Two-dose SARS-CoV-2 vaccine effectiveness with mixed schedules and extended dosing intervals: test-negative design studies from British Columbia and Quebec, Canada

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ABSTRACT

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

Methods—Two-dose VE against SARS-CoV-2 infection or hospitalization among adults ≥18-years-old, including due to Alpha, Gamma and Delta variants of concern (VOC), was assessed at ≥14 days post-vaccination by test-negative design studies separately conducted in British Columbia and Quebec, Canada between May 30 and November 27 (epi-weeks 22-47), 2021.

Results—In both provinces, all homologous or heterologous mRNA and/or ChAdOx1 two-dose schedules were associated with ≥90% reduction in SARS-CoV-2 hospitalization risk for at least 7 months. With slight decline from a peak of >90%, VE against infection was ≥80% for at least 6 months following homologous mRNA vaccination, lower by ~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 vs. manufacturer-specified 3–4-week interval 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.

Key words: SARS-CoV-2; vaccine effectiveness; test-negative design; heterologous; waning

BACKGROUND

The first SARS-CoV-2 vaccines in Canada were mRNA formulations, including BNT162b2 (Pfizer-BioNTech) authorized on December 9 (epi-week 50), 2020 and mRNA-1273 (Moderna) on December 23 (epi-week 52), both as two-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], suggesting the likely interchangeability of vaccines to facilitate subsequent completion of the two-dose schedule(**Supplementary_Material_1**). 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 March 3 (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 February 26 (epi-week 8),2021, a chimpanzee adenoviral-vectored (ChAdOx1) vaccine (AstraZeneca) was also authorized in Canada as a two-dose schedule, 4–12-weeks apart. On March 29 (epi-week 13), NACI recommended that ChAdOx1 be restricted to adults ≥55-years owing to vaccine safety concerns (thrombosis with thrombocytopenia), lowering to ≥30-years on April 23 (epi-week 16). On June 1 (epi-week 22), NACI 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 eight weeks(**Supplementary_Table_1**), by which time ≥70% of adults≥18-years-old had received at least one dose and <10% had received two doses. To maximize two-dose coverage by autumn, both provinces reduced the dosing-interval to four weeks such that by early-September (epi-week 35) 80% of adults were considered fully-vaccinated. The timeline of one- and two-dose vaccine coverage in BC and Quebec is provided in **Supplementary_Figure_1**.

We report two-dose vaccine effectiveness (VE) against infection and hospitalization among adults ≥18-years-old in BC and Quebec, spanning May 30—November 27 (epi-weeks 22-47), 2021 including early Alpha/Gamma and later Delta variant of concern (VOC) circulation. Mixed vaccine schedules and modified dosing intervals uniquely 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 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. VE and 95%CIs were computed as (1-AOR)x100%. Adjusted models included age group (18–49/50–69/70–79/≥80 years), sex (men/women), epi-week (categorical) and region. The latter includes the five health authorities in BC, with 18 administrative regions of Quebec also regrouped into five categories (Greater Montreal/Greater Quebec City/Central Quebec/Northern Quebec/Other).

Case and control selection

Specimens collected from adults ≥18-years-old between epi-weeks 22-47 and assessed for SARS-CoV-2 by publicly-funded nucleic-acid-amplification-test (NAAT) were eligible. In both provinces, publicly-funded, foremost symptom-based SAR-CoV-2 NAAT testing was broadly-accessible through community-based assessment centres, 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 centres for symptomatic individuals only (not possible in BC). Hospitalized cases were admitted on or ≤30days 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 (PIR). 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/before the specimen collection date, those who had received two doses of BNT162b2, mRNA-1273 or ChAdOx1 were considered vaccinated, those who had received just one dose of any vaccine were excluded, and those who received no doses were considered unvaccinated. In overall VE analysis, vaccination was defined by second-dose receipt ≥14days before specimen collection, excluding those vaccinated 0–13days prior; however, a range of time since 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 respective provincial public health legislation without requirement for research ethics board review.

FINDINGS

Case and control contribution

The total number of specimens collected from adults ≥18-years-old between epi-weeks 22-47 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 (not shown). Of the latter, 44,964 (75%) and 31,718 (79%) cases, respectively, were eligible for VE analyses, among

whom 3173 (7%) and 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 ≤2 test-negative specimens each. After randomly-selecting one 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, >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% 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 to provincial coverage estimates, the weekly percentage twice-vaccinated among study controls was higher in the early analysis period (as expected given 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, ~90% received two 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_3-4)**. Mixed mRNA recipients comprised 7% in BC and 2% in Quebec, with ~5% in both provinces receiving mixed ChAdOx1+mRNA doses.

Among twice-vaccinated controls, median interval between first and second doses of mRNA or ChAdOx1vaccines was 63 and 62days, respectively, in BC, longer at 69 and 73days in Quebec. In both provinces, few mRNA or ChAdOx1 recipients were revaccinated <7-weeks apart (~10% and 5%, respectively). More ChAdOx1 recipients in Quebec were revaccinated at 9-11-week-interval with more in Quebec also who were revaccinated at ≥12-weeks among recipients of both kinds of vaccine(**Supplementary_Tables_3-4**). Among twice-vaccinated controls in both provinces, median follow-up post-second-dose was ~12 weeks, slightly longer for ChAdOx1 recipients at ~14-15 weeks(**Supplementary_Tables_3-4**).

Vaccine effectiveness

Overall

At ≥14days post-second-dose, all schedules of homologous or heterologous mRNA and/or ChAdOx1 vaccines were associated with ≥95% reduction in SARS-CoV-2 hospitalization risk(**Figure_1**). VE against infection was 88-90% for two homologous or heterologous mRNA doses(**Figure_1; Supplementary_Table_5**), significantly lower for two 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_9-10**).

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, recognizing reduced sample size and other differences by province (e.g. dosing intervals).

By time since vaccination

Two-dose VE ≥95% against hospitalization lasted at least 8 months for mRNA recipients and 5 months for ChAdOx1, remaining ≥90% for at least 7 months for both products(**Figure_3; Supplementary_Table_12**). Against infection, two-dose mRNA VE was >90% through at least the 3rd month, declining slightly but still ≥80% through 6-7 months post-vaccination, including adults≥70-years-old(**Figure_3;Figure_4;Supplementary_Tables_12-13**). Findings were similar for schedules including at least one mRNA dose(**Supplementary_Table_12**), by age group(**Supplementary_Table_13**), and for Delta-specific outcomes(**Supplementary_Table_14**). In Quebec, two-dose ChAdOx1 VE against infection was ≥80% through 4months post-vaccination while ranging 74-77% in BC and ≥70% in both provinces through the 6th 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 ≥7-week vs. 3-4-week-interval between doses, BNT162b2 VE was significantly higher by 5% (absolute) in BC and 10% in Quebec. Similar but less pronounced pattern was observed for mRNA-1273. ChAdOx1 VE gradually increased with longer dosing-interval in Quebec but not BC where confidence intervals were wider(**Figure_5; Supplementary_Table_15**). VE 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 7-8-week vs. 3-4-week-interval 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 confidence intervals. Similar pattern was observed for mRNA-1273, but could not be assessed for ChAdOx1.

CONCLUSIONS

We report concordant findings from two 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 two-dose schedule using any combination of available homologous or heterologous vaccines was associated with ≥90% reduction in hospitalization risk for at least 7 months, spanning early-Alpha and late-Delta circulation. With slight decline from a peak of >90%, two-dose VE against infection was still ≥80% for at least 6 months following homologous mRNA vaccination, lower by ~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 RCT findings. In extended follow-up of participants in the BNT162b2 (Pfizer-BioNTech) RCT, two-dose efficacy against clinical infection peaked at 96% during the first two months, remaining >80% from four months to end of follow-up[4,5]. In the mRNA-1273 (Moderna) RCT, two-dose efficacy against COVID-19 illness was 93%, without waning across a median of 5.2 months[6,7]. In a two-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 ~1.6-times greater than among the placebo recipients later vaccinated (median 7.9 months follow-up)[8]. Applying relative risk (RR) of 1.6 to the COVID-19 incidence among individuals vaccinated during the Moderna RCT corresponds to minor efficacy drop from 93% to 89%[7,8].

Sustained two-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 UK, VE against Delta hospitalization remained >90% by five months after the second BNT162b2 dose, 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 reality check for some of the more dramatic-declines in reported VE. For example, a VE=50% from California corresponds with RR=2 for COVID-19 in unvaccinated vs. fully-vaccinated people. Statewide surveillance instead showed RR>7 between September 26—October 2,2021[17], crudely corresponding to VE=87% five 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 >90% and of 8 and 3.6, respectively, against infection correspond to VE >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) vs. matched (homologous) SARS-CoV-2 vaccine efficacy. Immunogenicity studies show higher antibody following heterologous ChAdOx1+mRNA versus homologous vector-based vaccination, with titres 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 two-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 two-dose ChAdOx1 vs. 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 interval between doses: 55% at <6-weeks, 60% at 6-8-, 64% at 9-11-, and 81% at ≥12-weeks. Among RCT participants, 82% were revaccinated at <12-week-interval, two-thirds of these at the shortest <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 <12-weeks, about half at 7-8- and 40% at 9-11-weeks, with overall VE=74%. In Quebec, 86% were revaccinated at <12-weeks, about one-third of them at 7-8- but more (60%) at longer 9-11-week-interval, yielding overall higher ChAdOx1 VE=78%, and exceeding 80% at ≥12-week-interval, as per RCT analysis[24].

Improved two-dose VE with longer spacing between 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 ≥7- vs. 3-5-week dosing-interval in TND analysis restricted to BC healthcare workers[29]. Epidemiological findings from

the UK, however, have been more variable[25,30,31]. In TND study of adults≥50-years-old, Amirthalingam found higher BNT162b2 VE at >6-week vs. 3-week authorized schedule between doses[25], whereas longitudinal studies among UK households[30] and healthcare workers[31] found no difference by interval. In dichotomizing dosing-intervals, however, the latter two studies combined 7-8-weeks with shorter spacing (<9 weeks and ≥6 weeks, respectively), without displaying participant distributions at finer categories and potentially obscuring VE differences on that basis.

Ultimately, the optimal interval between first and second doses represents a balance between rapid vs. enhanced protection. Rapid revaccination may prevent some additional cases on 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 ~5–10% increment in VE we report could ultimately prevent more cases and hospitalizations on 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 WHO in January (epi-week 3),2022[32], and the US CDC 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. Intended exclusion of cases before the analysis period will have been incomplete, recognizing 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 co-morbidity, ethnicity or socio-economic status. HCWs 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 under-estimation 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 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, two 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 global implications for low-coverage areas and/or future cohorts of children. VE estimates reflect the prevailing conditions of vaccine-relatedness to predominantly-circulating VOC during the study period. As conditions change (e.g. emergence and spread of Omicron or other immunological-escape variants), further vaccine and program adjustments (e.g. antigen update and/or additional doses) should be guided by ongoing, real-time, risk-benefit assessment.

NOTES

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Conflicts of interests

GDS received a grant paid to his institution for a meningococcal seroprevalence study from Pfizer in 2016. MK 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. MS 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. MS is also the Chair/Deputy Chair of two DSMBs for COVID-19 vaccine trials, involving different vaccines. RG received honoraria for an RSV Coordinators Workshop funded by AbbVie (payment to author). ANJ reports the following grants or contracts unrelated to this work: CFI (2020-25): Linking Transmission Metadata to Viral Genotype and Serological Response of COVID-19; CFI (2020-25): Linking Transmission Metadata to Viral Genotype and

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Table 1. Profile of participants ≥18-year-olds, by case and vaccine status (regardless of time since vaccination), British Columbia and Quebec, Canada

	British Columbia						Quebec					
	Overall [N=513877] (column %)			Vaccinated [N=409195] (row %)[1]			Overall [N=1017359] (column %)			Vaccinated [N=852594] (row %)[1]		
	Cases	Hosp	Controls	Cases	Hosp	Controls	Cases	Hosp	Controls	Cases	Hosp	Controls
Total	44964 (9)	3131 (7)[2]	468913 (91)	17835 (40)	537 (17)	391360 (83)	31718 (3)	1452 (5)	985641 (97)	15096 (48)	386 (27)	837498 (85)
Age group (years)												
18-49	31031 (69)	1043 (33)	294946 (63)	10984 (35)	77 (7)	236104 (80)	22923 (72)	527 (36)	581213 (59)	9435 (41)	65 (12)	463887 (80)
50-69	10817 (24)	1228 (39)	119581 (26)	5111 (47)	187 (15)	105464 (88)	6802 (21)	502 (35)	272785 (28)	4123 (61)	99 (20)	249170 (91)
70-79	2201 (5)	511 (16)	35608 (8)	1197 (54)	128 (25)	32817 (92)	1371 (4)	222 (15)	88922 (9)	1041 (76)	93 (42)	84744 (95)
80+	915 (2)	349 (11)	18778 (4)	543 (59)	145 (42)	16975 (90)	622 (2)	201 (14)	42721 (4)	497 (80)	129 (64)	39697 (93)
Median (Interquartile range)	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	22218 (49)	1302 (42)	263608 (56)	9520 (43)	216 (17)	224240 (85)	16480 (52)	639 (44)	574263 (58)	8209 (50)	169 (26)	490303 (85)
Male	22746 (51)	1829 (58)	205305 (44)	8315 (37)	321 (18)	167120 (81)	15238 (48)	813 (56)	411378 (42)	6887 (45)	217 (27)	347195 (84)
Epidemiological week, 2021												
22-26 (May 30-July 3)	1603(4)	137 (4)	24989(5)	106 (7)	5 (4)	9993 (40)	1383 (4)	74 (5)	78552 (8)	108 (8)	8 (11)	38666 (49)
27-30 (July 4-July 31)	1490 (3)	79 (3)	30236 (6)	337 (23)	12 (13)	21443 (71)	966 (3)	39 (3)	83187 (8)	211 (22)	6 (15)	63379 (76)
31-34 (August 1-28)	9515 (21)	526 (17)	74181 (16)	2556 (27)	64 (9)	59702 (80)	4513 (14)	212 (15)	120864 (12)	1376 (30)	42 (20)	100335 (83)
35-39 (Aug 29-Oct 2)	14827(33)	1036 (33)	133760 (29)	5702 (38)	171 (20)	115241 (86)	10613 (33)	599 (41)	251348 (26)	4368 (41)	134 (22)	222203 (88)
40-43 (Oct 3-Oct 30)	10227 (23)	808 (26)	114252 (24)	5022 (49)	153 (19)	102338 (90)	5958 (19)	290 (20)	221372 (22)	3316 (56)	102 (35)	201376 (91)
44-47 (Oct 31-Nov 27)	7302 (16)	545 (17)	91495 (20)	4112 (56)	132 (24)	82643 (90)	8285 (26)	238 (16)	230318 (23)	5717 (69)	94 (39)	211539 (92)
Two-dose vaccine status[3,4]												
Unvaccinated	27129 (60)	2594 (83)	77553 (17)	NA	NA	NA	16622 (52)	1066 (73)	148143 (15)	NA	NA	NA
Twice vaccinated, any vaccine	17835 (40)	537 (17)	391360 (83)	17835 (100)	537 (100)	391360 (100)	15096 (48)	386 (27)	837498 (85)	15096 (100)	386 (100)	837498 (100)
Two any mRNA vaccines	15625 (35)	497 (16)	356578 (76)	15625 (88)	497 (93)	356578 (91)	13854 (44)	344 (24)	771821 (78)	13854 (92)	344 (89)	771821 (92)
Two BNT162b2	11411 (25)	347 (11)	256357 (55)	11411 (64)	347 (65)	256357 (66)	10943 (35)	275 (19)	580186 (59)	10943 (72)	275 (71)	580186 (69)
Two mRNA-1273	3007 (7)	100 (3)	71406 (15)	3007 (17)	100 (19)	71406 (18)	2554 (8)	61 (4)	170714 (17)	2554 (17)	61 (16)	170714 (20)
Two mixed mRNA	1207 (3)	50 (2)	28815 (6)	1207 (7)	50 (9)	28815 (7)	357 (1)	8 (1)	20921 (2)	357 (2)	8 (2)	20921 (2)
Two ChAdOx1	1246 (3)	33 (1)	12682 (3)	1246 (7)	33 (6)	12682 (3)	597 (2)	30 (2)	22740 (2)	597 (4)	30 (8)	22740 (3)
Two mixed ChAdOx1/mRNA	962 (2)	6 (<1)	22094 (5)	962 (5)	6 (<1)	22094 (6)	645 (2)	12 (1)	42937 (4)	645 (4)	12 (3)	42937 (5)
Interval between doses[3]												
21-34 days (3-4 weeks)	NA	NA	NA	659 (4)	24 (5)	11738 (3)	NA	NA	NA	1151 (8)	38 (10)	40264 (5)
35-48 days (5-6 weeks)	NA	NA	NA	1611 (9)	46 (9)	25028 (6)	NA	NA	NA	1158 (8)	14 (4)	50667 (6)
49-62 days (7-8 weeks)	NA	NA	NA	6473 (36)	88 (16)	151324 (39)	NA	NA	NA	4346 (29)	53 (14)	220589 (26)
63-83 days (9-11 weeks)	NA	NA	NA	5787 (32)	180 (34)	138467 (35)	NA	NA	NA	4926 (33)	108 (28)	289152 (35)
84-111 days (12-15 weeks)	NA	NA	NA	2805 (16)	161 (30)	55546 (14)	NA	NA	NA	2242 (15)	99 (26)	154183 (18)
112+ days (16+ weeks)	NA	NA	NA	500 (3)	38 (7)	9257 (2)	NA	NA	NA	1273 (8)	74 (19)	82643 (10)
Median (Interquartile range) days	NA	NA	NA	63 (55-77)	76 (60-91)	63 (56-75)	NA	NA	NA	65 (56-82)	80 (59-100)	69 (57-87)
Time since second dose[3]												
0-13 days (0-1 weeks)	NA	NA	NA	1206 (7)	29 (5)	19806 (5)	NA	NA	NA	917 (6)	17 (4)	51377 (6)
14-27 days (2-3 weeks)	NA	NA	NA	498 (3)	14 (3)	24902 (6)	NA	NA	NA	425 (3)	21 (5)	58734 (7)
28-55 days (4-7 weeks)	NA	NA	NA	2016 (11)	45 (8)	63850 (16)	NA	NA	NA	1640 (11)	35 (9)	137333 (16)
56-83 days (8-11 weeks)	NA	NA	NA	3361 (19)	95 (18)	83821 (21)	NA	NA	NA	2821 (19)	59 (15)	167477 (20)
84-111 days (12-15 weeks)	NA	NA	NA	4051 (23)	121 (23)	87149 (22)	NA	NA	NA	3300 (22)	98 (25)	175612 (21)
112-139 days (16-19 weeks)	NA	NA	NA	3750 (21)	114 (21)	67778 (17)	NA	NA	NA	3428 (23)	87 (23)	148369 (18)
140-167 days (20-23 weeks)	NA	NA	NA	1739 (10)	87 (16)	29354 (8)	NA	NA	NA	1847 (12)	55 (14)	71897 (9)
168-195 days (24-27 weeks)	NA	NA	NA	381 (2)	12 (2)	5815 (1)	NA	NA	NA	455 (3)	9 (2)	18520 (2)
196+ days (28+ weeks)	NA	NA	NA	833 (5)	20 (4)	8885 (2)	NA	NA	NA	263 (2)	5 (1)	8179 (1)
Median, Interquartile range	NA	NA	NA	96 (63-127)	103 (71-133)	85 (51-116)	NA	NA	NA	98 (64-129)	102 (72-127)	84 (48-118)

NA = Not applicable; Hosp = hospitalized cases

[1] 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.
[2] Displayed is the percentage of cases who were hospitalized.
[3] 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 %
[4] In British Columbia, two cases (one hospitalized) and six controls from vaccinated individuals had unspecified vaccine type for first or second dose.

FIGURE LEGENDS

Figure 1. Adjusted two-dose vaccine effectiveness against infection and hospitalization (overall and Delta-specific), by vaccine type, adults ≥18 years old, British Columbia and Quebec, Canada, epi-weeks 22-47 (May 30 – November 27) of 2021

Shown are adjusted VE and 95% CIs against infection (blue) and hospitalization (orange) ≥14 days after the second dose by vaccine type, overall (panel A) and for the Delta variant of concern (panel B) among adults ≥18 years old in the provinces of BC and Quebec, Canada. In Quebec, VE against Delta hospitalization was assessed only between epi-weeks 31-47 because no hospitalized Delta variant cases were identified prior to that period. For additional details including corresponding sample sizes, 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; VE, vaccine effectiveness.

Figure 2. Adjusted two-dose vaccine effectiveness against infection and hospitalization, by age group, sex and vaccine type, adults ≥18 years old, British Columbia and Quebec, Canada, epi-weeks 22-47 (May 30 – November 27) of 2021

Shown are adjusted VE estimates and 95% CIs against infection (blue) and hospitalization (orange) ≥14 days after the second dose by age group (panel A) and sex (panel B) and by vaccine type in BC and QC, Canada. In Quebec, adjusted VE against hospitalization in ≥70-year-old adults required collapse of epi-week categories (tri-weekly) owing to sample size considerations. For additional details including corresponding sample sizes, 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 ≥100%; QC, Quebec; VE, vaccine effectiveness.

Figure 3. Adjusted two-dose mRNA and ChAdOx1 vaccine effectiveness against infection and hospitalization by time since vaccination, adults ≥18 years old, British Columbia and Quebec, Canada, epi-weeks 22-47 (May 30 – November 27) 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 two mRNA vaccines and panel B displays for those who received two ChAdOx1 vaccines. Owing to sparse data, mRNA estimates are not displayed beyond the 8th month post-vaccination against hospitalization in Quebec or beyond the 7th month post-vaccination for ChAdOx1 in either province. Displayed are the point estimates against hospitalization for BC and against infection for Quebec. For additional details including 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 sub-groups 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.

Figure 4. Adjusted two-dose vaccine effectiveness against infection and hospitalization, by time since mRNA vaccination, adults ≥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 ≥70 years old in BC (solid lines) and Quebec (dashed lines). In Quebec, adjusted VE against hospitalization required collapse of epi-week categories (tri-weekly) owing to sample size considerations. Displayed are the point estimates against hospitalization for BC and against infection for Quebec. For additional details including 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.

Figure 5. Adjusted two-dose vaccine effectiveness against infection and hospitalization, by interval between doses, mRNA and ChAdOx1 vaccines, adults ≥18 years old, British Columbia and Quebec, Canada

Shown are adjusted VE estimates and 95% CIs against infection (blue) and hospitalization (orange) at ≥14 days after the second dose, by interval between the first and second dose among adults ≥18 years old who were vaccinated with any two mRNA vaccines or two ChAdOx1 vaccines 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 ≥100%; VE, vaccine effectiveness; w, weeks.

Figure 6. Adjusted two-dose BNT162b2 vaccine effectiveness against infection by interval between doses and time since second dose, adults ≥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 ≥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: CI, confidence interval; d, days; VE, vaccine effectiveness; V1, dose one; V2, dose two; w, weeks.

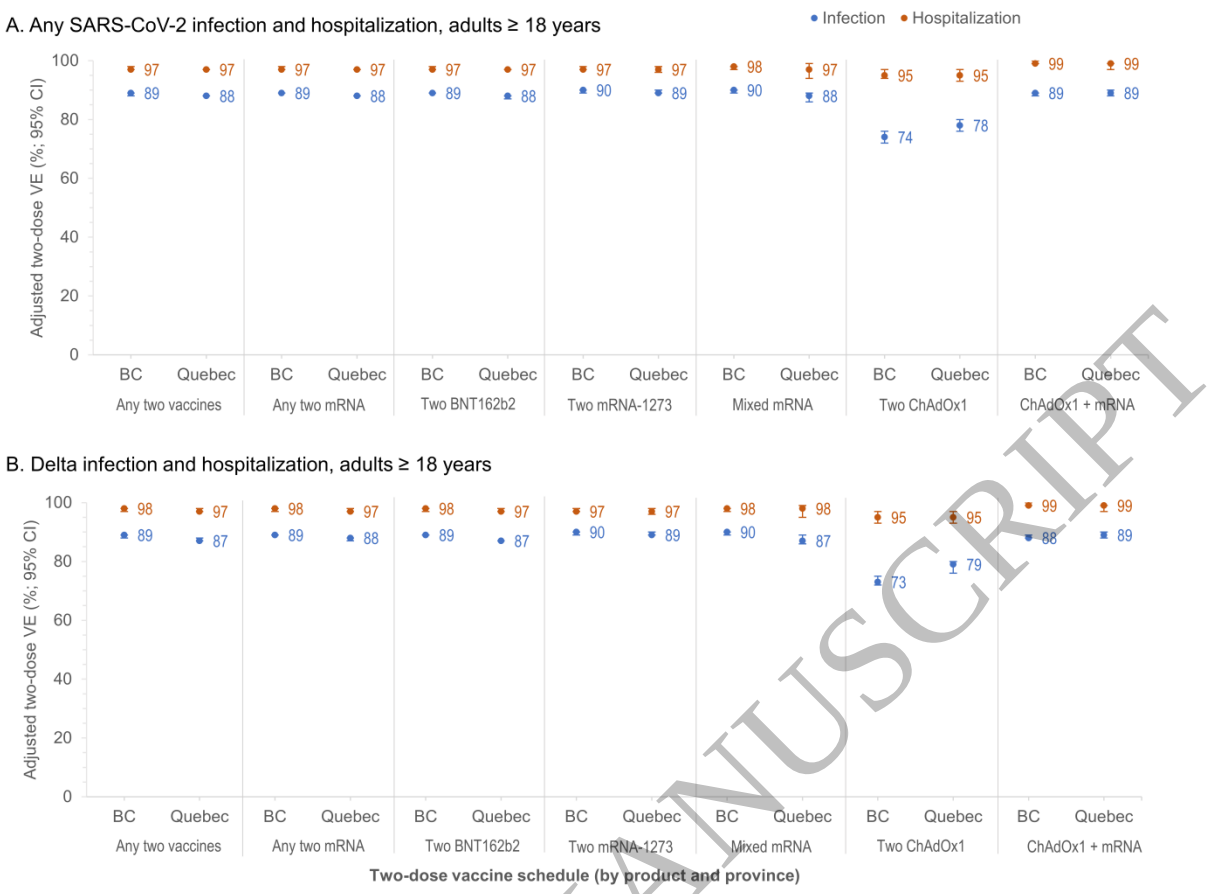

Figure 1
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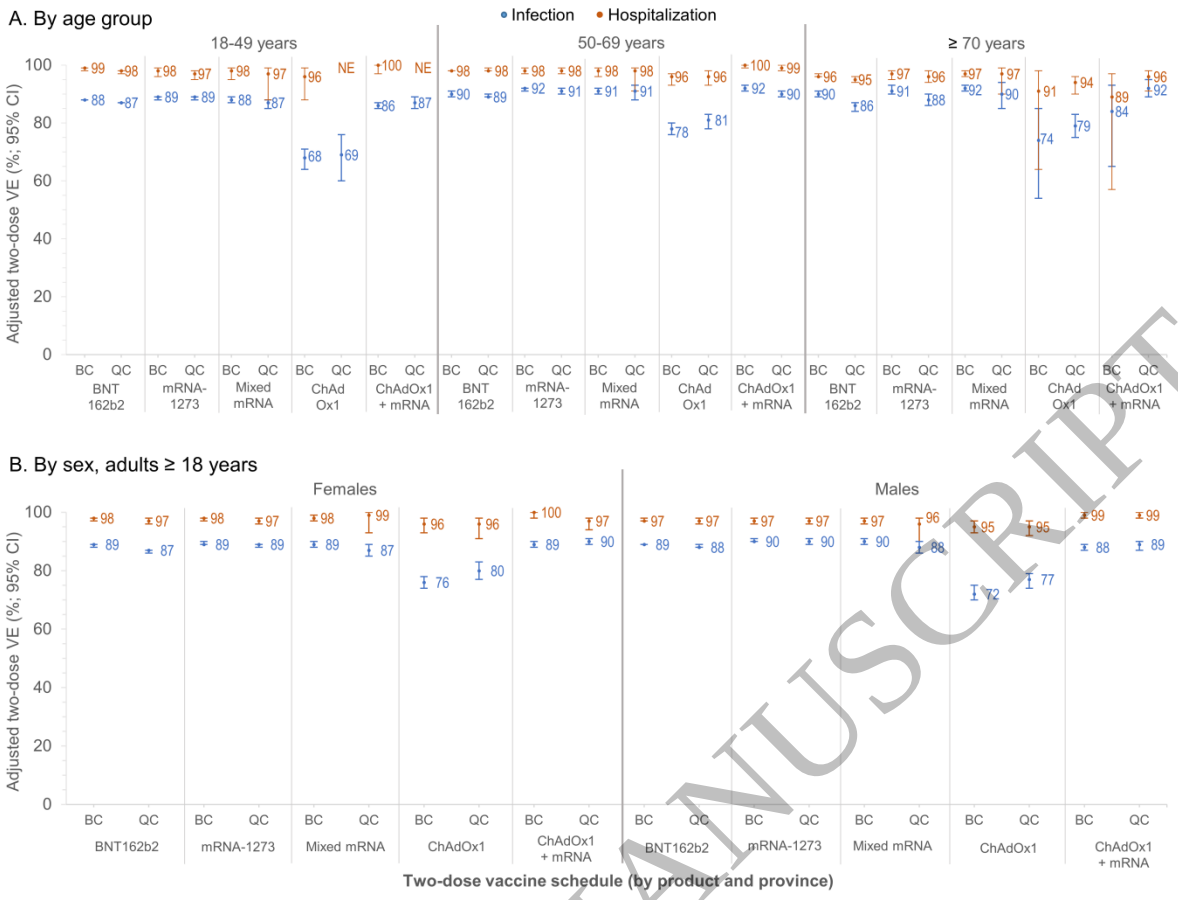

Figure 2
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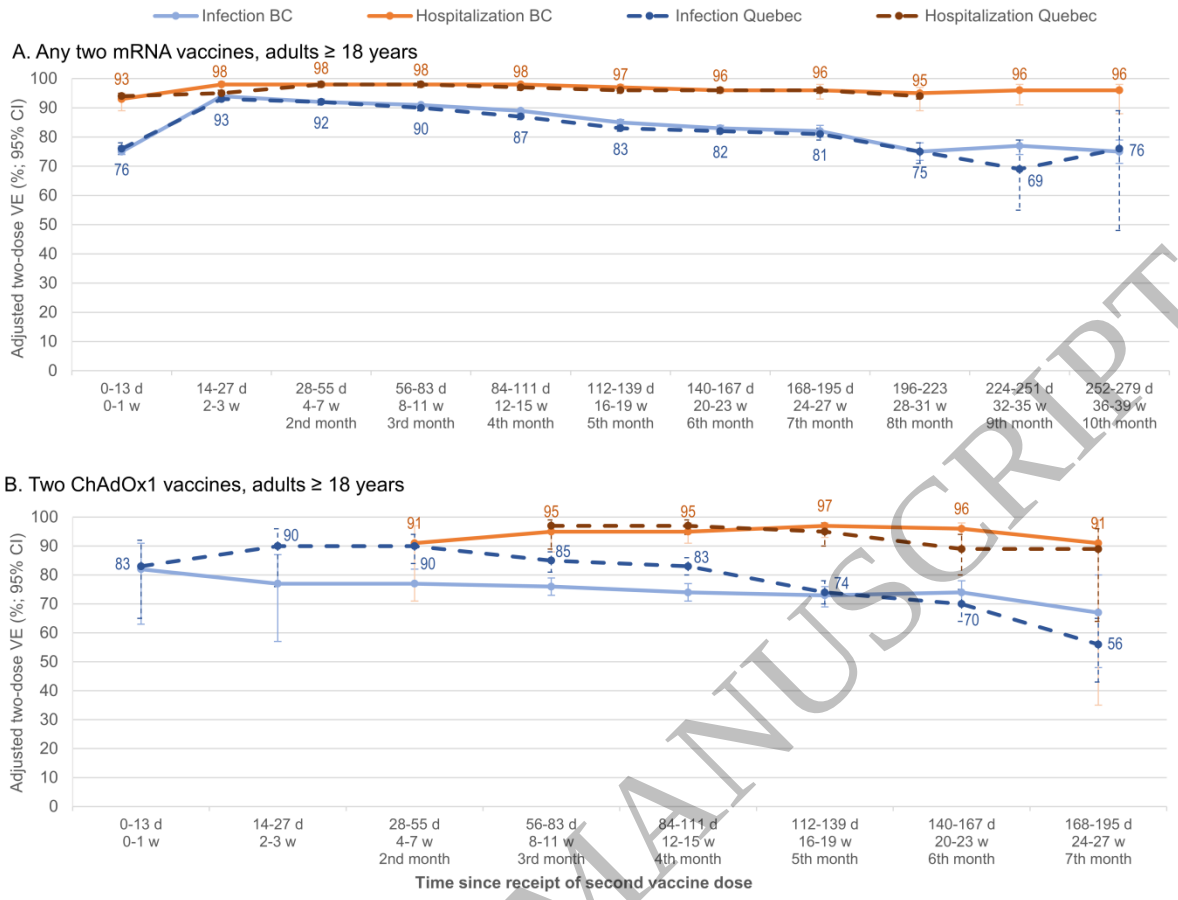

Figure 3

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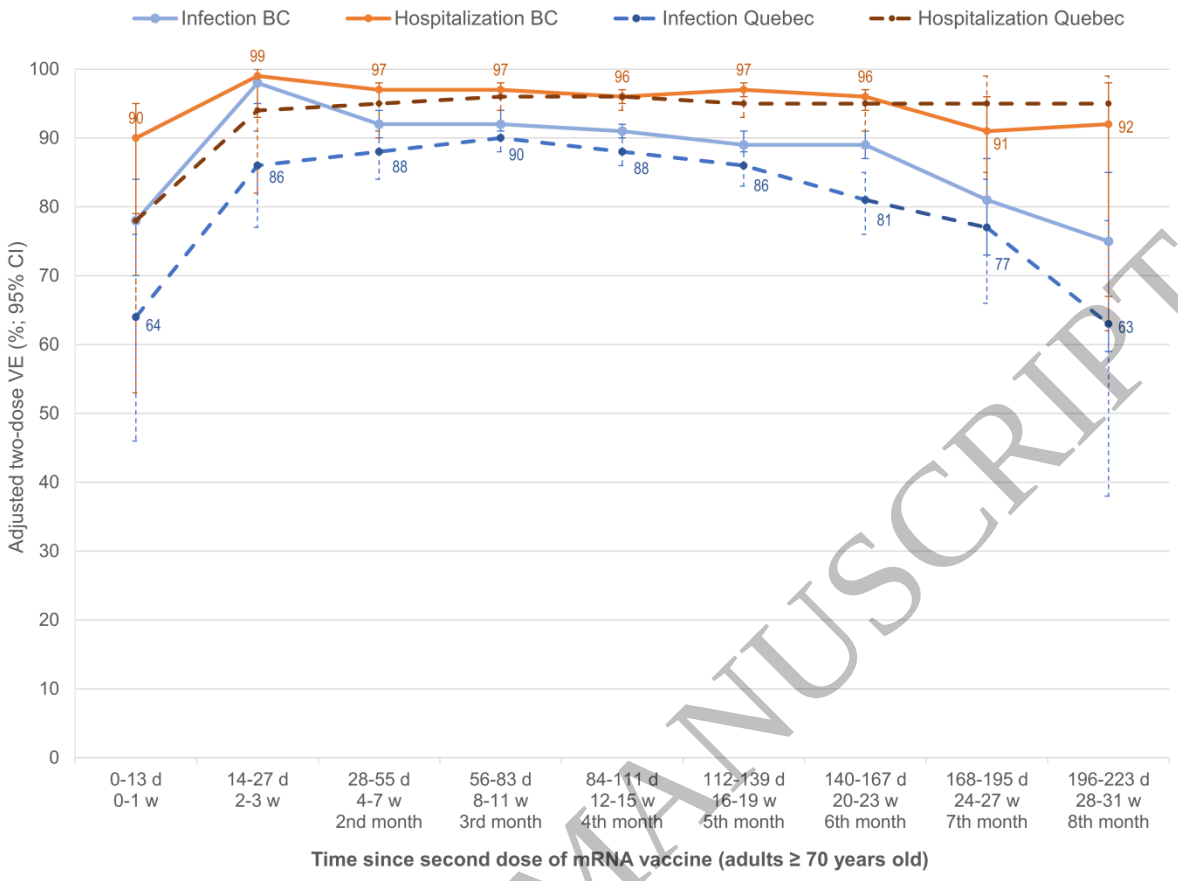

Figure 4
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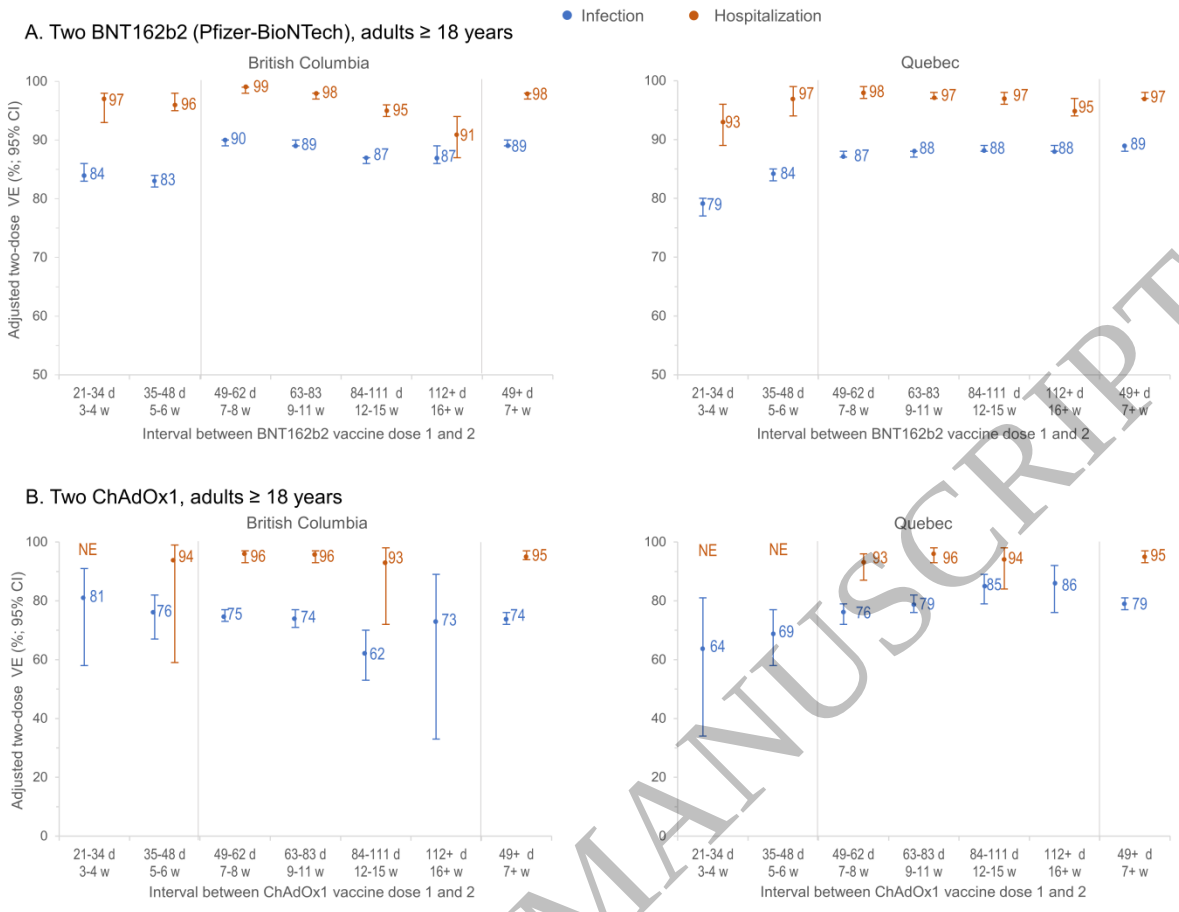

Figure 5
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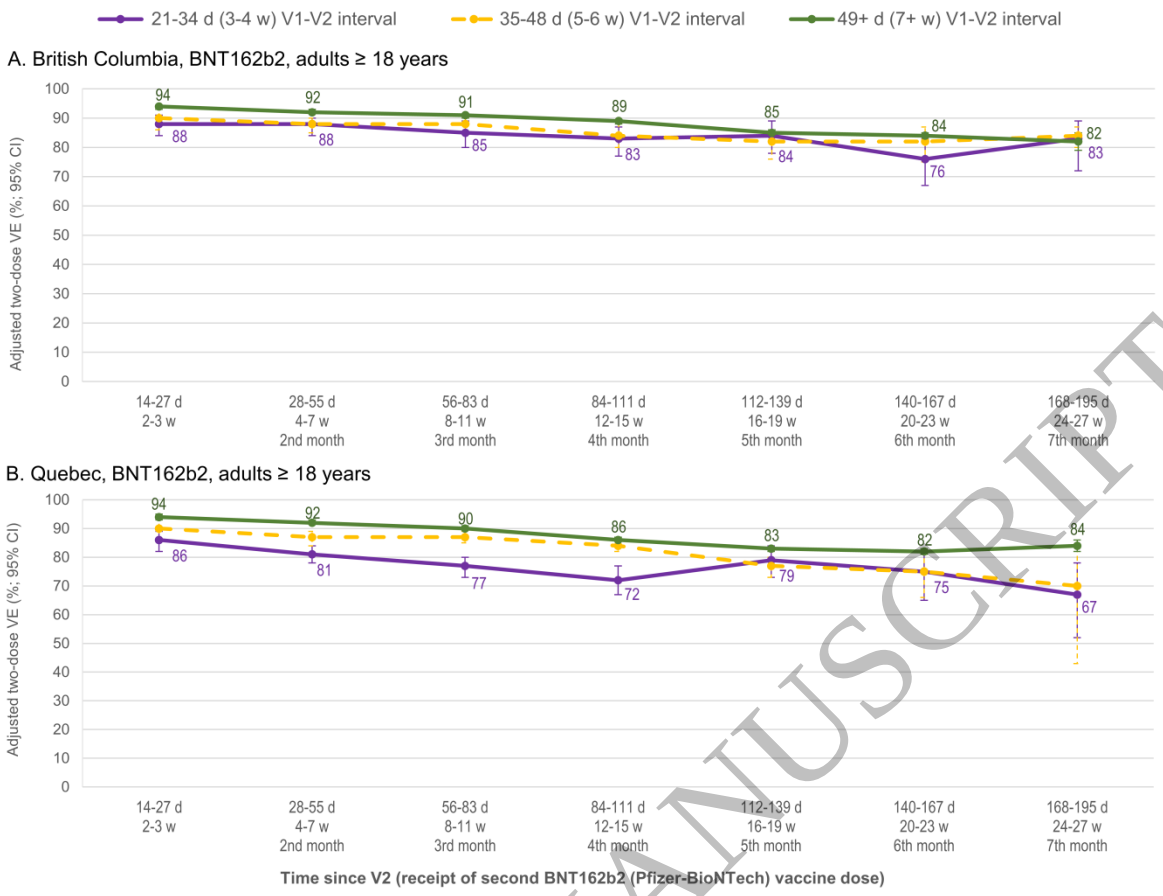

Figure 6
159x90 mm (8.8 x DPI)