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Effectiveness of COVID-19 Vaccines Over Time Prior to Omicron Emergence in Ontario, Canada: Test-Negative Design Study

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Background. Waning protection from 2 doses of coronavirus disease 2019 (COVID-19) vaccines led to third dose availability in multiple countries even before the emergence of the Omicron variant.

Methods. We used the test-negative study design to estimate vaccine effectiveness (VE) against any severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, any symptomatic infection, and severe outcomes (COVID-19-related hospitalizations or death) by time since second dose of any combination of BNT162b2, mRNA-1273, and ChAdOx1 between January 11, and November 21, 2021, for subgroups based on patient and vaccine characteristics.

Results. We included 261 360 test-positive cases (of any SARS-CoV-2 lineage) and 2 783 699 individuals as test-negative controls. VE of 2 mRNA vaccine doses decreased from 90% (95% CI, 90%–90%) 7–59 days after the second dose to 75% (95% CI, 72%–78%) after ≥240 days against infection, decreased from 94% (95% CI, 84%–95%) to 87% (95% CI, 85%–89%) against symptomatic infection, and remained stable (98% [95% CI, 97%–98%] to 98% [95% CI, 96%–99%]) against severe outcomes. Similar trends were seen with heterologous ChAdOx1 and mRNA vaccine schedules. VE estimates for dosing intervals <35 days were lower than for longer intervals (eg, VE of 2 mRNA vaccines against symptomatic infection at 120–179 days was 86% [95% CI, 85%–88%] for dosing intervals <35 days, 92% [95% CI, 91%–93%] for 35–55 days, and 91% [95% CI, 90%–92%] for ≥56 days), but when stratified by age group and subperiod, there were no differences between dosing intervals.

Conclusions. Before the emergence of Omicron, VE of any 2-dose primary series, including heterologous schedules and varying dosing intervals, decreased over time against any infection and symptomatic infection but remained high against severe outcomes.

Keywords. SARS-CoV-2; COVID-19; vaccine effectiveness; waning immunity.

Concerns about waning protection from a 2-dose primary series of coronavirus disease 2019 (COVID-19) vaccines led to third dose recommendations in many countries starting in late summer 2021, but at that time, much was unknown about the need for and optimal timing of third doses. A recent metaregression demonstrated sustained protection against severe outcomes (ie, hospitalization or death) of 2 homologous doses of COVID-19 vaccines (Pfizer-BioNTech BNT162b2 [Comirnaty], Moderna mRNA-1273 [Spikevax], AstraZeneca ChAdOx1 [Vaxzevria]) for 6 months after the second dose; however, protection against infection and symptomatic disease decreased over time [1]. These patterns were seen even during the predominance of the Delta variant (B.1.617.2), a variant that COVID-19 vaccines seem to be modestly less effective against compared with the Alpha variant (B.1.1.7) [2–7].

Due to vaccine supply constraints during early 2021, Canada's National Advisory Committee on Immunization recommended delaying the second dose of the primary vaccine series by up to 16 weeks after the first dose [8]. As vaccine supplied increased, most Canadian jurisdictions gradually reduced the interval between doses (dosing interval) toward the manufacturers' recommendations. Improved immunological responses [9, 10] and greater effectiveness [11] have been observed with longer dosing intervals, but individuals with longer dosing intervals have less observation time for waning vaccine effectiveness (VE) to manifest.

Due to safety concerns about vaccine-induced thrombocytic thrombocytopenia following ChAdOx1, Canadian jurisdictions discontinued its routine use in May 2021 [12] and recommended mRNA vaccines for the second primary dose. Both immunogenicity and safety data support the use of schedules combining ChAdOx1 and mRNA vaccines [13–18]. Furthermore, individuals were allowed to receive different mRNA products for their primary vaccine series based on the recommendation of interchangeable mRNA vaccines [19].

There are relatively limited data on the real-world effectiveness of heterologous schedules and extended dosing intervals against clinical outcomes [11, 20–24], and evaluating VE in Ontario, Canada, where these recommendations were implemented, presents a unique opportunity to assess different COVID-19 vaccine schedules. The objective of this study was to evaluate the duration of effectiveness of various 2-dose primary series COVID-19 vaccine schedules against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, symptomatic infection, and severe outcomes.

METHODS

Study Population, Setting, and Design
We conducted a test-negative design study among Ontario residents who were aged ≥16 years, registered for provincial health insurance, and not residing in a long-term care facility as of December 14, 2020 (the start of Ontario's vaccination program). Study subjects must have had ≥1 diagnostic reverse transcription polymerase chain reaction (RT-PCR) test for SARS-CoV-2 between January 11, 2021 (the earliest date for postvaccination outcomes given the initial 21-day dosing interval for BNT162b2 and allowing 7 days following the second dose before evaluating VE), and November 21, 2021 (the date before the first diagnosed Omicron [B.1.1.529] case in Ontario).

We divided our study period into 3 subperiods that aligned with the predominance of SARS-CoV-2 variants of concern (VOCs; January 11, 2021, to April 4, 2021 [mixed circulation of wild-type SARS-CoV-2 and Alpha], April 5, 2021, to June 27, 2021 [~77% Alpha], and June 28, 2021, to November 21, 2021 [~97% Delta] [25]) to mitigate the impact of changing VOCs over time on VE estimates.

We excluded tests from individuals who, on the testing date, had previously tested positive for SARS-CoV-2 or had received only a single vaccine dose, had received 2 doses but were <7 days from the second dose, had received any non–Health Canada–approved vaccines (including the Johnson & Johnson/Janssen Ad26.COV2.S vaccine, which was approved but rarely used in Ontario), or had received 3 doses.

Data Sources
We linked provincial SARS-CoV-2 laboratory testing, reportable disease, COVID-19 vaccination, and health administrative data sets using unique encoded identifiers and analyzed them at ICES (formerly the Institute for Clinical Evaluative Sciences). ICES is an independent, nonprofit research institute in Ontario, Canada, whose legal status under the province's health information privacy law allows it to collect and analyze health care and demographic data, without consent, for health system evaluation and improvement.

Outcomes
We assembled 3 non–mutually exclusive study populations to assess VE against any infection, symptomatic infection, and severe outcomes (COVID-19-associated hospitalizations or death) separately. Individuals who tested positive at least once during the study period were considered cases, and those who tested negative throughout were considered controls. For cases with multiple occurrences of the same outcome, we selected the first occurrence. For those considered controls, we randomly selected 1 negative test during each subperiod. Thus, controls could be included up to 3 times. Further details are available in the Supplementary Methods.

COVID-19 Vaccination
Using a centralized province-wide COVID-19 vaccine registry, we determined the interval between the date of second dose receipt and the index date (specimen collection date or hospitalization or death date, if earlier, for severe outcomes). We considered individuals ≥7 days after their second dose to be vaccinated. Additional details are provided in the Supplementary Methods.

Covariates
From various databases (Supplementary Table 1), we obtained information on age (categorized as 10-year age bands), sex, public health unit region of residence, number of SARS-CoV-2 RT-PCR tests during the 3 months before December 14, 2020 (proxy for individuals at increased risk of SARS-CoV-2 exposure), comorbidities, influenza vaccination status during the 2019/2020 and 2020/2021 influenza seasons, and neighborhood-level sociodemographic information on median household income, proportion of the working population employed as nonhealth essential workers, mean number of persons per dwelling, and proportion of the population who self-identify as a visible minority.

Statistical Analysis
For each outcome-specific study population and subperiod, we calculated means (continuous covariates) and frequencies (categorical covariates) and compared test-positive cases and test-negative controls using standardized differences.

We used multivariable logistic regression to estimate odds ratios (ORs) comparing the odds of being in each time-since-second-dose interval (7–59, 60–119, 120–179, 180–239, ≥240

days) with the odds of being unvaccinated between cases and controls, while adjusting for all listed covariates and biweekly period of test. VE at each time-since-second-dose interval was calculated using the formula $VE_{interval} = (1 - OR_{interval/unvaccinated}) \times 100\%$. For each outcome, we determined VE by time since second dose for the overall study population, and subgroups by dosing interval (15–34, 35–55, ≥56 days), vaccine schedule, and study subperiod. We also stratified by age group (16–69, ≥70 years), comorbidity status, and number of prior SARS-CoV-2 tests.

We also estimated VE by time since second dose within strata defined by combinations of age group, dosing interval, and subperiod to evaluate VE over time while controlling for factors hypothesized to impact VE (eg, variants with mutations that may evade immune responses, age-related immunosenescence) [26]. Where possible, we conducted analyses separately for 2-dose mRNA vaccine and ChAdOx1-containing schedules. However, as ChAdOx1 recipients were recommended to wait at least 8 weeks before receiving their second dose [27], analyses assessing dosing intervals were not conducted for ChAdOx1-containing schedules.

We conducted the following sensitivity analyses to assess some biases that could affect estimates of VE duration [1]. First, we repeated all analyses but included individuals who tested positive for SARS-CoV-2 previously to assess whether differential depletion of susceptibles between vaccinated and unvaccinated individuals contributed to trends in VE over time [28]. We adjusted for prior SARS-CoV-2 infection in those models. Second, for higher outcome specificity, we restricted the analysis to Delta cases (confirmed by whole-genome sequencing [WGS] or mutation screening) in the last subperiod. Third, we used different definitions for severe outcomes of varying specificity to determine whether effectiveness differed between severe outcomes *due to* COVID-19 vs those incidentally diagnosed near the time of hospitalization or death. These definitions and methods for VOC categorization are summarized in the Supplementary Methods.

All analyses were conducted using SAS, version 9.4 (SAS Institute Inc., Cary, NC, USA). All tests were 2-sided and used $P < .05$ as the level of statistical significance. We did not report estimates of VE when 95% confidence intervals were extremely imprecise (ie, ranging between a very large negative number and nearly 100) or when VE was estimated based on 0 vaccinated test-positive cases and the 95% CIs were essentially infinite.

RESULTS

Creation of the 3 outcome-specific study populations and characteristics by case and control status are presented in the Supplementary Results (Supplementary Figure 1; Supplementary Tables 2–4). The distribution of 2-dose primary series vaccine schedules between individuals in our study population and the Ontario general population (not tested during the study period) was similar, but dosing intervals were longer for those not tested (Supplementary Figures 2A and 2B; Supplementary Table 5).

For both 2-dose mRNA and ChAdOx1-containing schedules, VE was highest against severe outcomes (ranging from 95% to 99%, depending on the time since second dose), intermediate against symptomatic infection (82%–94%), and lowest against any infection (74%–92%) (Table 1; Supplementary Tables 6 and 7). VE for each time-since-second-dose category generally differed by ≤15 percentage points (mostly within 5 percentage points) across strata by patient or vaccine characteristics for the same outcome and type of vaccine schedule. Notably, similar estimates were seen between individuals with and without comorbidities. VE estimates for heterologous ChAdOx1 and mRNA vaccine schedules were similar to 2-dose mRNA schedules (eg, VE against symptomatic infection at 120–179 days was 94% [95% CI, 92%–95%] for ChAdOx1/BNT162b2, 93% [95% CI, 91%–94%] for ChAdOx1/mRNA-1273, 90% [95% CI, 89%–91%] for 2 BNT162b2 doses, 91% [95% CI, 90%–92%] for 2 mRNA-1273 doses, and 93% [95% CI, 91%–94%] for mixed mRNA schedules) and distinctly higher than for 2 doses of ChAdOx1 (eg, VE against symptomatic infection at 120–179 days was 80% [95% CI, 76%–84%]) (Figure 1). For 2-dose mRNA schedules, consistently across all characteristics, VE against any infection and symptomatic infection decreased by larger magnitudes over time; for example, VE against any infection decreased 15 percentage points (from 90% [95% CI, 90%–90%] 7–59 days after the second dose to 75% [95% CI, 72%–78%] after ≥240 days), and VE against symptomatic infection decreased 7 percentage points (from 94% [95% CI, 84%–95%] to 87% [95% CI, 85%–89%]). VE at each time-since-second dose category for dosing intervals <35 days was lower than for longer intervals (eg, at 120–179 days since second dose, VE against symptomatic infection was 86% [95% CI, 85%–88%] for dosing interval <35 days, 92% [95% CI, 91%–93%] for 35–55 days, and 91% [95% CI, 90%–92%] for ≥56 days) but the magnitudes of the decline over time did not differ by dosing interval (Figure 2).

When stratified by age group, dosing interval, and subperiod, the decreases in VE for 2 mRNA doses by time since second dose were consistent across strata, though the peak VE depended on the dosing interval and outcome (Figures 3, 4; Supplementary Tables 8–13). For the subperiod June 28 to November 21, 2021 (when longer time-since-second-dose intervals could be assessed), we observed the largest decreases in VE against any infection among subjects aged 16–69 years with a dosing interval of ≥56 days (from 91% [95% CI, 90%–92%] at 7–59 days to 75% [95% CI, 64%–83%] at 180–239 days) and those aged ≥70 years with a dosing interval of 35–55 days (from 89% [95% CI, 81%–94%] to 68% [95% CI,

Table 1. Vaccine Effectiveness of Any 2-Dose mRNA Vaccine or Any 2-Dose ChAdOx1-Containing Schedule Against SARS-CoV-2 Infection, Symptomatic SARS-CoV-2 Infection, and Severe Outcomes Between January 11, 2021, and November 21, 2021, in Ontario, Canada, by Time Since Second Dose, by Various Factors

Vaccine Effectiveness (95% CI)[a]

Overall

Time Since Second Dose, d	Any Infection mRNA[b]	Any Infection ChAdOx1[c]	Symptomatic Infection mRNA[b]	Symptomatic Infection ChAdOx1[c]	Severe Outcomes mRNA[b]	Severe Outcomes ChAdOx1[c]
7–59	90 (90, 90)	88 (87, 90)	94 (94, 95)	93 (92, 95)	98 (97, 98)	97 (95, 98)
60–119	86 (86, 87)	83 (82, 85)	93 (92, 93)	91 (89, 92)	98 (98, 98)	98 (97, 99)
120–179	82 (82, 83)	75 (73, 77)	91 (90, 91)	88 (86, 89)	97 (97, 98)	98 (97, 99)
180–239	74 (72, 75)	92 (69, 98)	82 (80, 84)	d	95 (93, 96)	d
≥240	75 (72, 78)	d	87 (85, 89)	d	98 (96, 99)	d

BNT162b2 only

Time Since Second Dose, d	Any Infection	Symptomatic Infection	Severe Outcomes
7–59	89 (89, 90)	94 (93, 94)	98 (97, 98)
60–119	85 (85, 86)	92 (91, 92)	98 (98, 98)
120–179	81 (80, 82)	90 (89, 91)	97 (96, 97)
180–239	73 (71, 75)	83 (81, 85)	94 (92, 96)
≥240	74 (71, 77)	87 (84, 89)	98 (95, 99)

mRNA-1273 only

Time Since Second Dose, d	Any Infection	Symptomatic Infection	Severe Outcomes
7–59	92 (92, 93)	95 (94, 96)	97 (95, 98)
60–119	88 (88, 89)	94 (94, 95)	99 (98, 99)
120–179	85 (84, 86)	91 (90, 92)	98 (97, 99)
180–239	75 (71, 79)	79 (73, 83)	97 (93, 99)
≥240	79 (70, 86)	87 (78, 92)	98 (88, 100)

ChAdOx1 only

Time Since Second Dose, d	Any Infection	Symptomatic Infection	Severe Outcomes
7–59	83 (79, 86)	86 (80, 90)	95 (89, 98)
60–119	72 (69, 75)	84 (81, 87)	96 (94, 98)
120–179	67 (63, 71)	80 (76, 84)	97 (94, 98)
180–239	96 (71, 99)	d	d
≥240	d	d	d

ChAdOx1 and BNT162b2

Time Since Second Dose, d	Any Infection	Symptomatic Infection	Severe Outcomes
7–59	90 (88, 92)	94 (92, 95)	98 (94, 99)
60–119	88 (86, 90)	94 (92, 95)	96 (94, 98)
120–179	77 (73, 80)	90 (87, 92)	98 (96, 99)
180–239	e	d	d

ChAdOx1 and mRNA-1273

Time Since Second Dose, d	Any Infection	Symptomatic Infection	Severe Outcomes
7–59	91 (89, 93)	96 (94, 97)	98 (94, 99)
60–119	87 (86, 89)	93 (91, 94)	100 (98, 100)
120–179	80 (77, 83)	93 (91, 95)	98 (96, 99)
180–239	d	d	d

Mixed mRNA vaccine schedule

Time Since Second Dose, d	Any Infection	Symptomatic Infection	Severe Outcomes
7–59	92 (91, 92)	96 (96, 97)	99 (98, 99)
60–119	88 (87, 88)	94 (93, 94)	99 (98, 99)
120–179	83 (82, 85)	93 (92, 94)	99 (97, 99)
180–239	d	d	d

Aged 16–69 y

Time Since Second Dose, d	Any Infection mRNA[b]	Any Infection ChAdOx1[c]	Symptomatic Infection mRNA[b]	Symptomatic Infection ChAdOx1[c]	Severe Outcomes mRNA[b]	Severe Outcomes ChAdOx1[c]
7–59	90 (90, 91)	89 (87, 90)	94 (94, 95)	93 (91, 95)	98 (98, 99)	98 (95, 99)
60–119	86 (86, 87)	84 (82, 85)	93 (92, 93)	91 (89, 92)	99 (98, 99)	99 (98, 99)
120–179	83 (82, 84)	75 (73, 77)	91 (90, 91)	88 (86, 89)	99 (98, 99)	98 (97, 99)
180–239	74 (72, 76)	90 (61, 98)	83 (81, 85)	d	98 (96, 99)	d
≥240	75 (72, 78)	d	87 (84, 89)	d	99 (96, 100)	d

Aged ≥70 y

Time Since Second Dose, d	Any Infection mRNA[b]	Any Infection ChAdOx1[c]	Symptomatic Infection mRNA[b]	Symptomatic Infection ChAdOx1[c]	Severe Outcomes mRNA[b]	Severe Outcomes ChAdOx1[c]
7–59	89 (87, 90)	88 (75, 94)	94 (92, 95)	97 (80, 100)	95 (94, 96)	96 (74, 100)
60–119	84 (83, 86)	76 (65, 83)	93 (92, 94)	88 (79, 93)	97 (96, 97)	93 (84, 97)
120–179	77 (74, 79)	67 (50, 78)	92 (90, 93)	87 (76, 93)	95 (93, 96)	97 (88, 99)

Aged 16–69 y with a comorbidity

Time Since Second Dose, d	Any Infection mRNA[b]	Any Infection ChAdOx1[c]	Symptomatic Infection mRNA[b]	Symptomatic Infection ChAdOx1[c]	Severe Outcomes mRNA[b]	Severe Outcomes ChAdOx1[c]
7–59	90 (89, 91)	88 (86, 90)	94 (93, 95)	94 (91, 96)	98 (97, 98)	97 (93, 98)
60–119	86 (85, 86)	84 (82, 86)	93 (92, 93)	91 (89, 92)	98 (98, 99)	98 (97, 99)
120–179	83 (82, 84)	75 (72, 78)	91 (90, 92)	88 (85, 90)	98 (97, 99)	98 (96, 99)
180–239	72 (69, 75)	81 (23, 95)	82 (78, 85)	d	98 (96, 99)	d
≥240	76 (71, 80)	d	87 (83, 91)	d	99 (96, 100)	d

Aged 16–69 y with no comorbidities

Time Since Second Dose, d	Any Infection mRNA[b]	Any Infection ChAdOx1[c]	Symptomatic Infection mRNA[b]	Symptomatic Infection ChAdOx1[c]	Severe Outcomes mRNA[b]	Severe Outcomes ChAdOx1[c]
7–59	90 (90, 91)	89 (86, 90)	94 (94, 95)	93 (90, 95)	99 (99, 100)	99 (95, 100)
60–119	86 (86, 87)	83 (81, 85)	93 (92, 93)	91 (89, 92)	99 (99, 99)	99 (98, 100)
120–179	83 (82, 84)	76 (72, 78)	91 (90, 92)	88 (85, 90)	100 (99, 100)	d
180–239	76 (73, 78)	d	84 (81, 87)	d	99 (94, 100)	d
≥240	74 (70, 78)	d	87 (83, 90)	d	d	d

Aged ≥70 y with a comorbidity

Time Since Second Dose, d	Any Infection mRNA[b]	Any Infection ChAdOx1[c]	Symptomatic Infection mRNA[b]	Symptomatic Infection ChAdOx1[c]	Severe Outcomes mRNA[b]	Severe Outcomes ChAdOx1[c]
7–59	89 (87, 90)	86 (70, 93)	94 (92, 95)	97 (78, 100)	95 (94, 96)	96 (71, 99)
60–119	84 (83, 86)	76 (64, 84)	93 (92, 94)	87 (77, 93)	97 (96, 97)	93 (84, 97)
120–179	77 (74, 79)	67 (48, 79)	91 (89, 93)	87 (75, 93)	94 (93, 96)	97 (86, 99)

Aged ≥70 y with no comorbidities

Time Since Second Dose, d	Any Infection mRNA[b]	Any Infection ChAdOx1[c]	Symptomatic Infection mRNA[b]	Symptomatic Infection ChAdOx1[c]	Severe Outcomes mRNA[b]	Severe Outcomes ChAdOx1[c]
7–59	91 (86, 94)	d	96 (90, 99)	d	97 (90, 99)	d
60–119	84 (79, 88)	71 (26, 88)	95 (91, 97)	95 (59, 99)	99 (98, 100)	d
120–179	76 (66, 83)	65 (-15, 89)	95 (91, 98)	90 (59, 98)	99 (97, 100)	d

Table 1. Continued

Time Since Second Dose, d	Any Infection mRNA[b]	Any Infection ChAdOx1[c]	Symptomatic Infection mRNA[b]	Symptomatic Infection ChAdOx1[c]	Severe Outcomes mRNA[b]	Severe Outcomes ChAdOx1[c]
Vaccine Effectiveness (95% CI)[a]						
(continued)						
180–239	64 (56, 70)	d	85 (80, 89)	d	91 (87, 94)	d
≥240	77 (61, 87)	…	89 (77, 95)	…	95 (83, 98)	…
Aged 16–69 y (0 prior SARS-CoV-2 test)						
7–59	91 (90, 91)	89 (88, 90)	95 (94, 95)	93 (91, 95)	99 (98, 99)	97 (95, 99)
60–119	87 (87, 88)	84 (83, 85)	93 (93, 93)	91 (89, 92)	99 (99, 99)	99 (98, 99)
120–179	85 (84, 85)	76 (74, 78)	92 (91, 93)	88 (86, 90)	99 (98, 99)	99 (98, 99)
180–239	77 (75, 79)	88 (53, 97)	85 (82, 87)	d	97 (93, 98)	d
≥240	80 (76, 83)	d	89 (86, 92)	d	98 (95, 99)	d
Aged 16–69 y (1 prior SARS-CoV-2 test)						
7–59	89 (88, 90)	85 (79, 88)	92 (91, 93)	93 (86, 96)	99 (98, 99)	99 (95, 99)
60–119	84 (83, 85)	83 (79, 86)	90 (89, 91)	90 (86, 93)	99 (99, 99)	99 (98, 99)
120–179	80 (78, 82)	71 (64, 77)	87 (85, 89)	83 (75, 88)	98 (94, 99)	92 (75, 97)
180–239	75 (71, 79)	d	81 (74, 86)	d	98 (84, 100)	d
≥240	81 (75, 86)	…	91 (84, 95)	…	d	d
Aged 16–69 y (≥2 prior SARS-CoV-2 tests)						
7–59	87 (85, 88)	94 (82, 98)	93 (90, 95)	97 (76, 100)	95 (89, 98)	90 (24, 99)
60–119	79 (77, 81)	79 (69, 86)	90 (87, 92)	93 (84, 97)	100 (97, 100)	92 (64, 98)
120–179	76 (73, 79)	76 (60, 85)	85 (81, 89)	93 (82, 97)	98 (94, 99)	d
180–239	73 (69, 77)	d	81 (75, 86)	d	d	d
≥240	71 (65, 76)	…	83 (78, 87)	…	98 (89, 99)	…
Aged ≥70 y (0 prior SARS-CoV-2 tests)						
7–59	89 (87, 90)	89 (74, 95)	93 (92, 95)	97 (80, 100)	95 (93, 96)	97 (74, 100)
60–119	84 (83, 86)	77 (65, 84)	94 (92, 95)	89 (79, 94)	97 (96, 98)	94 (84, 97)
120–179	77 (74, 80)	70 (52, 81)	92 (91, 94)	90 (80, 95)	95 (94, 97)	99 (90, 100)
180–239	60 (50, 68)	d	84 (77, 89)	…	91 (85, 95)	…
≥240	81 (60, 91)	…	90 (73, 96)	…	98 (78, 99)	…
Aged ≥70 y (1 prior SARS-CoV-2 test)						
7–59	90 (86, 93)	76 (-75, 97)	97 (93, 99)	d	98 (95, 100)	d
60–119	84 (79, 88)	71 (6, 91)	91 (86, 95)	93 (37, 99)	95 (91, 98)	d
120–179	72 (60, 80)	44 (-66, 81)	88 (78, 93)	e	90 (80, 95)	e
180–239	83 (70, 90)	d	93 (84, 97)	d	95 (85, 98)	d
≥240	80 (17, 95)	…	88 (5, 99)	…	d	…
Aged ≥70 y (≥2 prior SARS-CoV-2 tests)						
7–59	84 (78, 88)	d	90 (79, 95)	d	98 (95, 99)	d
60–119	86 (80, 90)	e	89 (79, 94)	e	94 (85, 98)	e
120–179	79 (67, 87)	d	89 (73, 95)	d	90 (71, 96)	d
180–239	73 (54, 84)	d	78 (47, 91)	d	84 (52, 94)	d
≥240	83 (54, 93)	…	83 (15, 97)	…	86 (-28, 98)	…
Dosing interval 15–34 d						
7–59	89 (88, 90)	NA	92 (91, 93)	NA	94 (93, 96)	NA
60–119	83 (82, 84)	NA	90 (89, 91)	NA	97 (95, 98)	NA
120–179	80 (78, 81)	NA	86 (85, 88)	NA	95 (93, 97)	NA
180–239	73 (70, 75)	NA	80 (77, 83)	NA	95 (92, 96)	NA
≥240	75 (72, 78)	NA	86 (83, 88)	NA	98 (95, 99)	NA
Dosing interval 35–55 d						
7–59	92 (91, 93)	NA	94 (94, 95)	NA	99 (98, 99)	NA
60–119	86 (86, 87)	NA	93 (92, 93)	NA	99 (98, 99)	NA
120–179	84 (83, 85)	NA	92 (91, 93)	NA	98 (97, 99)	NA
180–239	74 (71, 77)	NA	85 (82, 88)	NA	97 (92, 99)	NA
≥240	72 (66, 77)	NA	90 (85, 93)	NA	98 (89, 100)	d
Dosing interval ≥56 d						
7–59	91 (91, 92)	NA	95 (95, 96)	NA	99 (98, 99)	NA
60–119	87 (87, 88)	NA	93 (93, 94)	NA	99 (98, 99)	NA
120–179	81 (81, 82)	NA	91 (90, 92)	NA	98 (97, 99)	NA
180–239	71 (59, 80)	NA	87 (76, 93)	NA	94 (57, 99)	NA
≥240	d	NA	NA	NA	NA	NA
Jan 11 to Apr 4, 2021 (Mixed wild-type SARS-CoV-2 & Alpha circulating)						
7–59	92 (91, 93)	89 (84, 93)	94 (91, 96)	d	95 (90, 97)	…
60–119	84 (83, 85)	e	93 (79, 98)	d	d	…
Apr 5 to Jun 17, 2021 (Alpha predominating)						
7–59	92 (91, 93)	94 (84, 93)	94 (94, 95)	94 (84, 97)	94 (92, 95)	92 (79, 97)
60–119	88 (86, 90)	d	88 (86, 90)	d	97 (95, 98)	d
Jun 28 to Nov 21, 2021 (Delta predominating)						
7–59	90 (90, 90)	89 (88, 91)	95 (95, 96)	95 (93, 96)	98 (98, 99)	98 (97, 99)
60–119	87 (86, 87)	84 (83, 85)	93 (93, 94)	92 (91, 93)	98 (98, 99)	99 (98, 99)

Table 1. Continued

Time Since Second Dose, d	Any Infection	Symptomatic Infection	Severe Outcomes	Any Infection	Symptomatic Infection	Severe Outcomes	Any Infection	Symptomatic Infection	Severe Outcomes
						Vaccine Effectiveness (95% CI)[a]			
120–179	…	…	…	82 (79, 85)	86 (78, 91)	…[d]	83 (82, 83)	90 (90, 91)	97 (97, 98)
180–239	…	…	…	…	…	…	77 (75, 79)	85 (83, 87)	95 (93, 97)[d]
≥240	…	…	…	…	…	…	78 (76, 80)[d]	88 (86, 90)	98 (95, 99)[d]

Abbreviations: COVID-19, coronavirus disease 2019; NA, not assessed (As ChAdOx1 recipients needed to wait at least 8 weeks before receiving their second dose of any COVID-19 vaccine, analyses by dosing interval were not conducted.); SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; VE, vaccine effectiveness.

[a] Models were adjusted for age (10-year age bands), sex, public health unit region, biweekly period of test, number of SARS-CoV-2 tests in the 3 months before December 14, 2020, presence of any comorbidity that increases the risk of severe COVID-19, receipt of influenza vaccination in the current or prior influenza season, and neighborhood-level household income, persons per dwelling, proportion of persons employed as nonhealth essential workers, and self-identified visible minority quintiles (unless that characteristic was used to stratify into subgroups).

[b] Any 2-dose mRNA schedule, including BNT162b2/BNT162b2, mRNA-1273/mRNA-1273, and BNT162b2/mRNA-1273.

[c] Any ChAdOx1-containing schedule, including ChAdOx1/ChAdOx1, ChAdOx1/BNT162b2, and ChAdOx1/mRNA-1273.

[d] VE estimated as 100% based on 0 vaccinated test-positive cases.

[e] VE not reported due to extremely imprecise 95% CI.

46%–81%]). Generally, for the same outcome, the CIs of the estimates for each time-since-second-dose interval overlapped with at least 1 other interval within the same stratum, suggesting that the extent of VE decline may not be pronounced. Also, within each age group, the CIs for estimates across dosing intervals for the same time-since-second-dose interval overlapped, suggesting that the difference by dosing interval is not substantial.

In sensitivity analyses, we found similar results as the primary analyses when we included individuals with prior SARS-CoV-2 infection (Supplementary Tables 14–18). There were also no differences in the VE estimates or trends when using alternative severe outcomes definitions (Supplementary Table 19). When we restricted to Delta cases that were confirmed by WGS or mutation screening, the results were similar with analyses using all cases (Supplementary Table 20).

DISCUSSION

Using the test-negative study design, we observed that the effectiveness of any combination of 2 doses of BNT162b2, mRNA-1273, or ChAdOx1 against SARS-CoV-2 infection and symptomatic infection gradually decreased over time since second dose in the pre-Omicron era. However, VE against severe outcomes was sustained over a 7–8-month period. This pattern was consistently observed across subgroups. VE estimates and trends over time were similar between 2-dose mRNA and heterologous ChAdOx1 and mRNA vaccine schedules, and higher than homologous ChAdOx1 schedules. In analyses conducted to assess the duration of protection separately from patient characteristics that influence immunity levels and the Delta variant, VE also decreased over time. Furthermore, similar results were observed when including previously infected individuals, which suggests that declines may not be due to protection conferred from naturally acquired immunity from previous SARS-CoV-2 infection in the unvaccinated population [28].

The meta-analysis by Feikin et al. (2022) showed that VE of 2-dose homologous schedules of BNT162b2, mRNA-1273, and ChAdOx1 for individuals aged ≥12 years declined 21 percentage points against infection, 25 points against COVID-19 symptomatic disease, and only 10 points against severe disease. However, these results combined estimates of all vaccine schedules, and the included studies were heterogeneous [1]. Nevertheless, our results were comparable with some of the included test-negative design studies. In England, VE against Delta-associated symptomatic infection decreased from 92% (95% CI, 92%–93%) to 66% (95% CI, 66%–67%) for a BNT162b2 series and from 65% (95% CI, 64%–66%) to 44% (95% CI, 43%–45%) for a ChAdOx1 series over a 6-month period, but protection was sustained against hospitalizations and deaths for BNT162b2 and decreased minimally for ChAdOx1
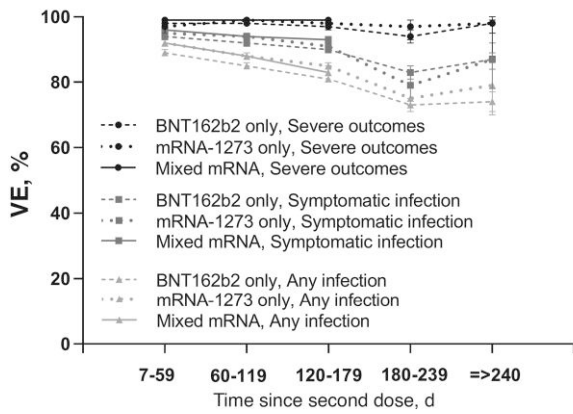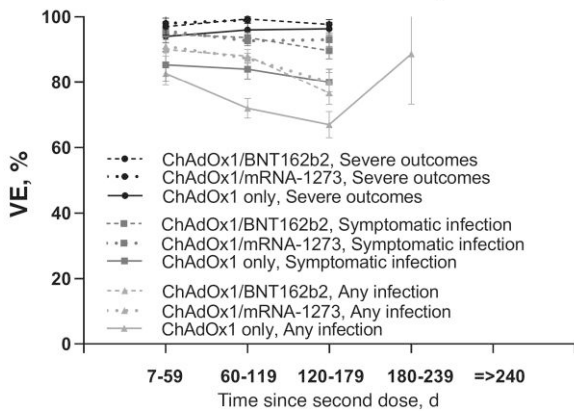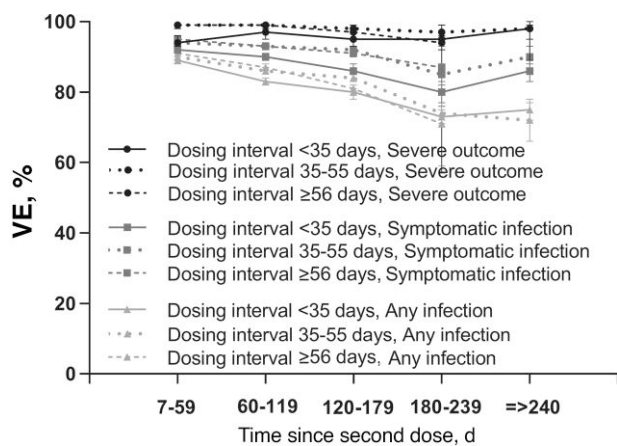
Figure 1. Vaccine effectiveness against SARS-CoV-2 infection, symptomatic infection, and severe outcomes over time since the second dose among those who received a 2-dose mRNA vaccine schedule (*A*) and a 2-dose ChAdOx1-containing schedule (*B*) in Ontario, Canada, for adults ≥16 years. Abbreviations: SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; VE, vaccine effectiveness.

[29]. We found similar results for 2 mRNA doses when we restricted the analysis to the Delta-predominant period and to WGS- and mutation screening–confirmed cases. In contrast, our results showed that homologous ChAdOx1 schedules started with ample protection (VE ≥80%) but did not have a decline as pronounced, which is likely due to the shorter follow-up time. Similar results were observed in 2 other populous Canadian provinces, where VE against infection for 2-dose mRNA recipients declined modestly from ≥90% within weeks of the second dose to ≥80% over 7 months, and there was essentially no change in VE against hospitalizations [11].

However, our results do not align with studies from Qatar; although they showed robust VE against severe, critical, and

Figure 2. Vaccine effectiveness against SARS-CoV-2 infection, symptomatic infection, and severe outcomes over time since the second dose among those who received 2 doses of mRNA vaccines, by dosing interval, in Ontario, Canada, for adults ≥16 years. Abbreviations: SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; VE, vaccine effectiveness.

fatal COVID-19 cases over time, VE against infection decreased starkly to ~20% by 5–7 months after the second BNT162b2 dose (down from 78% within a week after the second dose) and ~30% by 7 months after the second mRNA-1273 dose (down from 91% at 2 months) [30, 31]. Qatar used the manufacturer's recommended interval between primary doses. Two retrospective cohort studies from the United States, which also used the manufacturers' recommended intervals between mRNA doses, showed apparent decreases in VE. Tartof et al. (2021) found that VE against infection for 2 doses of BNT162b2 decreased from 88% (95% CI, 86%–89%) 1 month after the second dose to 47% (95% CI, 43%–51%) after 5 months [32]. Lin et al. (2022) showed that VE among 2-dose BNT162b2 recipients decreased from 95% (95% CI, 94%–95%) 2 months after their first dose to 67% (95% CI, 65%–68%) at 7 months. However for 2-dose mRNA-1273 recipients, the decrease (from 96% [95% CI, 95%–96%] to 80% [95% CI, 79%–81%]) was comparable to ours [33]. Our results and those from other studies showed that protection with shorter dosing intervals was lower than with longer intervals [11, 22, 23]. However, in stratified analyses, we showed that there were no differences in VE between dosing intervals for the same time-since-second-dose category. Thus, although serological studies show that longer dosing intervals are associated with greater immunological response [9, 10] and comparisons between populations with different COVID-19 vaccination policies show differences in the extent of waning VE (although differing population structures, epidemiological conditions, RT-PCR testing eligibility and practices, and public health measures likely contributed to these differences as well), more real-world evidence is needed to determine the clinical significance of extended dosing intervals and its impact on waning immunity.
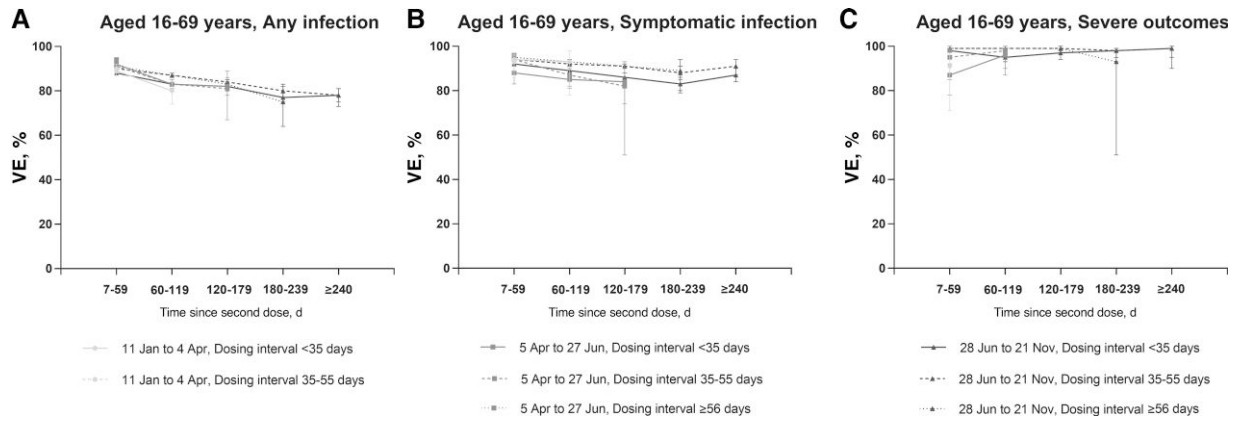
Figure 3. Vaccine effectiveness against SARS-CoV-2 infection (*A*), symptomatic infection (*B*), and severe outcomes (*C*) over time since the second dose among those who received 2 doses of any mRNA vaccine, stratified by dosing interval and study subperiod in Ontario, Canada, for adults aged 16–69 years. Abbreviation: SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; VE, vaccine effectiveness.

To our knowledge, few studies have evaluated the effectiveness of heterologous 2-dose schedules. Two other studies also found that heterologous and homologous mRNA vaccine schedules had equivalent VE estimates [11, 24]. A Danish study found that VE against any infection for heterologous ChAdOx1 and mRNA vaccine schedules was 88% (95% CI, 83%–92%) ≥14 days after the second dose, which is comparable to our VE estimates against any infection at 7–59 days ($VE_{ChAdOx1/BNT162b2} = 90\%$ [95% CI, 88%–92%]; $VE_{ChAdOx1/mRNA-1273} = 91\%$ [95% CI, 89%–93%]), but did not assess duration of effectiveness [20]. Consistent with our results, the other Canadian study demonstrated that protection from ChAdOx1 followed by any mRNA vaccine was comparable to 2-dose mRNA vaccine schedules and was distinctly higher than homologous ChAdOx1 schedules, but the extent of waning for heterologous and homologous ChAdOx1 schedules was comparable to mRNA schedules [11]. In contrast, a Swedish study showed that heterologous ChAdOx1 and mRNA vaccine schedules had slower waning than homologous BNT162b2, but VE for homologous ChAdOx1 schedules rapidly declined to undetectable levels after day 121 [21]. Collectively, these results validate the use of heterologous schedules.

Decreases in VE over time could be a real trend representing waning immunity but could also be spuriously caused by biases. One possibility is the "depletion of susceptibles" bias, where the proportion of individuals at risk of infection decreases faster among unvaccinated individuals than vaccinated individuals; thus each group's risk of infection converges over time [34]. This occurs if previously infected unvaccinated individuals who are conferred protection through naturally acquired immunity are included in the cohort [1]. To minimize this potential bias, we excluded individuals with prior RT-PCR-confirmed SARS-CoV-2 infection, but individuals with undocumented infections and false-negative controls would be misclassified and remain in our cohort. Adjusting for prior infection could approximate the true VE range [28]. Our sensitivity analysis that included previously infected individuals showed similar results as our main analyses, suggesting that our results excluding individuals with documented prior infections were not subject to substantial bias.

Our study had some limitations. First, we were unable to account for time-varying individual behaviors. For instance, individuals who completed their 2-dose primary series had more liberties to access high-risk indoor public settings (eg, restaurants, sporting venues), and despite having some vaccine-induced immunity, they are likely at increased risk of exposure (and consequently infection) [35]. In Ontario, proof of vaccination to access these settings started on September 22, 2021 [36], which represented the last 2 months of our study period. If individuals who completed their primary series earlier engaged in these activities and were infected, waning VE may be overestimated. Conversely, proof of vaccination policies might have prompted individuals to receive their second (and first) doses. If these individuals subsequently acquired breakthrough infections, VE at shorter intervals since second dose would be low, which might underestimate the extent of waning VE. Similarly, if vaccinated individuals were more likely to wear masks and adhere to public health guidelines, this may overestimate VE and make waning immunity appear minimal [37]. Second, we were unable to identify some high-risk individuals who were prioritized to receive their primary doses (eg, residents of congregate settings other than long-term care homes, health care workers, and caregivers). This risk heterogeneity could also show spurious waning because of the depletion of susceptibles [38]. These individuals are also frequently tested because of screening and outbreak management.
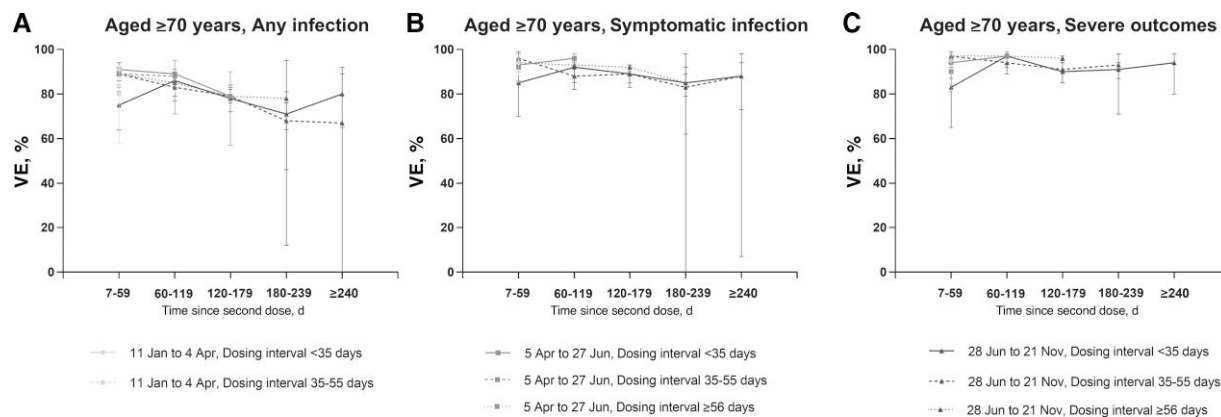
Figure 4. Vaccine effectiveness against SARS-CoV-2 infection (*A*), symptomatic infection (*B*), and severe outcomes (*C*) over time since the second dose among those who received 2 doses of any mRNA vaccine, stratified by dosing interval and study subperiod in Ontario, Canada, for adults aged ≥70 years. Abbreviation: SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; VE, vaccine effectiveness.

Consequently, they may be over-represented in longer time-since-second-dose categories, and because they have higher infection risk, we may have overestimated the extent of waning VE because of detection bias. Residual confounding may still be present despite adjusting for age, comorbidities, and the number of prior tests. However, we stratified by the number of prior SARS-CoV-2 tests and did not find any differences in waning VE. Third, even though selected high-risk groups were eligible for their third dose during the study period [39], we did not evaluate VE for the third dose against Delta because Omicron rapidly became the predominant variant (which accelerated the third dose rollout to the entire adult population in Ontario) in December 2021. When possible, it is important to evaluate waning immunity and the benefits of additional doses when a single variant is predominant for a sufficient duration to eliminate emerging variants as the cause for decreased effectiveness. Our analyses by subperiod attempted to disentangle the impact of variants; however, we were unable to assess longer time-since-second-dose intervals during the Alpha period. Notably, our VE estimates for 7–59, 60–119, and 120–179 days since the second dose in the Delta-predominant subperiod were equivalent to estimates for the same intervals in the Alpha-predominant subperiod, suggesting that Delta may not substantially impact waning VE. However, this needs to be evaluated with other variants. Last, we used testing date to calculate time since second dose because symptom onset date was unavailable in our data. VE could be underestimated because we included individuals who were once symptomatic (and likely positive) but were tested later in their course of illness and deemed negative. However, in vaccinated individuals with breakthrough infections, viral load increases with longer times since second dose [40]. By not restricting to tests within a finite period after symptom onset, we may be misclassifying breakthrough infections as false negatives (which would bias VE

away from the null) but would be properly classifying vaccinated cases over time (which would decrease VE).

CONCLUSIONS

Our results suggest that the VE of any 2-dose primary series against infection and symptomatic infection wanes over time but remains high against severe outcomes during the period before the emergence of Omicron in Ontario, Canada. Vaccine schedules containing at least 1 mRNA vaccine dose provide strong protection. Waning immunity of additional COVID-19 vaccine doses should be monitored to determine the need and optimal timing for subsequent doses.

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