 70% or higher in both provinces through the sixth month ([Figure 3](#), [Supplementary Table 12](#)).

#### By Interval Between Doses

As shown in [Figure 5](#), BNT162b2 VE against infection was significantly higher when the interval between doses was extended from 3–4 or 5–6 weeks to 7–8 weeks, without further improvement thereafter. At intervals of 7 weeks or more versus 3–4 weeks between doses, BNT162b2 VE was significantly higher by 5% (absolute) in BC and 10% in Quebec. A similar but less pronounced pattern was observed for mRNA-1273. ChAdOx1 VE gradually increased with a longer dosing interval in Quebec but not in BC where CIs were wider ([Figure 5](#), [Supplementary Table 15](#)). Vaccine effectiveness against hospitalization exceeded 90% regardless of dosing interval.

Since shorter dosing interval may have been associated with longer time since second dose, VE was stratified on both conditions. At intervals of 7–8 weeks versus 3–4 weeks between BNT162b2 doses, VE was 4–6% higher in BC and 8–14% higher in Quebec through the first 4 months post-second dose ([Figure 6](#), [Supplementary Table 16](#)). Thereafter, estimates had wide CIs. A similar pattern was observed for mRNA-1273, but could not be assessed for ChAdOx1.



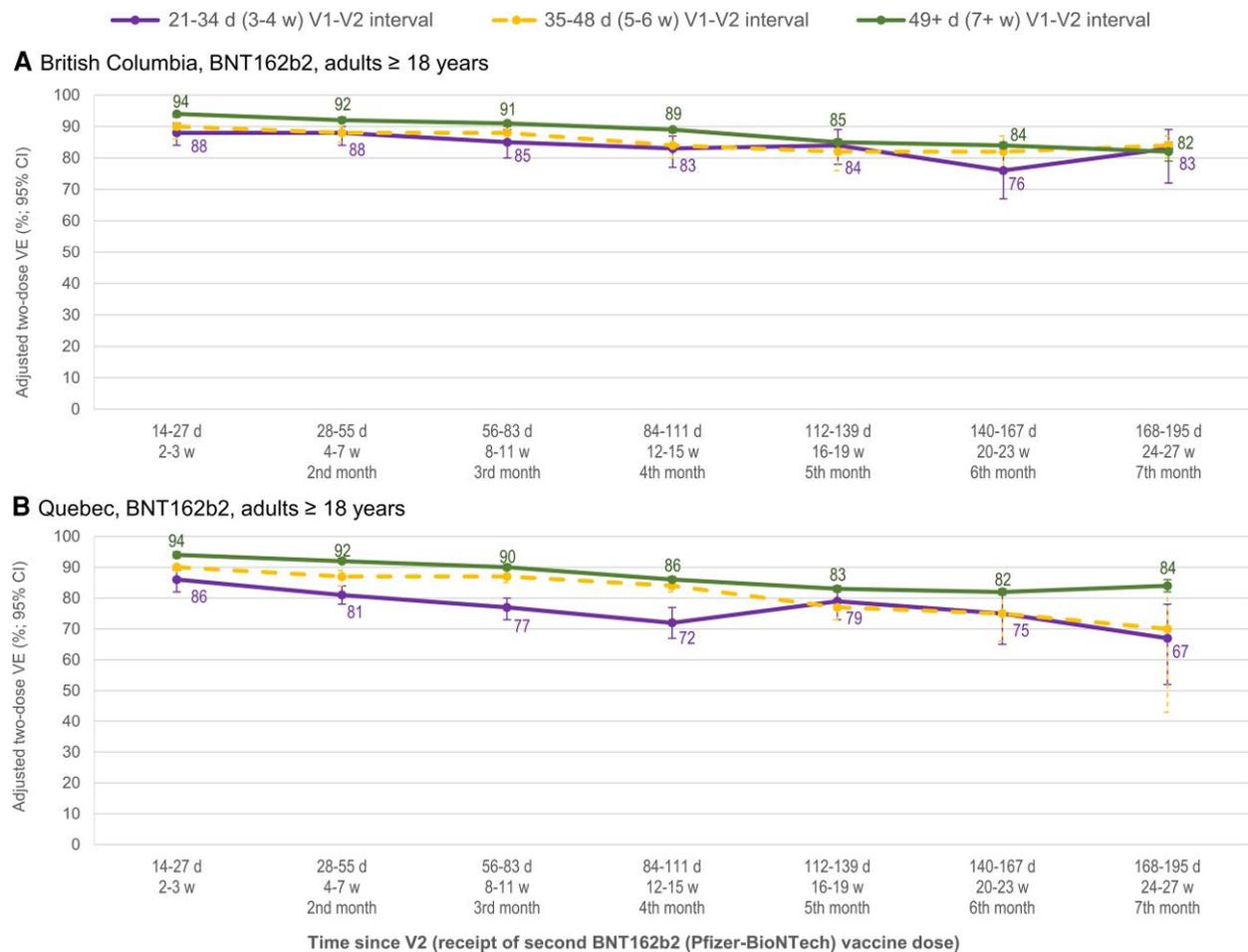
**Figure 5.** Adjusted 2-dose VE against infection and hospitalization, by interval between doses, mRNA and ChAdOx1 vaccines, in adults  $\geq 18$  years old: British Columbia and Quebec, Canada. Shown are adjusted VE estimates and 95% CIs against infection (blue) and hospitalization (orange) at  $\geq 14$  days after the second dose, by interval between the first and second dose among adults  $\geq 18$  years old who were vaccinated with any 2 mRNA vaccines (A) or 2 ChAdOx1 vaccines (B) in British Columbia and Quebec. For additional details including corresponding sample sizes and precise unadjusted and adjusted estimates with 95% CIs (and adjustment covariates specified), see [Supplementary Table 15](#) (including details by type of mRNA vaccine). Abbreviations: ChAdOx1, chimpanzee adenoviral vectored vaccine; CI, confidence interval; d, days; mRNA, messenger RNA; NE, not estimable or total span of CI is  $\geq 100\%$ ; VE, vaccine effectiveness; w, weeks.

## DISCUSSION

We report similar findings from 2 of Canada's larger provinces, where mixed SARS-CoV-2 vaccine schedules and extended dosing intervals were adopted in response to urgent public health need during the pandemic. In both provinces, a 2-dose schedule using any combination of available homologous or heterologous vaccines was associated with a 90% or greater reduction in hospitalization risk for at least 7 months, spanning early-Alpha and late-Delta circulation. With a slight decline from a peak of more than 90%, 2-dose VE against infection was still 80% or more for at least 6 months following homologous mRNA vaccination, lower by approximately 10% when both doses were ChAdOx1, but improved and comparably high with heterologous ChAdOx1 + mRNA receipt. Vaccine protection was also improved when first and second mRNA

doses were separated by 7–8 weeks rather than the manufacturer-specified 3–4 weeks apart.

Our observations of substantial and sustained mRNA VE align with randomized controlled trial (RCT) findings. In extended follow-up of participants in the BNT162b2 (Pfizer-BioNTech) RCT, 2-dose efficacy against clinical infection peaked at 96% during the first 2 months, remaining greater than 80% from 4 months to the end of follow-up [4, 5]. In the mRNA-1273 (Moderna) RCT, 2-dose efficacy against coronavirus disease 2019 (COVID-19) illness was 93%, without waning across a median of 5.2 months [6, 7]. In a 2-year open-label study initiated after unblinding of the Moderna RCT, COVID-19 incidence during the July/August 2021 Delta surge among earlier mRNA-1273-vaccinated participants (median, 13-month follow-up from first dose) was approximately 1.6



**Figure 6.** Adjusted 2-dose BNT162b2 VE against infection by interval between doses and time since second dose, in adults  $\geq 18$  years old: British Columbia and Quebec, Canada. Shown are adjusted VE estimates and 95% CIs against infection by interval between the first and second BNT162b2 dose (3–4 weeks in purple; 5–6 weeks in dashed gold; 7+ weeks in green) and time since the second dose among adults  $\geq 18$  years old in the provinces of British Columbia and Quebec. For additional details including corresponding sample sizes and precise unadjusted and adjusted estimates with 95% CIs (and adjustment covariates specified), see [Supplementary Table 16](#) (including both types of mRNA vaccine and ChAdOx1). Abbreviations: ChAdOx1, chimpanzee adenoviral vectored vaccine; CI, confidence interval; d, days; mRNA, messenger RNA; VE, vaccine effectiveness; V1, dose 1; V2, dose 2; w, weeks.

times greater than among the placebo recipients later vaccinated (median, 7.9-month follow-up) [8]. Applying a relative risk (RR) of 1.6 to the COVID-19 incidence among individuals vaccinated during the Moderna RCT corresponds to a minor decrease in efficacy from 93% to 89%, consistent with what we report [7, 8].

Sustained 2-dose VE against hospitalization, including Delta-associated, has been observed elsewhere, but with more variability in the reported duration of protection against infection [9–15]. Studies from Israel have reported greater risk of both infection and hospitalization with time since the second BNT162b2 dose [16]. Conversely, in the United Kingdom, VE against Delta hospitalization remained greater than 90% by 5 months after the second BNT162b2 dose, and lower against symptomatic infection at 70% [13]. Even lower mRNA VE against infection was reported by 5 months post-

second dose from California (50%) and Qatar (22%) [14, 15]. Methodological differences should be considered in comparing findings across these studies. Despite limitations, surveillance data may also provide a reality check for some of the more dramatic declines in reported VE. For example, a VE = 50% from California corresponds to RR = 2 for COVID-19 in unvaccinated versus fully vaccinated people. Statewide surveillance instead showed an RR > 7 between 26 September and 2 October 2021 [17], crudely corresponding to a VE = 87% at about 5 months after most fully vaccinated Californians had received their second dose. UK surveillance-based RRs seem more in keeping with their VE estimates [18]. Likewise, in BC and Quebec, surveillance-based (age-adjusted) RRs in November 2021 of 32 and 16, respectively, against hospitalization correspond to VE estimates of greater than 90%, and RRs of 8 and 3.6, respectively, against infection correspond to VE

estimates of greater than 70% [19, 20], in keeping with the sustained VE we report.

Pandemic vaccine program modifications in BC and Quebec were informed by ethical and vaccine principles, real-time risk-benefit assessment, and expert committee recommendations, but were implemented outside of regulatory approval. To date, there is still no head-to-head RCT comparison of mixed (heterologous) versus matched (homologous) SARS-CoV-2 vaccine efficacy. Immunogenicity studies show higher antibody titers following heterologous ChAdOx1 + mRNA versus homologous vector-based vaccination, with titers similar to homologous mRNA vaccination [21–23], but antibody thresholds for protection are not established. Our findings are thus important in providing epidemiological evidence in support of SARS-CoV-2 vaccine interchangeability and, moreover, the preferred use of mRNA vaccines to complete the 2-dose series initiated with ChAdOx1. The NACI recommendation in June 2021 enabling mixed schedules in Canada (Supplementary Table 1) removed the requirement to retain half of available doses in reserve for homologous series completion. This decision simplified vaccine logistics and likely improved protection for ChAdOx1 recipients during the ensuing Delta wave.

The lower 2-dose ChAdOx1 versus mRNA VE we report against infection is consistent with indirect comparison of efficacies across product-specific RCTs (~67% vs ~90%, respectively) [4, 6, 7, 24]. In pooled RCT meta-analysis, ChAdOx1 efficacy was better at longer intervals between doses: 55% at less than 6 weeks, 60% at 6–8 weeks, 64% at 9–11 weeks, and 81% at 12 weeks or more. Among RCT participants, 82% were revaccinated at the less-than-12-week interval, two-thirds of these at the shortest less-than-6-week spacing [24]. Our ChAdOx1 VE estimates are also weighted by and may reflect this variation by dosing interval. In BC, 94% of controls twice-vaccinated with ChAdOx1 were revaccinated at less than 12 weeks, about half at 7–8 weeks, and 40% at 9–11 weeks, with overall VE = 74%. In Quebec, 86% were revaccinated at less than 12 weeks, about one-third of them at 7–8 weeks, but more (60%) at the longer 9–11-week interval, yielding an overall higher ChAdOx1 VE = 78%, and exceeding 80% at the interval of 12 weeks or more, as per RCT analysis [24].

Improved 2-dose VE with longer spacing between the first and second doses may reflect improved opportunity for immune maturation between prime-boost events, reinforced empirically for mRNA vaccines in recent immunogenicity studies [25–28]. In addition to the population-based findings we report here, we also found 5–7% higher mRNA VE with the 7-week-or-greater compared with the 3–5-week dosing interval in TND analysis restricted to BC healthcare workers [29]. Epidemiological findings from the United Kingdom, however, have been more variable [25, 30, 31]. In a TND study of adults aged 50 years and older, Amirthalingam et al [25] found higher

BNT162b2 VE at an authorized schedule of more than 6 weeks versus 3 weeks between doses, whereas longitudinal studies among UK households [30] and healthcare workers [31] found no difference by interval. In dichotomizing dosing intervals, however, the latter 2 studies combined 7–8 weeks with shorter spacing (<9 weeks and  $\geq 6$  weeks, respectively), without displaying participant distributions by additional interval categories and potentially obscuring VE differences on that basis.

Ultimately, the optimal interval between first and second doses represents a balance between rapid and enhanced protection. Rapid revaccination may prevent some additional cases in the short term, but with substantial single-dose protection the absolute difference in severe outcomes prevented would be small outside periods of intense epidemic surge. Conversely, with a few added weeks between doses, the more durable immunity and approximately 5–10% increment in VE we report could ultimately prevent more cases and hospitalizations in the long term (depending upon evolving incidence and duration of protection). Informed by these and other considerations, including vaccine safety and routine schedule harmonization, Canada's NACI articulated 8 weeks as the preferred interval between mRNA doses in October (epi-week 42), 2021 (Supplementary Table 1), as did the World Health Organization in January (epi-week 3), 2022 [32], and the US Centers for Disease Control and Prevention in February (epi-week 8), 2022 [33].

Our study, based on general laboratory submissions and surveillance data, has limitations. Provincial immunization registries and NAAT-specific detection mitigated vaccination or outcome misclassification, but incomplete information remains possible. Exclusion of cases before the analysis period will have been incomplete, recognizing that not all infections were tested. The TND standardizes for the likelihood of being tested, but case ascertainment may vary by testing indication and vaccine status. Testing in both provinces was foremost, but not exclusively, symptom based. With restriction to outpatient symptom-based testing in Quebec, however, findings were similar to overall estimates against any infection in both provinces. We cannot rule out residual confounding such as associated with comorbidity, ethnicity, or socioeconomic status. Healthcare workers or immunocompromised individuals targeted for more rapid second-dose administration may have contributed to lower VE with shorter dosing intervals; however, weighted by their small percentage of the population, such underestimation would be minor. With high vaccine coverage, the subset remaining unvaccinated may differ, with the direction of resulting bias unknown and likely to vary with other public health measures. Reduced sample size affects the stability and precision of VE estimates, especially with greater sub-stratification. Finally, our studies were conducted in community-dwelling adults and may not be generalizable to other groups such as care-facility residents.

In conclusion, 2 doses of homologous or heterologous mRNA and/or ChAdOx1 vaccines provided powerful and persistent protection against hospitalization, spanning the duration of Delta dominance. Our findings support interchangeability and extended intervals between SARS-CoV-2 vaccine doses, with potential global implications for low-coverage areas and/or future cohorts of children. Vaccine effectiveness estimates reflect the prevailing conditions of vaccine-relatedness to predominantly circulating VOCs during the study period. As conditions change (eg, emergence and spread of Omicron or other immunological-escape variants), further vaccine and program adjustments (eg, antigen update and/or additional doses) should be guided by ongoing, real-time, risk–benefit assessment.

### 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

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**Ethics statement.** In both British Columbia (BC) and Quebec, vaccine effectiveness valuations were conducted as legally mandated public health investigations. Data linkages and analyses by the BC Centre for Disease Control were authorized under the Public Health Act as a delegated function of the Provincial Health Officer and by the Institut national de santé publique du Québec by direct order of the National Director of Public Health. Lead investigators in BC (Skowronski) and Quebec (De Serres) additionally sought independent research ethics board review which was waived by the University of British Columbia Clinical Research Ethics Board and granted by the Centre Hospitalier Universitaire (CHU) de Québec-Université Laval Research Ethics Board.

**Potential conflicts of interest.** G. D. S. received a grant paid to his institution for a meningococcal seroprevalence study from Pfizer in 2016. M. K. received grants/contracts paid to his institution from Roche (related to human papillomavirus), Hologic (related to human papillomavirus), and Siemens (related to human papillomavirus), unrelated to this work. M. S. has been an investigator on projects, unrelated to the current work, funded by GlaxoSmithKline, Merck, Moderna, Pfizer, Sanofi-Pasteur, Seqirus, Symvivo, and VBI Vaccines. All funds have been paid to his institute, and he has not received any personal payments. M. S. is also the Chair/Deputy Chair of 2 Data Safety Monitoring Boards (DSMBs) for coronavirus

disease 2019 (COVID-19) vaccine trials, involving different vaccines. R. G. received honoraria for an RSV Coordinators Workshop funded by AbbVie (payment to author). A. N. J. has received funding for other severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) sequencing and COVID-19 vaccine projects, paid to her institution and unrelated to the current work, from Genome BC, the Public Health Agency of Canada and the Canada Foundation for Innovation. D. M. S. reports contracts or grants, paid to her institution and unrelated to the current work, from Michael Smith Foundation for Health Research, Public Health Agency of Canada, and the Canadian Institutes of Health Research. G. D. reports a grant or contract paid to his institution from the Ministère de la Santé et des Services Sociaux du Québec. E. G. reports that their spouse is employed by QHR Tech, an electronic medical records company (no payments to author and author owns no stock in the company). All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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