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

Hannah Chung, Peter C. Austin, Kevin A. Brown, Sarah A. Buchan, Deshayne B. Fell, Cindy Fong, Jonathan B. Gubbay, Sharifa Nasreen, Kevin L. Schwartz, Maria E. Sundaram, Mina Tadrous, Kumanan Wilson, Sarah E. Wilson, and Jeffrey C. Kwong, on behalf of the Canadian Immunization Research Network (CIRN) Provincial Collaborative Network (PCN) Investigators

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 supply 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 (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%] 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, 61%–75%]).
| Time Since Second Dose, d | Any Infection | Symptomatic Infection | Severe Outcomes | Any Infection | Symptomatic Infection | Severe Outcomes | Any Infection | Symptomatic Infection | Severe Outcomes |
|--------------------------|----------------|----------------------|----------------|----------------|----------------------|----------------|----------------|----------------------|----------------|
| Overall                  | mRNA        | ChAdOx1       | mRNA        | ChAdOx1       | mRNA        | ChAdOx1       | mRNA        | ChAdOx1       | mRNA        |
| 7–59                     | 90 (90, 90) | 88 (87, 90) | 94 (94, 95) | 91 (92, 93) | 98 (97, 98) | 97 (95, 98) | ...         | ...         | ...         |
| 60–119                   | 88 (88, 90) | 83 (82, 85) | 93 (92, 93) | 91 (92, 93) | 98 (98, 98) | 98 (97, 98) | ...         | ...         | ...         |
| 120–179                  | 82 (82, 83) | 75 (73, 77) | 91 (90, 91) | 88 (86, 88) | 97 (97, 98) | 97 (97, 98) | ...         | ...         | ...         |
| 180–239                  | 74 (72, 75) | 92 (90, 95) | 82 (80, 83) | ...         | ...         | ...         | 86 (86, 86) | ...         | ...         |
| ≥240                     | 75 (72, 76) | 87 (82, 88) | 90 (89, 90) | ...         | ...         | ...         | 97 (96, 98) | ...         | ...         |
| ...                      | BNT162b2 only | mRNA        | 12.73 only | Mixed mRNA vaccine schedule | ...         | ...         | ...         | ...         | ...         |
| 7–59                     | 88 (88, 90) | 86 (85, 89) | 95 (94, 96) | 99 (98, 99) | 90 (88, 92) | ...         | ...         | ...         |
| 60–119                   | 95 (95, 96) | 92 (91, 92) | 98 (98, 99) | 93 (94, 95) | ...         | 98 (98, 99) | 93 (94, 95) | ...         |
| 120–179                  | 81 (81, 82) | 80 (79, 81) | 96 (95, 97) | 90 (88, 90) | ...         | 96 (94, 95) | ...         | ...         |
| 180–239                  | 73 (71, 75) | 83 (81, 85) | 94 (93, 96) | ...         | ...         | 93 (93, 94) | ...         | ...         |
| ≥240                     | 74 (71, 77) | 87 (84, 88) | 98 (95, 99) | ...         | ...         | ...         | ...         | ...         |
| ...                      | ChAdOx1 only | mRNA        | 12.73 only | ChAdOx1 and BNT162b2 | ...         | ...         | ...         | ...         |
| 7–59                     | 80 (80, 82) | ...         | ...         | ...         | ...         | ...         | ...         | ...         |
| 60–119                   | 72 (69, 73) | 84 (81, 87) | 96 (94, 98) | 94 (93, 95) | ...         | 96 (93, 95) | ...         | ...         |
| 120–179                  | 67 (63, 71) | 80 (76, 84) | 97 (94, 98) | ...         | ...         | 93 (91, 94) | ...         | ...         |
| 180–239                  | 91 (88, 93) | 83 (82, 85) | ...         | ...         | ...         | 93 (91, 94) | ...         | ...         |
| ≥240                     | 96 (91, 99) | 87 (84, 88) | ...         | ...         | ...         | ...         | ...         | ...         |
| ...                      | Aged 16–69 y only | ChAdOx1 and BNT162b2 | ...         | ...         | ...         | ...         | ...         | ...         |
| 7–59                     | ...         | ...         | ...         | ...         | ...         | ...         | ...         | ...         |
| 60–119                   | ...         | ...         | ...         | ...         | ...         | ...         | ...         | ...         |
| 120–179                  | ...         | ...         | ...         | ...         | ...         | ...         | ...         | ...         |
| 180–239                  | ...         | ...         | ...         | ...         | ...         | ...         | ...         | ...         |
| ≥240                     | ...         | ...         | ...         | ...         | ...         | ...         | ...         | ...         |
| ...                      | Aged ≥70 y only | ...         | ...         | ...         | ...         | ...         | ...         | ...         |

**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.
| Time Since Second Dose | Any Infection | Symptomatic Infection | Severe Outcomes | Any Infection | Symptomatic Infection | Severe Outcomes |
|------------------------|---------------|----------------------|-----------------|---------------|----------------------|-----------------|
| 0–14 d                 | 64 (55, 74)   | 86 (79, 95)          | 87 (79, 97)     | 65 (59, 72)   | 86 (79, 94)          | 91 (84, 98)     |
| 15–29 d                | 70 (63, 78)   | 91 (85, 98)          | 91 (85, 98)     | 68 (62, 75)   | 91 (84, 96)          | 94 (87, 99)     |
| 30–69 d                | 70 (63, 78)   | 91 (85, 98)          | 91 (85, 98)     | 68 (62, 75)   | 91 (84, 96)          | 94 (87, 99)     |
| 70–129 d               | 95 (90, 99)   | 98 (95, 99)          | 98 (95, 99)     | 81 (76, 86)   | 98 (95, 99)          | 99 (98, 99)     |
| ≥130 d                 | 99 (98, 99)   | 99 (98, 99)          | 99 (98, 99)     | 96 (93, 98)   | 99 (98, 99)          | 100 (100, 100)  |

Table 1. Continued

COVID-19 Vaccine Effectiveness Over Time • OFID • 5
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.
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 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.
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\textsubscript{ChAdOx1/BNT162b2} = 90% [95% CI, 88%–92%]; VE\textsubscript{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.
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.

Supplementary Data

Supplementary materials are available at Open Forum 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.

Acknowledgments

We would like to acknowledge Public Health Ontario for access to case-level data from CCM and COVID-19 laboratory data, as well as assistance with data interpretation. We also thank the staff of Ontario’s public health units who are responsible for COVID-19 case and contact management and data collection within CCM. We thank IQVIA Solutions Canada Inc. for use of their Drug Information File. The authors are grateful to the residents of Ontario, without whom this research would not be possible.

Financial support. This work was supported by the Canadian Immunization Research Network (CIRN) through a grant from the Public Health Agency of Canada and the Canadian Institutes of Health Research (CNF 151944). This project was also supported by funding from the Public Health Agency of Canada through the Vaccine Surveillance Working Party and the COVID-19 Immunity Task Force. This study was also supported by ICES, which is funded by an annual grant from the Ontario Ministry of Health (MOH). J.C.K. is supported by a Clinician-Scientist Award from the University of Toronto Department of Family and Community Medicine. P.C.A. is supported by a Mid-Career Investigator Award from the Heart and Stroke Foundation. This study...
was supported by ICES, which is funded by an annual grant from the Ontario Ministry of Health (MOH) and the Ministry of Long-Term Care (MLTC). This study was supported by the Ontario Health Data Platform (OHDP), a Province of Ontario initiative to support Ontario’s ongoing response to COVID-19 and its related impacts. The study sponsors did not participate in the design or conduct of the study; collection, management, analysis, or interpretation of the data; preparation, review, or approval of the manuscript; or the decision to submit the manuscript for publication. Parts of this material are based on data and/or information compiled and provided by MOH, the Canadian Institute for Health Information (CIHI) and by Ontario Health (OH). However, the analyses, conclusions, opinions, and statements expressed herein are solely those of the authors and do not reflect those of the funding or data sources; no endorsement by ICES, MOH, MLTC, OHDP, its partners, the Province of Ontario, CIHI, or OH is intended or should be inferred.

Potential conflicts of interest. K.W. is CEO of CANImmunize and serves on the data safety board for the Medicago COVID-19 vaccine trial. The other authors declare no conflicts of interest. 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.

Author contributions. H.C. and J.C.K. designed and oversaw the study. H.C. obtained the data and conducted all analyses (data set and variable creation and statistical modeling). H.C. and J.C.K. drafted the manuscript. All authors contributed to the analysis plan, interpreted the results, critically reviewed and edited the manuscript, approved the final version, and agreed to be accountable for all aspects of the work.

Patient consent. ICES is a prescribed entity under Ontario’s Personal Health Information Protection Act (PHIPA). Section 45 of PHIPA authorizes ICES to collect personal health information, without consent, for the purpose of analysis or compiling statistical information with respect to the management of, evaluation or monitoring of, the allocation of resources to or planning for all or part of the health system. Projects that use data collected by ICES under section 45 of PHIPA, and use no other data, are exempt from Research Ethics Board (REB) review. The use of the data in this project is authorized under section 45 and approved by ICES’ Privacy and Legal Office.

Data availability. The data set from this study is held securely in coded form at ICES. While legal data-sharing agreements between ICES and data providers (eg, health care organizations and government) prohibit ICES from making the data set publicly available, access may be granted to those who meet prespecified criteria for confidential access, available at www.ices.on.ca/DAS (email: das@ices.on.ca).

Code availability. The full data set creation plan and underlying analytic code are available from the authors upon request, understanding that the computer programs may rely upon coding templates or macros that are unique to ICES and therefore either are inaccessible or may require modification.

References
1. Feikin DR, Higdon MM, Abu-Raddad LJ, et al. Duration of effectiveness of vaccines against SARS-CoV-2 infection and COVID-19 disease: results of a systematic review and meta-regression. Lancet 2022; 399:924–44.
2. Britton A, Fleming-Dutra KE, Shang N, et al. Association of COVID-19 vaccination with symptomatic SARS-CoV-2 infection by time since vaccination and Delta variant predominance. JAMA 2022; 327:1032–41.
3. Fabiani M, Puopolo M, Morciano C, et al. Effectiveness of mRNA vaccines and waning of protection against SARS-CoV-2 infection and severe COVID-19 during predominant circulation of the delta variant in Italy: retrospective cohort study. BMJ 2022; 376:e690952.
4. Katikireddi SV, Cerqueira-Silva T, Vasilieou E, et al. Two-dose ChAdOx1 nCoV-19 vaccine protection against COVID-19 hospital admissions and deaths over time: a retrospective, population-based cohort study in Scotland and Brazil. Lancet 2022; 399:25–35.
5. Wright BJ, Tideman S, Diaz GA, et al. Comparative vaccine effectiveness against severe COVID-19 over time in US hospital administrative data: a case-control study. Lancet Respir Med. 2022; 10(6):557-565.
6. McKeigue PM, McAllister DA, Hutchinson SJ, et al. Vaccine efficacy against severe COVID-19 in relation to Delta variant (B.1.617.2) and time since second dose in patients in Scotland (REACT-SCOT): a case-control study. Lancet Respir Med. 2022; 10(6):566–572.
7. Lopez Bernal J, Andrews N, Gower C, et al. Effectiveness of COVID-19 vaccines against the B.1.617.2 (Delta) variant. N Engl J Med 2021; 385:585–94.
8. National Advisory Committee on Immunization (NACI). Extended dose intervals for COVID-19 vaccines to optimize early vaccine rollout and population protection in Canada in the context of limited vaccine supply. 2021. Available at: https://www.canada.ca/en/public-health/services/immunization/national-advisory-committee-on-immunization-naci/extended-dose-intervals-covid-19-vaccines-early-vaccine-rollout-population-protection.html#s6. Accessed April 13, 2022.
9. Grunau B, Goldfarb DM, Asamoah-Boaheng M, et al. Immunogenicity of extended mRNA SARS-CoV-2 vaccine dosing intervals. JAMA 2022; 327:279–81.
10. Grunau B, Asamoah-Boaheng M, Lavoie PM, et al. A higher antibody response is generated with a 6- to 7-week (vs standard) severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccine dosing interval. Clin Infect Dis. 2022; 7(15):e888–e891.
11. Skowronski DM, Setayeshgar S, Febriani Y, et al. Two-dose SARS-CoV-2 vaccine effectiveness with mixed schedules and extended dosing intervals: test-negative design studies from British Columbia and Quebec. Clin Infect Dis. 2022; ciac290.
12. Government of Ontario. Ontario pauses administration of AstraZeneca vaccine. 2021. Available at: https://news.ontario.ca/en/statement/1000103/ontario-pauses-administration-of-astrazeneca-vaccine. Accessed April 13, 2022.
13. Hillsu D, Schwarz T, Tober-Lau P, et al. Safety, reactogenicity, and immunogenicity of homologous and heterologous prime-boost immunisation with ChAdOx1 nCoV-19 and BNT162b2: a prospective cohort study. Lancet Respir Med 2021; 9:1255–65.
14. Shaw RH, Stuart A, Greenland M, Liu X, Van-Tam JSN, Snape MD. Heterologous prime-boost COVID-19 vaccination: initial reactogenicity data. Lancet 2021; 397:2043–6.
15. Schmidt T, Klemis V, Schuh D, et al. Immunogenicity and reactogenicity of heterologous ChAdOx1 nCoV-19/mRNA vaccination. Nat Med 2021; 27:1330–5.
16. Borobia AM, Cargas AJ, Pérez-Olmeda M, et al. Immunogenicity and reactogenicity of BNT162b2 booster in ChAdOx1-S-primed participants (CombivacS): a multicentre, open-label, randomised, controlled, phase 2 trial. Lancet 2021; 398:121–30.
17. Normark J, Vikström L, Gwon Y-D, et al. Heterologous ChAdOx1 nCoV-19 and mRNA-1273 vaccination. N Engl J Med 2021; 385:1049–51.
18. Tenbusch M, Schumacher S, Vogel E, et al. Heterologous prime-boost vaccination with ChAdOx1 nCoV-19 and BNT162b2. Lancet Infect Dis 2021; 21:1212–3.
19. National Advisory Committee on Immunization (NACI). NACI rapid response: interchangeability of authorized COVID-19 vaccines. 2021. Available at: https://www.canada.ca/en/public-health/services/immunization/national-advisory-committee-on-immunization-naci/recommendations-use-covid-19-vaccinesrapid-response-interchangeability.html#m_rNA-COVID-19-vaccine. Accessed April 13, 2022.
20. Gram MA, Nielsen J, Schêlde AB, et al. Vaccine effectiveness against SARS-CoV-2 infection, hospitalization, and death when combining a first dose ChAdOx1 vaccine with a subsequent mRNA vaccine in Denmark: a nationwide population-based cohort study. PLoS Med 2021; 18:e1003874.
21. Nordström P, Ballin M, Nordström A. Risk of infection, hospitalisation, and death up to 9 months after a second dose of COVID-19 vaccine: a retrospective, total population cohort study in Sweden. Lancet 2022; 399:814–23.
22. Adam S E, Zou M, Kim S, Henry B, Krajden M, Skowronski DM. SARS-CoV-2 mRNA vaccine effectiveness in health care workers by dosing interval and time since vaccination: test-negative design, British Columbia, Canada. Open Forum Infect Dis 2022; 9:XXX–XX.
23. Amirthalingam G, Bernal JL, Andrews NJ, et al. Serological responses and vaccine effectiveness for extended COVID-19 vaccine schedules in England. Nat Commun 2021; 12:7217.
24. Starrfelt J, Daniesens AS, Buanes EA, et al. Age and product dependent vaccine effectiveness against SARS-CoV-2 infection and hospitalisation among adults in Norway: a national cohort study, July – November 2021. medRxiv 2022.03.29.22273086 [Preprint]. March 30, 2022. Available at: https://www.medrxiv.org/content/10.1101/2022.03.29.22273086v1. Accessed August 5, 2022.
25. Ontario Agency for Health Protection and Promotion (Public Health Ontario). Estimating the prevalence and growth of SARS-CoV-2 variants in Ontario using mutation profiles. 2021. Available at: https://www.publichealthontario.ca/-/media/documents/inco/epi/covid-19-prevalence-growth-voc-mutation-epi-summary.pdf?sc_lang=en. Accessed April 13, 2022.
26. Kovaiu RD, Herndler-Brandstetter D, Grubeck-Loebenstein B. Age-related changes in immunity: implications for vaccination in the elderly. Expert Rev Med Mol 2007; 9:1–17.
27. National Advisory Committee on Immunization (NACI). COVID-19 vaccine: Canadian immunization guide. Available at: https://www.canada.ca/en/public-health/services/publications/healthy-living/canadian-immunization-guide-part-4-active-vaccines/page-26-covid-19-vaccine.html. Accessed May 11, 2022.
28. Kahn R, Schrag SJ, Verani JR, et al. Identifying and alleviating bias due to differential depletion of susceptible people in post-marketing evaluations of COVID-19 vaccines. Am J Epidemiol. 2022; 191(5):800–811.
29. Andrews N, Tessier E, Stowe J, et al. Duration of protection against mild and severe disease by COVID-19 vaccines. N Engl J Med 2022; 386:340–50.
30. Chemaitelly H, Tang P, Hasan MR, et al. Waning of BNT162b2 vaccine protection against SARS-CoV-2 infection in Qatar. N Engl J Med 2021; 385:e83.
31. Abu-Raddad LJ, Chemaitelly H, Bertollini R. Waning mRNA-1273 vaccine effectiveness against SARS-CoV-2 infection in Qatar. N Engl J Med 2022; 386:1091–3.
32. Tartof SY, Slezak JM, Fischer H, et al. Effectiveness of mRNA BNT162b2 COVID-19 vaccine up to 6 months in a large integrated health system in the USA: a retrospective cohort study. Lancet 2021; 398:1407–16.
33. Lin D-Y, Gu Y, Wheeler B, et al. Effectiveness of COVID-19 vaccines over a 9-month period in North Carolina. N Engl J Med 2022; 386:933–41.
34. Ray GT, Lewis N, Klein NP, Daley MF, Lipsitch M, Fireman B. Depletion-of-susceptibles bias in analyses of intra-season waning of influenza vaccine effectiveness. Clin Infect Dis 2020; 70:1484–6.
35. Ioannidis JPA. Factors influencing estimated effectiveness of COVID-19 vaccines in non-randomised studies. BMJ Evid Based Med. In press. doi:10.1136/bmjebm-2021-111901.
36. Government of Ontario. O. reg. 645/21: rules for areas at step 3 and at the road-map exit step. 2021. Available at: https://www.ontario.ca/laws/regulation/r21645. Accessed April 13, 2022.
37. Matytsin A. The mask-wearing bias in the estimates of vaccine efficacy. medRxiv 2021.10.19.21265093 [Preprint]. October 23, 2021. Available at: https://www.medrxiv.org/content/10.1101/2021.10.19.21265093v1. Accessed April 13, 2022.
38. Fay MP, Hunsberger S, Follmann D. Risk heterogeneity and the illusion of waning vaccine efficacy. Ann Intern Med 2022; 175:444–5.
39. Government of Ontario. Ontario expanding booster eligibility to more Ontarians. 2021. Available at: https://news.ontario.ca/en/release/1001100/ontario-expanding-booster-eligibility-to-more-ontarians. Accessed April 13, 2022.
40. Levine-Tiefenbrun M, Yelin I, Alapi H, et al. Viral loads of Delta-variant SARS-CoV-2 breakthrough infections after vaccination and booster with BNT162b2. Nat Med 2021; 27:2108–10.