*Clinical Infectious Diseases*

MAJOR ARTICLE

# Single-Dose Messenger RNA Vaccine Effectiveness Against Severe Acute Respiratory Syndrome Coronavirus 2 in Healthcare Workers Extending 16 Weeks Postvaccination: A Test-Negative Design From Québec, Canada

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***Background.*** In Canada, first and second doses of messenger RNA (mRNA) vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) were uniquely spaced 16 weeks apart. We estimated 1- and 2-dose mRNA vaccine effectiveness (VE) among healthcare workers (HCWs) in Québec, Canada, including protection against varying outcome severity, variants of concern (VOCs), and the stability of single-dose protection up to 16 weeks postvaccination.

***Methods.*** A test-negative design compared vaccination among SARS-CoV-2 test–positive and weekly matched (10:1), randomly sampled, test-negative HCWs using linked surveillance and immunization databases. Vaccine status was defined by 1 dose ≥14 days or 2 doses ≥7 days before illness onset or specimen collection. Adjusted VE was estimated by conditional logistic regression.

***Results.*** Primary analysis included 5316 cases and 53 160 controls. Single-dose VE was 70% (95% confidence interval [CI], 68%–73%) against SARS-CoV-2 infection; 73% (95% CI, 71%–75%) against illness; and 97% (95% CI, 92%–99%) against hospitalization. Two-dose VE was 86% (95% CI, 81%–90%) and 93% (95% CI, 89%–95%), respectively, with no hospitalizations. VE was higher for non-VOCs than VOCs (73% Alpha) among single-dose recipients but not 2-dose recipients. Across 16 weeks, no decline in single-dose VE was observed, with appropriate stratification based upon prioritized vaccination determined by higher vs lower likelihood of direct patient contact.

***Conclusions.*** One mRNA vaccine dose provided substantial and sustained protection to HCWs extending at least 4 months postvaccination. In circumstances of vaccine shortage, delaying the second dose may be a pertinent public health strategy.

**Keywords.** SARS-CoV-2; COVID-19; vaccine effectiveness; healthcare workers; test-negative design.

In December 2020, 2 messenger RNA (mRNA) vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) were authorized in Canada based upon a schedule of 2 doses spaced 3 weeks (BNT162b2 [Pfizer-BioNTech]) or 4 weeks (mRNA-1273 [Moderna]) apart [1]. Phase 3 randomized controlled trials showed vaccine efficacy that exceeded 90% for both products beginning from 14 days after a single dose but did not inform protection beyond 3–4 weeks postvaccination [2–5]. Healthcare workers (HCWs) were among the first prioritized for coronavirus disease 2019 (COVID-19) vaccination; several observational studies have since reported vaccine effectiveness (VE) after a single dose, but most had short follow-up periods, the longest extending 8 weeks postvaccination [6–10].

In the context of limited vaccine supply, the Québec Immunization Committee (QIC) recommended that the province of Québec, Canada, defer the second dose of vaccine in order to optimize first-dose coverage and provide protection to as many high-risk individuals as possible against COVID-19–related hospitalizations and deaths [11]. The QIC did not prespecify the interval for second-dose administration, relying upon real-time monitoring of single-dose VE and adaptation in the event of waning protection [12]. The vaccination campaign in Québec began 14 December 2020, and initially targeted long-term care facility residents and HCWs with direct patient contact. On 3 March 2021, the Canadian National Advisory Committee on Immunization and the Québec Ministry of Health set the interval between doses at 16 weeks based upon expected vaccine supply,

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ethical considerations, and short-term but reassuring VE findings [13, 14]. Herein, we compare 1- and 2-dose mRNA VE against SARS-CoV-2, including varying outcome severity and variants of concern (VOCs), among HCWs in Québec and assess the stability of single-dose protection across 16 weeks postvaccination.

## METHODS

### Study Design

The study used a test-negative design: HCWs who tested positive by reverse-transcription polymerase chain reaction (RT-PCR) for SARS-CoV-2 during the study period were cases; HCWs who tested RT-PCR negative were controls.

The case reference date was defined hierarchically as the date of symptom onset (83.5%) or, if not available, the date of specimen collection (16.5%). The control reference date was defined by specimen collection date. To account for time-varying likelihoods of SARS-CoV-2 exposure and vaccination [15], a density sampling approach was used with 10 randomly sampled controls per case matched by week of reference date. An HCW could be sampled several times as a control over the study period (but only once per week) and could subsequently be included as a case. All cases were censored at their reference date.

### Population

The study population included all salaried healthcare workers publicly funded by the Ministry of Health (eg, hospital, long-term care facility, community clinic staff), as well as staff of private facilities under agreement with the ministry (Supplementary Figure 1). Neither physicians who are funded on a fee-for-service basis through a separate source (Medicare) nor HCWs in private-pay settings (eg, certain clinics, private seniors' residences, pharmacies) are included within this database.

Participants were excluded if they had confirmed SARS-CoV-2 infection (RT-PCR confirmed or epidemiologically linked) before 17 January 2021; were missing a unique personal identifying number (PIN) used for data linkage; had an invalid vaccination date (before 14 December 2020); or were <18 or ≥75 years old. HCWs in child and youth protection centers or those hired temporarily for pandemic work by ministerial order were also excluded. Finally, AstraZeneca vaccine recipients were excluded from the date of vaccination because their limited number precluded VE estimation.

### Data Sources

Using the unique PIN, the cohort of all publicly funded HCWs in the province was linked with (1) the provincial database of all SARS-CoV-2 infections reported to public health since pandemic start, including associated clinical details collected during case investigation by public health authorities; (2) the administrative hospitalization database and the chronic disease surveillance system, which integrates information on preexisting medical conditions; (3) the Québec provincial immunization registry, which is a census of all Québec residents insured under the universal publicly funded healthcare system, including vaccination status, vaccination date(s), and type of vaccine received; (4) the provincial centralized laboratory database, including the dates, results, and reason for all RT-PCR tests for SARS-CoV-2 across the province; and (5) VOC PCR screening assay results used to identify signature mutations (69-70 deletion, N501Y, E484K) to genetically characterize and categorize viruses. VOC screening was undertaken on a convenience sample of 10% of SARS-CoV-2–positive specimens in January 2021; on nearly 100% of specimens in February and March; and on about 85% of specimens from April 2021 onward when the VOC prevalence exceeded 90% [16]. As of 6 June 2021, 89% of identified VOC cases were the Alpha variant (Pango lineage: B.1.1.7) [17].

The study period included HCWs with specimen reference date between 17 January 2021 (epidemiological week 3) and 5 June 2021 (week 22) (Figure 1), taking into account the immunization start date and a several-week lag for vaccine effect. Data were extracted on 17 June 2021, allowing additional 14-day lag to capture associated hospitalizations.

### Vaccination and Outcome Definitions

Vaccination status was defined in relation to the reference date. In primary analysis, a participant was deemed a single- or 2-dose vaccinee if the doses were received ≥14 days or ≥7 days, respectively, before the reference date (with day of vaccination being day 0), requiring ≥3 weeks between doses. HCWs who received no vaccine doses at any time on or before the reference date were considered unvaccinated, whereas those who received the first dose <14 days or second dose <7 days prior were excluded. RT-PCR–confirmed SARS-CoV-2 outcomes of varying severity were explored, including any infection; symptomatic infection of any severity (specified hereafter as COVID-19); and COVID-19–related hospitalization (occurring within 30 days of illness onset).

### VE Analysis

Odds ratios (ORs) and their 95% confidence intervals (CIs) among 1- and 2-dose vaccinees relative to unvaccinated HCWs were estimated by multivariate conditional logistic regression using the matching week as strata and adjusting for potential confounders. VE and 95% CIs were derived as: $(1 - OR_{adjusted}) \times 100$.

Adjustment variables included age group, sex, job category, healthcare setting, region of the healthcare setting (18 in Québec), and presence of 17 possible comorbidities associated with increased COVID-19 hospitalization risk (known for ~90% of HCWs) [18].

In addition to overall primary analyses by outcome severity, sensitivity analyses included (1) stratifying by HCW priority group based upon those targeted before 31 January (week

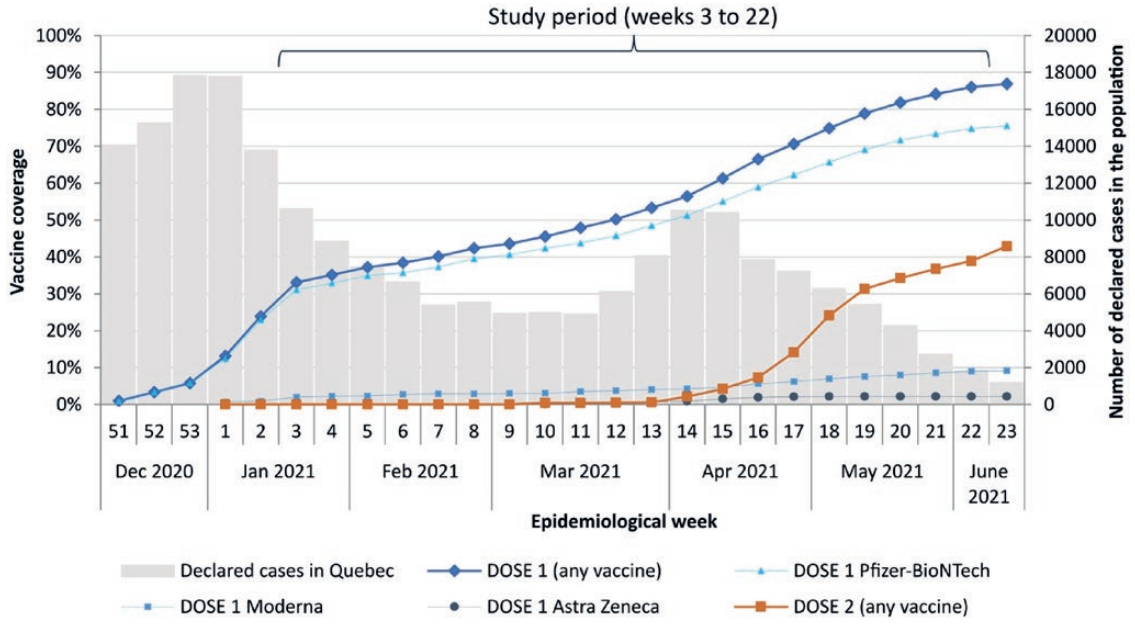


**Figure 1.** Vaccination coverage in the cohort of healthcare workers and total number of reported coronavirus disease 2019 cases in the population per week, Québec, Canada.

5) or since 21 February (week 8), reflecting higher and lower frequency of direct patient contact and baseline infection risk, respectively; (2) stratifying by VOC status; (3) restricting to HCWs with data on 17 preexisting conditions of comorbidity (≥1, ≥2, or by 0, 1, 2, 3, 4, ≥5 conditions); and (4) stratifying by reason for testing (compatible symptoms, outbreak, or systematic screening).

#### Ethical Aspects

This study was conducted as a surveillance and evaluation protocol with the legal mandate of the National Director of Public Health of Québec and with the requirement for ethics approval thereby waived under the Public Health Act.

## RESULTS

#### Study Population

Of the 342 138 HCWs in the initial cohort, 333 832 (97.6%) were successfully linked with the immunization registry. As of 5 June 2021 (end of week 22), 86.0% of individual HCWs in the cohort had received at least 1 vaccine dose (88.0% Pfizer-BioNTech, 9.4% Moderna, and 2.6% AstraZeneca vaccine) and 38.9% had received 2 doses (Figure 1).

We excluded 8% of HCWs who were confirmed COVID-19 cases before 17 January 2021; 4% who worked in child and youth protection centers; 3% with missing PIN; 1% temporarily hired by ministerial order; and <1% with an invalid vaccination date. Among the 284 637 remaining HCWs, 115 288 had no testing during the study period, leaving 169 349 HCWs with 548 796 specimens for VE analysis. There were 5316 cases with 53 160 controls randomly sampled among negative tests (Supplementary Figure 1), of which 10.8% cases and 11.8% controls vaccinated 0–13 days or 0–6 days before the first or second dose, respectively, were excluded from primary analyses.

#### Characteristics of Cases and Controls

At their reference date, 23.8% of cases and 49.1% of controls had received 1 dose ≥14 days earlier and 0.9% of cases and 3.9% of controls had received 2 doses ≥7 days earlier. The percentage of controls vaccinated with at least 1 dose ≥14 days before the reference date increased with age, from 49.1% in 18- to 29-year-olds to 61.5% among 60- to 74-year-olds (Supplementary Figure 2). For those who received 2 doses, the median interval between doses was nearly 16 weeks (111 days for cases and 112 days for controls). The median follow-up time for 1-dose vaccinees was 56 days and for 2-dose vaccinees was 18 days. Among all cases, 80.5% had COVID-19–related symptoms, 1.7% were hospitalized, and 1 unvaccinated HCW died (Table 1). For symptomatic COVID-19 cases, the median and mean interval between symptom onset and testing was 1.0 and 1.3 days, respectively.

Screening PCR for VOC was performed on 2889 (54.4%) positive specimens (91.5% during weeks 8–20): 1620 (56.1%) were a VOC and among them 73.0% were the Alpha variant (Table 1), distributed across the study period as displayed in Supplementary Figure 3. Demographic and employment characteristics are provided in detail in Table 1.

**Table 1. Vaccination Status, Demographic, and Employment Characteristics of Cases and Controls**

| Characteristic | Cases | | | | | | Controls | |
|---|---|---|---|---|---|---|---|---|
| | Any SARS-CoV-2 Infections (n = 5316) | | COVID-19 (n = 4277) | | Hospitalizations (n = 92) | | (n = 53 160) | |
| Vaccination status (days before illness onset/testing) | | | | | | | | |
| 1-dose vaccinees (≥14 d) | 1266 | (23.8) | 970 | (22.7) | 4 | (4.4) | 26 118 | (49.1) |
| Pfizer-BioNTech vaccine | 1202 | (22.6) | 924 | (21.6) | 4 | (4.4) | 24 589 | (46.3) |
| Moderna vaccine | 64 | (1.2) | 46 | (1.1) | 0 | (0.0) | 1529 | (2.9) |
| 2-dose vaccinees (≥7 d) | 50 | (0.9) | 20 | (0.5) | 0 | (0.0) | 2081 | (3.9) |
| Pfizer-BioNTech vaccine | 48 | (0.9) | 20 | (0.5) | 0 | (0.0) | 1954 | (3.7) |
| Moderna vaccine | 2 | (0.0) | 0 | (0.0) | 0 | (0.0) | 126 | (0.2) |
| Vaccinated with at least 1 dose (≥14 d)[a] | 1373 | (25.8) | 1029 | (24.1) | 4 | (4.4) | 29 201 | (54.9) |
| Unvaccinated | 3424 | (64.4) | 2813 | (65.8) | 86[b] | (93.5) | 18 663 | (35.1) |
| Delay between doses, d, median (IQR) | 111 | (106–112) | 112 | (109–114) | NA | NA | 112 | (107–112) |
| Reasons for testing | | | | | | | | |
| Symptoms compatible with COVID-19 | 2751 | (51.8) | 2619 | (61.2) | 44 | (47.8) | 8094 | (15.2) |
| Testing in the presence of an outbreak | 629 | (11.8) | 407 | (9.5) | 6 | (6.5) | 12 517 | (23.6) |
| Systematic screening (asymptomatic) | 653 | (12.3) | 373 | (8.7) | 7 | (7.6) | 23 940 | (45.0) |
| Other reason or unknown | 1283 | (24.1) | 878 | (20.5) | 35 | (38.0) | 8609 | (16.2) |
| VOCs (among 2889 positive specimens) | | | | | | | | |
| Any VOC | 1620 | (56.1) | 1368 | (58.1) | 43 | (67.2) | NA | NA |
| Alpha variant (lineage B.1.1.7) | 1182 | (40.9) | 1003 | (42.6) | 31 | (48.4) | NA | NA |
| VOC not detected | 944 | (32.7) | 784 | (33.3) | 15 | (23.4) | NA | NA |
| Uninterpretable result | 325 | (11.2) | 203 | (8.6) | 6 | (9.4) | NA | NA |
| Demographic, clinical, and employment characteristics | | | | | | | | |
| Age, y, median (IQR) | 39 | (30–49) | 39 | (30–49) | 48.5 | (38–56) | 41 | (31–51) |
| 18–29 | 1295 | (24.4) | 1049 | (24.5) | 9 | (9.8) | 10 826 | (20.4) |
| 30–39 | 1403 | (26.4) | 1157 | (27.1) | 17 | (18.5) | 13 642 | (25.7) |
| 40–49 | 1343 | (25.3) | 1067 | (25.0) | 24 | (26.1) | 13 569 | (25.5) |
| 50–59 | 1049 | (19.7) | 828 | (19.4) | 31 | (33.7) | 11 957 | (22.5) |
| 60–74 | 226 | (4.3) | 176 | (4.1) | 11 | (12.0) | 3166 | (6.0) |
| Sex, female | 4233 | (79.6) | 3459 | (80.9) | 69 | (75.0) | 44 280 | (83.3) |
| Comorbidity (n = 53 075 [90.8%])[c] | | | | | | | | |
| At least 1 medical condition | 1617 | (30.8) | 1302 | (30.6) | 49 | (53.3) | 15 963 | (33.1) |
| At least 2 medical conditions | 502 | (9.5) | 415 | (9.8) | 21 | (22.8) | 4845 | (10.1) |
| Job category | | | | | | | | |
| Nurse | 975 | (18.3) | 801 | (18.7) | 16 | (17.4) | 12 519 | (23.6) |
| Nursing assistant | 474 | (8.9) | 372 | (8.7) | 12 | (13.0) | 4516 | (8.5) |
| Healthcare support worker | 1108 | (20.8) | 817 | (19.1) | 29 | (1.1) | 12 357 | (23.2) |
| Other health assisting occupations | 662 | (12.5) | 503 | (11.8) | 10 | (31.5) | 5430 | (10.2) |
| Technical assisting occupations | 424 | (8.0) | 337 | (7.9) | 3 | (10.9) | 3154 | (5.9) |
| Administrative and management staff | 849 | (16.0) | 739 | (17.3) | 15 | (3.3) | 5305 | (10.0) |
| Healthcare technician | 349 | (6.6) | 289 | (6.8) | 4 | (16.3) | 5084 | (9.6) |
| Social worker | 402 | (7.6) | 360 | (8.4) | 2 | (4.4) | 3200 | (6.0) |
| Other | 73 | (1.4) | 59 | (1.4) | 1 | (2.2) | 1595 | (3.0) |
| Healthcare setting | | | | | | | | |
| Hospital/local community health center | 2857 | (53.7) | 2348 | (54.9) | 54 | (58.7) | 28 563 | (53.7) |
| LTC facility | 1063 | (20.0) | 772 | (18.1) | 21 | (22.8) | 14 890 | (28.0) |
| Rehabilitation centers | 283 | (5.3) | 229 | (5.4) | 1 | (1.1) | 1353 | (2.6) |
| Home care | 283 | (5.3) | 235 | (5.5) | 1 | (1.1) | 3029 | (5.7) |
| Other | 830 | (15.6) | 693 | (16.2) | 15 | (16.3) | 5325 | (10.0) |

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: COVID-19, coronavirus disease 2019; IQR, interquartile range; LTC, long-term care; NA, not applicable; VOC, variant of concern.

[a]Including those vaccinated with 2 doses <7 days before the reference date.

[b]Two hospitalized cases were vaccinated 0–13 days before illness onset.

[c]Seventeen medical conditions considered: hypertension, cardiovascular disease, neurological disorder, anemia, respiratory disease, diabetes, hypothyroidism, fluid and electrolyte disorder, cancer, kidney disease, obesity, psychosis, liver disease, immune disease, coagulopathy, and paralysis.

### Vaccine Effectiveness

#### *Overall, by Outcome Severity*

The overall adjusted single-dose mRNA VE was 70.4% (95% CI, 68.2%–72.5%) against any SARS-CoV-2 infection, 72.9% (95% CI, 70.6%–75.0%) against COVID-19, and 97.2% (95% CI, 92.3%–99.0%) against COVID-19–related hospitalization (Table 2). The overall adjusted 2-dose mRNA VE was 85.8% (95% CI, 81.0%–89.5%) and 92.7% (95% CI, 88.5%–95.4%), respectively, with no associated hospitalizations. No differences were found by vaccine type (Pfizer-BioNTech or Moderna) (Table 2) or age group (Supplementary Figure 2).

One-dose VE against COVID-19 was 76%–78% between 2 and 7 weeks postvaccination, declining slightly to about 70% between 9 and 16 weeks postvaccination (<1% were vaccinated >16 weeks prior) (Figure 2). Follow- up after 2 doses was too short for corresponding interval analyses.

#### *By HCW Priority Group*

Among HCWs first targeted for vaccination before week 5 (because of highest likelihood of direct patient contact and baseline infection risk), VE during the period 0–13 days after the first dose (when no vaccine effect is expected) was highly negative (–101.6% [95% CI, –139.9% to –69.5%). Conversely, among HCWs first vaccinated after week 8 (at lower baseline infection risk), VE during the period 0–13 days was significantly higher at 43.7% (95% CI, 31.9%–53.5%). Thereafter, the earlier vs later targeted HCWs had lower VE overall across the 2- to 16-week analysis period (52.2% [95% CI, 47.1%–56.9%] vs 77.4% [95% CI, 73.0%–81.1%]), with neither target group

**Table 2. Overall Vaccine Effectiveness by Outcome Severity and Variant of Concern Status**

| | | | Model Adjusted (Stratified) for the Matching Week | | Model Fully Adjusted[a] | |
|---|---|---|---|---|---|---|
| Outcome | Cases, No. (%) | Controls, No. (%) | VE, % | (95% CI) | VE, % | (95% CI) |
| Overall, by outcome severity | | | | | | |
| VE against any SARS-CoV-2 infection | | | | | | |
| 1-dose vaccinees (≥14 d) | 1266 (26.7) | 26 118 (55.7) | 74.7 | (72.9–76.4) | 70.4 | (68.2–72.5) |
| Pfizer-BioNTech vaccine | 1202 (25.7) | 24 589 (54.4) | 74.5 | (72.6–76.2) | 70.3 | (68.1–72.4) |
| Moderna vaccine | 64 (1.8) | 1529 (7.5) | 78.0 | (71.6–82.9) | 68.7 | (59.5–75.9) |
| 2-dose vaccinees (≥7 d) | 50 (1.0) | 2081 (4.4) | 89.3 | (85.6–92.0) | 85.8 | (81.0–89.5) |
| Pfizer-BioNTech vaccine | 48 (1.0) | 1954 (4.3) | 89.0 | (85.2–91.8) | 85.5 | (80.4–89.3) |
| Moderna vaccine | 2 (0.1) | 126 (0.6) | 90.4 | (61.2–97.6) | 84.1 | (34.9–96.1) |
| Unvaccinated | 3424 (72.2) | 18 663 (39.8) | | | | |
| VE against COVID-19 | | | | | | |
| 1-dose vaccinees (≥14 d) | 970 (25.5) | 26 118 (55.7) | 76.7 | (74.9–78.5) | 72.9 | (70.6–75.0) |
| Pfizer-BioNTech vaccine | 924 (24.6) | 24 589 (54.4) | 76.4 | (74.5–78.2) | 72.8 | (70.5–74.9) |
| Moderna vaccine | 46 (1.6) | 1529 (7.5) | 80.9 | (74.3–85.8) | 80.9 | (74.3–85.8) |
| 2-dose vaccinees (≥7 d) | 20 (0.5) | 2081 (4.4) | 94.4 | (91.3–96.5) | 92.7 | (88.5–95.4) |
| Pfizer-BioNTech vaccine | 20 (0.5) | 1954 (4.3) | 94.0 | (90.7–96.2) | 92.2 | (87.8–95.1) |
| Moderna vaccine | 0 (0) | 126 (0.6) | 100 | NE | NE | NE |
| Unvaccinated | 2813 (74.0) | 18 663 (39.8) | … | … | … | … |
| VE against COVID-19–related hospitalization | | | | | | |
| 1-dose vaccinees (≥14 d) | 4 (4.4) | 26 118 (55.7) | 97.1 | (92.0–98.9) | 97.2 | (92.3–99.0) |
| 2-dose vaccinees (≥7 d) | 0 (0.0) | 2081 (4.4) | 100 | NE | NE | NE |
| Unvaccinated | 86 (96.6) | 18 663 (39.8) | … | … | … | … |
| By VOC status | | | | | | |
| Any VOC detected | | | | | | |
| 1-dose vaccinees (≥14 d) | 454 (36.3) | 26 118 (55.7) | 67.4 | (63.2–71.1) | 62.5 | (57.4–67.0) |
| 2-dose vaccinees (≥7 d) | 13 (1.0) | 2081 (4.4) | 94.8 | (90.8–97.0) | 93.5 | (88.7–96.3) |
| Unvaccinated | 784 (62.7) | 18 663 (39.8) | … | … | … | … |
| Alpha variant | | | | | | |
| 1-dose vaccinees (≥14 d) | 337 (37.4) | 26 118 (55.7) | 63.9 | (58.5–68.7) | 60.0 | (53.6–65.5) |
| 2-dose vaccinees (≥7 d) | 13 (1.4) | 2081 (4.4) | 94.0 | (89.5–96.6) | 92.6 | (87.1–95.8) |
| Unvaccinated | 551 (61.2) | 18 663 (39.8) | … | … | … | … |
| VOC not detected | | | | | | |
| 1-dose vaccinees (≥14 d) | 187 (25.2) | 26 118 (55.7) | 81.4 | (77.9–84.3) | 77.0 | (72.6–80.7) |
| 2-dose vaccinees (≥7 d) | 3 (0.4) | 2081 (4.4) | 90.2 | (68.6–97.0) | 86.5 | (56.8–95.8) |
| Unvaccinated | 552 (74.4) | 18 663 (39.8) | … | … | … | … |

Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019; NE, not estimable; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; VE, vaccine effectiveness; VOC, variant of concern.

[a]Conditional logistic regression model adjusted for age group (18–29, 30–39, 40–49, 50–59, 60–74 years); sex; job category (nurse, nursing assistant, personal healthcare support worker, other technical and health assisting occupations, administrative and management staff, healthcare technician, social workers, others); healthcare setting; health region; and matching week.

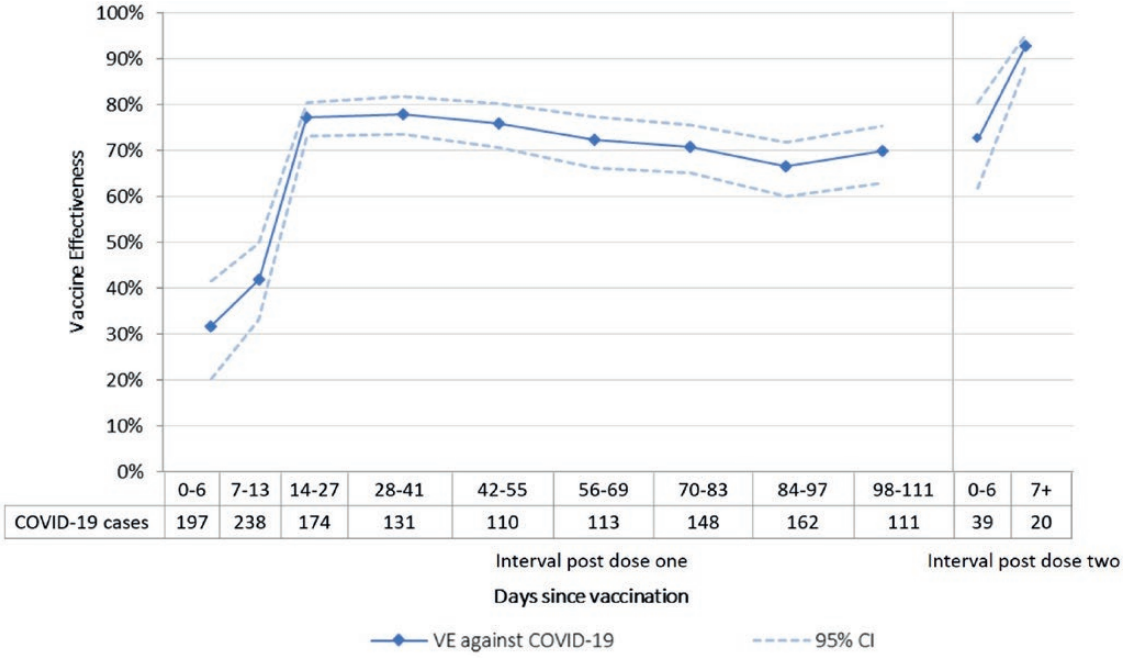


**Figure 2.** Vaccine effectiveness against coronavirus disease 2019, by interval since vaccination. Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019; VE, vaccine effectiveness.

showing decline in protection over that extended follow-up period (Supplementary Table 1 and Figure 3).

***By VOC Status***

With restriction to cases with screening VOC results, VE against COVID-19 was higher for non-VOCs than VOCs among single-dose (77.0% [95% CI, 72.6%–80.7%] vs 62.5% [95% CI, 57.4%–67.0%]) but not 2-dose recipients (86.5% [95% CI, 56.8%–95.8%] vs 93.5% [95% CI, 88.7%–96.3%]). The Alpha-specific VE did not differ from VE against any VOC (including those with undetermined lineage) (Table 2) but was consistently lower than for non-VOCs across the entire follow-up period

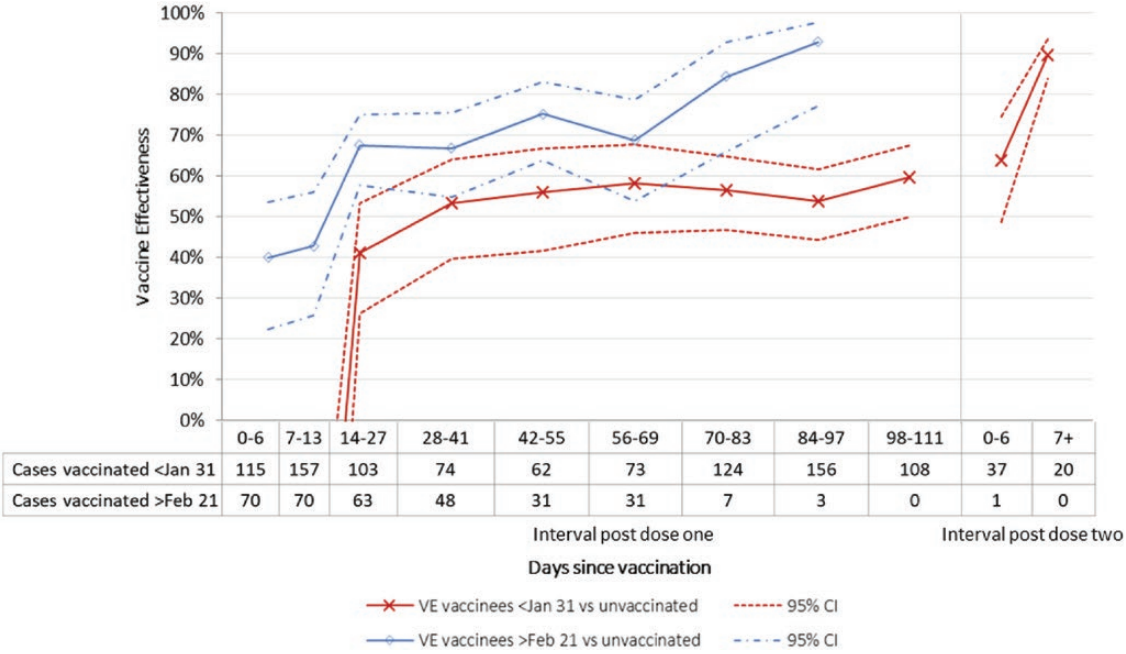


**Figure 3.** Vaccine effectiveness against coronavirus disease 2019 in healthcare workers vaccinated before 31 January 2021 (highest contacts with patients) and those vaccinated after 20 February 2021 (fewer contacts with patients), by interval since vaccination. Abbreviations: CI, confidence interval; VE, vaccine effectiveness.

(Figure 4). Among 90 hospitalized cases, 63 were analyzed for VOCs, with the only vaccinated case bearing the Alpha variant.

***By Comorbidity and Testing Indication***

Adjustment for the presence of comorbidity did not meaningfully affect VE estimates (data not shown). In analyses stratified by testing indication, 1-dose VE was lower for COVID-19–compatible symptoms (62.7% [95% CI, 58.6%–66.4%]) vs outbreak-related testing (73.0% [95% CI, 64.7%–79.4%]) or screening-related testing (73.1% [95% CI, 64.9%–79.4%]). Two-dose estimates were higher for HCWs tested for symptomatic illness but with overlapping 95% CIs (Supplementary Table 1).

## DISCUSSION

In this observational study, we report single-dose mRNA VE of 70% against any SARS-CoV-2 infection and 73% against COVID-19 illness among HCWs in Québec, Canada. Although VE was higher at 86% and 93%, respectively, after a second dose, VE against COVID-19 hospitalization was comparably high at >95% for both 1- and 2-dose recipients. Importantly, we provide the longest single-dose vaccination follow-up to date, showing substantial protection maintained for at least 16 weeks after receipt of just 1 dose of mRNA vaccine. Overall, our findings reinforce the recommendation for second-dose deferral and show that the interval between doses can be extended to at least 4 months where indicated due to scarce vaccine supply.

Other observational studies from the United States (US), Israel, and Europe have reported comparable Pfizer-BioNTech VE among HCWs beginning 14 and 7 days after dose 1 or 2, respectively, but these involved only short follow-up periods. In 2 US studies, single-dose VE among HCWs, vaccinated according to the manufacturer's schedule, was 78% against any infection [6], and 74% against symptomatic infection [7], with 2-dose VE of 97% and 94%, respectively [6, 7]. Similarly, in an Israeli HCW cohort, single-dose VE was 75% against any SARS-CoV-2 infection from 15 to 28 days postvaccination [9]. In Italy, single-dose VE between 14 and 21 days postvaccination in HCWs was 83% against symptomatic infection and lower at 66% for ≥21 days without specification of the longest duration of follow-up [8]. In the United Kingdom, where the second dose was also deferred [19], the SARS-CoV-2 Immunity and Reinfection Evaluation (SIREN) study reported VE against any SARS-CoV-2 infection of 72% from 21 to 69 days postvaccination in HCWs systematically tested over a maximum of 8 weeks [10].

In our study, single-dose mRNA VE against hospitalization among HCWs was 97% across a 16-week period. Although evidence elsewhere supports high 2-dose protection against hospitalization [20–22], few studies to date have reported single-dose protection and none over such an extended follow-up period. In population-based studies, 1-dose VE against hospitalizations among mostly older adults was 74% (14–20 days postvaccination) in Israel, 77% (>14 days postvaccination) in the US, and 91% (14–34 days postvaccination) in Scotland [21–23].

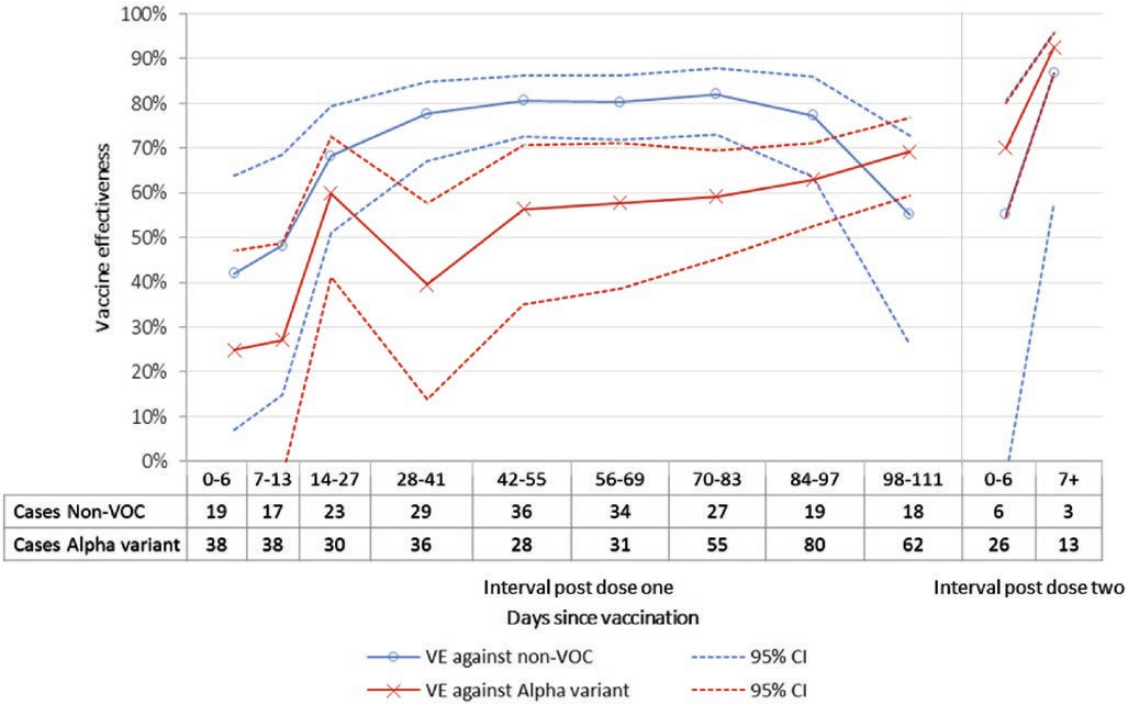


**Figure 4.** Vaccine effectiveness against coronavirus disease 2019, by variant of concern (VOC) status (non-VOC or Alpha variant) and interval since vaccination. Abbreviations: CI, confidence interval; VE, vaccine effectiveness; VOC, variant of concern.

The Alpha (B.1.1.7) variant was the most prevalent SARS-CoV-2 variant in circulation in Québec between late March and the end of our study period. The lower single-dose VE of 60% (95% CI, 54%–66%) we report against symptomatic Alpha infection among HCWs is consistent with the lower single-dose VE of 67% against Alpha infection recently reported for older adults ≥70 years of age from the province of British Columbia, Canada, also based upon test-negative design [24]. Lower VE against Alpha may also be explained by greater VOC screening in situations of high-risk exposure such as outbreaks. VE against both VOCs and non-VOCs during the nonprotective period of 0–6 days likely reflects a positive bias in the early period following vaccination, but VE was also lower for Alpha during this period. Our higher 2-dose estimate of 93% (95% CI, 87%–96%) is also consistent with estimates exceeding 90% from Israel [20] and Qatar [25]. Of note, the later predominant contribution by and lower VE against the Alpha variant, whose prevalence among SARS-CoV-2 infections was <30% in mid-March (week 12) but increased to >90% at the end of the study, may have contributed to an apparent but perhaps artefactual decline in overall single-dose protection across the analysis period.

Furthermore, with respect to the question of potential waning of single-dose vaccine protection, we highlight an important methodological issue, critical for other investigators to consider. In particular, we illustrate the impact that confounding by indication can have when averaging VE across subgroups with different exposure risks and who are sequentially prioritized or targeted for vaccination on that basis. HCWs who were earliest prioritized for vaccination because of highest baseline infection risk will also contribute most to the longest postvaccination analysis intervals. In pooled analysis, their systematically higher infection risk and lower VE will lead to an overall, but erroneous, impression of declining single-dose VE generally with time since vaccination. Conversely, with appropriate stratification based upon underlying differential in exposure and infection risk, we show single-dose VE to have been stable across the analysis period including both earlier and later prioritized HCW subsets. Properly addressing that methodological bias, we demonstrate no evidence for decrease in single-dose VE across a 4-month follow-up period.

This study has limitations, foremost related to its observational design, subject to bias and confounding, and reliance on surveillance data subject to misclassification and missing information. Like other researchers, we could not fully adjust for differential exposure risk or fully ascertain the symptom profile notably after specimen testing. Despite easy access to testing, some asymptomatic infections were likely missed. HCWs with undetected infections before the study period could not be excluded, leading to bias due to undiagnosed cases among vaccinated (overestimation) or unvaccinated (underestimation) participants [26]. A ministerial order issued on 9 April 2021 requiring unvaccinated HCWs to be systematically tested every 3 days [27] may have increased detection of asymptomatic infections in unvaccinated individuals, potentially leading to overestimation of VE against any infection at the end of the follow-up period but without affecting VE against COVID-19 or hospitalization. HCWs are active and relatively young adults and these results may not apply to older adults [28, 29]. Even if adjustment for comorbidities did not change VE estimates, HCWs with medical conditions putting them at high risk of severe disease were frequently removed from direct patient care duties during the pandemic and their VE might be lower than the estimates for all HCWs [22]. The Delta variant has more recently risen to prominence, but during the study period comprised <1% of characterized SARS-CoV-2 viruses in Québec [16], precluding its variant-specific VE estimation. Although the mix of circulating variants and vaccine match may change over time, the overarching insight we provide is that, once established, mRNA VE against a particular strain appears to then be stable across several months. Despite limitations, our study has strengths including its extended post-single-dose follow-up of a large and well-defined cohort and its several sensitivity and stratified analyses to address confounding due to time-dependent variables (vaccination prioritization and exposure risk) and variation in VOC circulation. Whereas VE estimates from our observational design may not precisely mimic short-term randomized controlled trial estimates, the stable pattern of persistent single-dose protection we report across several months of follow-up is a unique and informative advantage over prior studies and may be the most meaningful with respect to public health implications for other areas still grappling with vaccine shortage.

In conclusion, 1 dose of mRNA vaccine reduced the risk of COVID-19 among HCWs by at least three-quarters (preventing 3 of 4 symptomatic infections) and the associated risk of hospitalization by >95%, with such single-dose protection extending at least 16 weeks postvaccination. Our findings of substantial and sustained single-dose VE, including against the Alpha variant, reinforce the option to defer the second dose of mRNA vaccine in circumstances of scarce vaccine supply and where broad single-dose coverage is critically needed.

## Supplementary Data

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

## Notes

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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