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Single-dose mRNA Vaccine Effectiveness Against Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), Including Alpha and Gamma Variants: A Test-negative Design in Adults 70 Years and Older in British Columbia, Canada

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Background. Randomized-controlled trials of messenger RNA (mRNA) vaccine protection against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) included relatively few elderly participants. We assess single-dose mRNA vaccine effectiveness (VE) in adults ≥ 70 years old in British Columbia, Canada, where second doses were deferred by up to 16 weeks and where a spring 2021 wave uniquely included codominant circulation of Alpha (B.1.1.7) and Gamma (P.1) variants of concern (VOC).

Methods. Analyses included community-dwelling adults ≥ 70 years old with specimen collection between 4 April (epidemiological week 14) and 1 May (week 17) 2021. Adjusted VE was estimated by test-negative design. Cases were reverse-transcription polymerase chain reaction (RT-PCR) test-positive for SARS-CoV-2, and controls were test-negative. Vaccine status was defined by receipt of a single-dose ≥ 21 days before specimen collection, but a range of intervals was assessed. Variant-specific VE was estimated against viruses genetically characterized as Alpha, Gamma or non-VOC lineages.

Results. VE analyses included 16 993 specimens: 1226 (7%) test-positive cases and 15 767 test-negative controls. Of 1131 (92%) genetically characterized viruses, 509 (45%), 314 (28%), and 276 (24%) were Alpha, Gamma, and non-VOC lineages, respectively. At 0–13 days postvaccination, VE was negligible at 14% (95% confidence interval [CI], 0–26) but increased from 43% (95% CI, 30–53) at 14–20 days to 75% (95% CI, 63–83) at 35–41 days postvaccination. VE at ≥ 21 days postvaccination was 65% (95% CI, 58–71) overall: 72% (95% CI, 58–81), 67% (95% CI, 57–75), and 61% (95% CI, 45–72) for non-VOC, Alpha, and Gamma variants, respectively.

Conclusions. A single dose of mRNA vaccine reduced the risk of SARS-CoV-2 by about two-thirds in adults ≥ 70 years old, with protection only minimally reduced against Alpha and Gamma variants.

Keywords. case-control; SARS-CoV-2; test-negative design; vaccine effectiveness; variants of concern.

The first messenger RNA (mRA) vaccines against coronavirus disease 2019 (COVID-19) (Pfizer-BioNTech; Moderna) were authorized in Canada in December 2020 [1–3]. In randomized-controlled trials (RCT) of both products, 2 doses spaced 3–4 weeks apart were 94–95% efficacious against symptomatic, laboratory-confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection [2, 3]. When RCT data were reanalyzed applying the usual 2-week lag for vaccine effect, a single dose of either product was also substantially protective at 92–93% [3, 4]. Participants in these trials, however, were generally young and healthy with not more than 5% who were ≥ 75 years old [2, 3].

In the context of elevated epidemic activity and scarce vaccine supply, some jurisdictions have extended the interval between first and second doses of SARS-CoV-2 vaccines to enable more people to benefit from substantial single-dose protection. In the United Kingdom an interval of up to 12 weeks was recommended on 30 December 2020 [5]. In Canada, an even longer interval of up to 16 weeks was recommended beginning 3 March 2021 (epidemiological week 9) [6].

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As in most provinces, British Columbia initially prioritized available mRNA vaccines to long-term care facility (LTCF) residents and frontline healthcare workers. This was associated with dramatic reduction in reported LTCF outbreaks and associated cases [6, 7]. However, high vaccine coverage (>90%), including a majority (>60%) who were twice immunized before week 9 made it difficult to distinguish first- from second-dose and direct from indirect vaccine impact in that relatively closed setting.

Community vaccination in British Columbia subsequently followed an age-based strategy that first prioritized older adults ≥ 90, 80–89. and 70–79 years of age beginning around week 10. Although viral vector vaccines are also authorized in Canada [1], they were not prominently used in these age groups. In the spring 2021, British Columbia experienced its most substantial pandemic wave to date, including a majority of viruses that were characterized as variants of concern (VOC), and uniquely including co-dominant circulation of Alpha (Pango lineage: B.1.1.7) and Gamma (Pango lineage: P.1) viruses [8, 9]. A publicly funded, mostly symptom-based approach for SARS-CoV-2 diagnostic testing is broadly accessible in British Columbia. In that context, we applied a test-negative design (TND) to estimate the vaccine effectiveness (VE) of a single dose of mRNA vaccine against SARS-CoV-2, including variant-specific estimates, among community-dwelling adults ≥ 70 years old in British Columbia.

METHODS

Source Population, Analysis Period, and Study Design

There are about 673 000 adults ≥ 70 years old in British Columbia (13% of the total 5.1 million population) including ~437 000 (65%) 70–79 years, 188 000 (28%) 80–89 years, and 48 000 (7%) ≥90 years old with slightly more than half who are women (54%) [10].

The spring 2021 wave peaked in British Columbia in week 14 and gradually subsided with province-wide measures; however, weekly case reports continued to exceed the peak week of prior waves until week 17 [7]. The analysis period of the current study spanned weeks 14–17 (4 April to 1 May 2021), taking into account vaccine rollout and several-week delay for vaccine effect as well as community SARS-CoV-2 activity that remained elevated during this period.

VE was assessed by TND with multivariable logistic regression used to estimate the adjusted odds ratio (AOR) for vaccination among test-positive cases versus test-negative controls. VE and 95% confidence intervals (CI) were derived as (1-AOR) × 100%. The following covariates were included in adjusted models: age group, sex, epidemiological week, and health authority (HA) of residence, or if the latter were not available, then the HA of the clinician associated with the test.

Data Sources

Specimens collected between weeks 14 and 17 and tested by real-time reverse-transcription polymerase chain reaction (RT-PCR) for SARS-CoV-2 were eligible. Test-positive cases and test-negative controls were sampled from within the Public Health Laboratory Operations Viewer and Reporter (PLOVER) database. PLOVER was established by the BC Centre for Disease Control (BCCDC) Public Health Laboratory (PHL) to capture, in real time, all specimens tested province-wide for SARS-CoV-2 along with client, specimen collection, and testing details; however, symptoms and onset date are not consistently captured in PLOVER. Vaccination information was obtained from the provincial immunization registry (PIR), a centralized database that captures, also in real-time, all SARS-CoV-2 vaccinations in British Columbia, along with client and vaccination details. Individual-level linkage between PLOVER and PIR data sets was achieved through unique personal identifiers.

Case and Control Selection

Individuals could contribute a single test-positive specimen. In variant-specific analyses, test-positive cases were restricted to those in whom a VOC was detected, defined as in Supplementary Material 1 [9], and with separate VE estimates derived for Alpha (B.1.1.7), Gamma (P.1) or non-VOC. Three approaches were used for test-negative control selection. In the first specimen-based approach, all negative specimens from a single individual could contribute; however, specimens collected on the same day were counted only once or excluded if discordant. In the second individual-based approach, only the single latest negative specimen per individual could contribute. In an alternative individual-based approach, only one randomly-selected negative specimen per individual could contribute. We further explored with and without exclusion of negative specimens collected within 3 weeks before a positive specimen.

Vaccine Status Definition

Clients with record of a single dose of mRNA vaccine on or before the date of specimen collection were considered vaccinated; those without such record were considered unvaccinated. Because our VE analyses are timed on specimen collection rather than onset date, we incorporate additional lag beyond the usual 2-week grace period for vaccine effect. Among community-dwelling adults ≥ 70 years old with both dates available in PLOVER, the mean and median interval between onset and specimen collection date was 4 and 3 days, respectively, with interquartile range of 1–5 days. We base primary VE analyses on vaccine receipt at least 3 weeks before specimen collection date (≥21 days) but assess intervals of 0–13, 14–20, 21–27, 28–34, 35–41, and ≥ 42 days.

Inclusion/Exclusion Criteria

Specimens missing information for age, sex, HA, specimen collection date, vaccination date, or vaccine type were excluded as were those with missing or inconclusive RT-PCR results. Cases with collection date before the start of the analysis period were excluded, identified through further linkage with the notifiable disease list of confirmed COVID-19 cases reported by the HAs and maintained by the BCCDC. Specimens that were tested outside of public funding were excluded because of systematically lower likelihood of test-positivity [7]. Clients who received more than 1 vaccine dose were excluded as were those who received a viral vector vaccine [1]. Finally, any specimens identified within PLOVER and/or the PIR or notifiable disease list from LTCF, assisted-living or independent-living facilities were excluded.

Ethics Statement

Data linkages and analyses were conducted under a surveillance mandate, authorized by the Provincial Health Officer under the Public Health Act, and exempt from research ethics board review.

RESULTS

Participant Profiles

In total, 16 993 SARS-CoV-2 specimens contributed to VE analyses, including 1226 (7.2%) test-positive cases and 15 767 test-negative controls (Supplementary Figure 2). Viruses from 1131/1226 (92%) cases were genetically categorized with respect to VOC status, of which 509 (45%) were Alpha and 314 (28%) were Gamma variants (Supplementary Tables 1 and 7). An additional 4 (<1%) viruses belonged to the Beta (B.1.351) lineage and another 12 (1%) could not be differentiated as Gamma or Beta while 16 viruses (1%) were Delta (B.1.617.2) or Kappa (B.1.617.1) lineage viruses; these 32 viruses were excluded from variant-specific VE analyses (Supplementary Table 1). Of the remainder, 276 (24%) were designated non-VOC. The distributions of VOC and non-VOC by participant subgroup were similar (Supplementary Figure 1).

Decrease in test-positivity and case tallies by successive week of the analysis period mirrored provincial surveillance patterns (Figure 1; Table 1) [7]. The distributions of test-negative controls by age, sex, and HA were generally representative of the British Columbia source population (Table 1) [7, 10].

Among vaccinated cases and controls, 85% and 90%, respectively, had received their first dose by week 14 (Figure 1). Among test-negative controls, vaccine coverage was comparable to the provincial average for community-dwelling adults ≥ 70 years overall (74% vs 75%), and by week 14 (60% vs 64%), 15 (72% vs 75%), 16 (82% vs 80%), and 17 (84% vs 82%) (Table 2). Of specimens from vaccinated cases and controls, >90% were collected < 42 days since vaccination, limiting VE interpretation

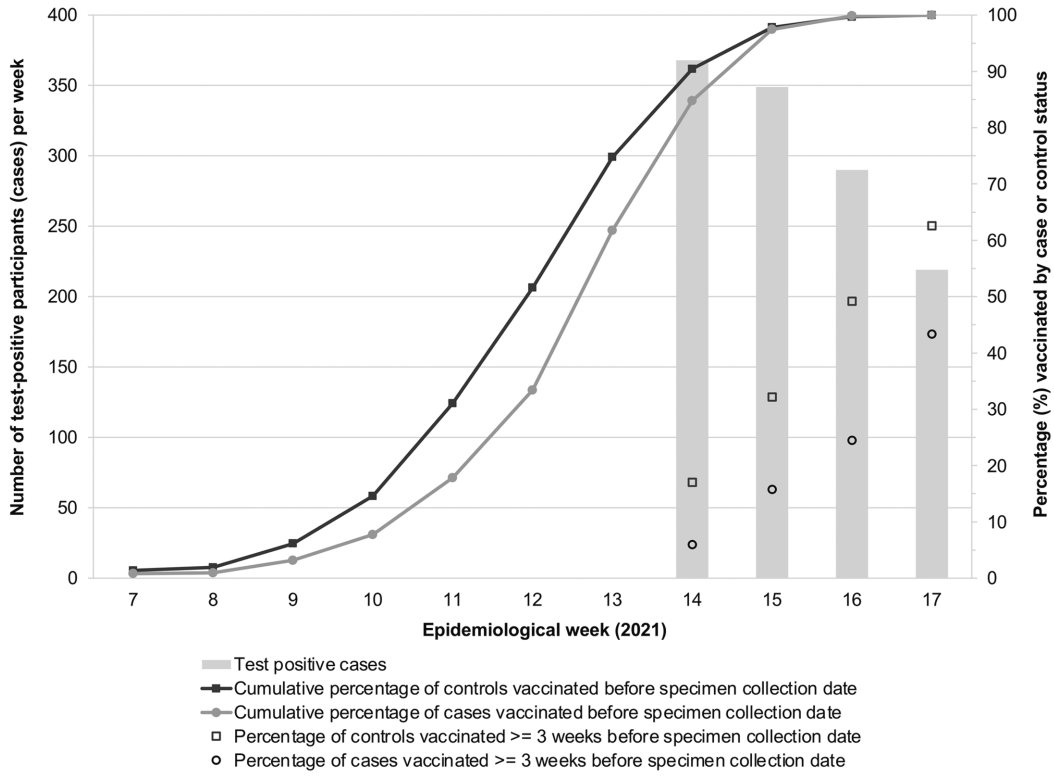

Figure 1. Percentage vaccinated among SARS-CoV-2 test-positive cases and test-negative controls and case tallies by epidemiological week, participating adults ≥ 70 years of age, British Columbia, Canada, weeks 14–17. Abbreviation: SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Table 1. Participant Characteristics by Case and Control Status, Adults ≥ 70 Years of Age, British Columbia, Canada, Weeks 14–17

			Distribution by Case Status				
	Overall		Cases		Controls[a]		
Characteristic	n	%	n	%	n	%	*P* value[b]
Overall ≥ 70 years N (%)	16 993	NA	1226	7.2	15 767	92.8	NA
Age group (years)							
70–79	10 460	61.6	913	74.5	9547	60.6	<.001
80–89	5184	30.5	271	22.1	4913	31.2	
≥90	1349	7.9	42	3.4	1307	8.3	
Median age (range)	77	70–>100	75	70–>100	77	70–>100	<.001
Sex							
Male	8336	49.1	614	50.1	7722	49.0	.46
Female	8657	50.9	612	49.9	8045	51.0	
Epidemiological week							
14	4295	25.3	368	30.0	3927	24.9	<.001
15	4474	26.3	349	28.5	4125	26.2	
16	4064	23.9	290	23.7	3774	23.9	
17	4160	24.5	219	17.9	3941	25.0	
Health authority (HA)[c]							
Fraser (FHA)	6777	39.9	431	35.2	6346	40.2	<.001
Interior (IHA)	3009	17.7	102	8.3	2907	18.4	
Northern (NHA)	334	2.0	33	2.7	301	1.9	
Vancouver Coastal (VCHA)	5007	29.5	590	48.1	4417	28.0	
Vancouver Island (VIHA)	1866	11.0	70	5.7	1796	11.4	

Abbreviation: NA, not applicable.

[a]As per approach 1 for control selection: includes all test-negative specimens collected from individuals before the end of the analysis period or becoming a test-positive case.

[b]*P* value compares distribution by characteristic and case status.

[c]British Columbia has 5 health authorities (HA) that administer health services and surveillance monitoring. Most of the general population ≥ 70 years old in British Columbia reside within Fraser HA (FHA: 32%) and Vancouver Coastal HA (VCHA: 22%). About one-fifth reside in Interior (IHA: 20%) and Vancouver Island (VIHA: 22%) HAs, with the remainder in Northern HA (NHA: 5%).

beyond that period. Most (85%) vaccinated individuals had received the Pfizer-BioNTech product.

VE Estimates

VE estimates did not vary meaningfully by the approach used to select test-negative controls and we therefore present VE based on all-specimen inclusion (approach 1) (Supplementary Table 2). VE findings are illustrated in Figure 2 with details in Supplementary Tables 2–8.

VE was negligible at 14% (95% CI 0–26) during the period 0–13 days postvaccination but increased by 1 week interval thereafter from 43% (95% CI 30–53) at 14–20 days to 75% (95% CI 63–83) at 35–41 days postvaccination (Figure 2). VE is also displayed for ≥ 42 days but warrants cautious interpretation given that a minority of vaccinated participants belonged within that extended interval. Summary VE at ≥ 21 days was 65% (95% CI 58–71) and was similar (within 10% absolute) in participant subgroup analyses, differing by 10% in women (70%; 95% CI 61–76) versus men (60%; 95% CI 48–70) (Figure 2; Supplementary Tables 2–6).

At ≥ 21 days since vaccination, a single dose of mRNA vaccine was also significantly protective in variant-specific analyses, with VE of 72% (95% CI 58–81), 67% (95% CI 57–75), and 61% (95% CI 45–72) for non-VOC, Alpha, and Gamma variants, respectively (Figure 2; Supplementary Table 7). VE did not meaningfully differ in sensitivity analyses defining Gamma variants by whole genome sequencing alone or inclusive of additional viruses classified presumptively by screening assay (Supplementary Tables 7–8).

DISCUSSION

We report substantial protection provided by a single dose of mRNA vaccine against SARS-CoV-2 infection in adults ≥ 70 years old. VE increased when longer intervals were used to define vaccine status, becoming statistically significant at approximately 40% after a 2-week lag, 60% after 3-week, 70% after 4-week, and 75% after 5-week interval between vaccination and specimen collection. Although delayed immunological response in the elderly may be hypothesized to explain this prolonged timeline to protection [11], a methodological explanation also exists, namely, misclassification of cases as vaccine-preventable at too-short intervals when based upon specimen collection rather than onset date. We underscore the need for studies to extend the interval used to define vaccine status when outcomes are timed on events such as specimen collection or testing that occur later or with more variability

Table 2. Participant Characteristics by Vaccine Status, Adults ≥ 70 Years of Age, British Columbia, Canada, Weeks 14–17

	Number of Participants			Number and Percent Vaccinated by Characteristic and Case Status[a]						
Characteristic	Overall	Cases	Controls[b]	Overall (n, %)		*P* value[c]	Cases (n, %)		Controls[b] (n, %)	
Overall ≥ 70 years	16 993	1226	15 767	12 451	73.3	NA	751	61.3	11 700	74.2
Age group (years) (row percentages displayed)										
70–79	10 460	913	9547	7073	67.6	<.001	529	57.9	6544	68.5
80–89	5184	271	4913	4279	82.5		191	70.5	4088	83.2
≥90	1349	42	1307	1099	81.5		31	73.8	1068	81.7
Median age	77	75	77	78	70–>100	>.05	76	70-99	78	70–>100
Sex										
Male	8336	614	7722	6095	73.1	.02	386	62.9	5709	73.9
Female	8657	612	8045	6356	73.4		365	59.6	5991	74.5
Epidemiological week of specimen collection (row percentages displayed)										
14	4295	368	3927	2532	59.0	<.001	180	48.9	2352	59.9
15	4474	349	4125	3172	70.9		210	60.2	2962	71.8
16	4064	290	3774	3303	81.3		208	71.7	3095	82.0
17	4160	219	3941	3444	82.8		153	69.9	3291	83.5
Health authority (HA) (row percentages displayed)										
Fraser (FHA)	6777	431	6346	5119	75.5	<.001	242	56.1	4877	76.9
Interior (IHA)	3009	102	2907	2072	68.9		56	54.9	2016	69.3
Northern (NHA)	334	33	301	222	66.5		20	60.6	202	67.1
Vancouver Coastal (VCHA)	5007	590	4417	3791	75.7		397	67.3	3394	76.8
Vancouver Island (VIHA)	1866	70	1796	1247	66.8		36	51.4	1211	67.4
Vaccine product (column percentages displayed)										
Pfizer BioNTech	NA	NA	NA	10 569	84.9	NA	646	86.0	9923	84.8
Moderna				1882	15.1		105	14.0	1777	15.2
Days since vaccination (DSV)[d] (column percentages displayed)										
0–13	NA	NA	NA	3432	27.6	NA	345	45.9	3087	26.4
14–20				2464	19.8		163	21.7	2301	19.7
21–27				2302	18.5		110	14.6	2192	18.7
28–34				1851	14.9		61	8.1	1790	15.3
35–41				1210	9.7		30	4.0	1180	10.1
42—99				1192	9.6		42	5.6	915	9.8
Median DSV (range)	NA	NA	NA	21	0-99	NA	14	0-82	22	0–99

Abbreviation: NA, not applicable.

[a]Single-dose recipients only without regard to interval between vaccination and specimen collection. Includes mRNA vaccine receipt only; viral vector vaccine recipients excluded.

[b]As per approach 1 for control selection: includes all test-negative specimens.

[c]*P* value compares percentage vaccinated by characteristic.

[d]Interval between first dose of vaccine and specimen collection date.

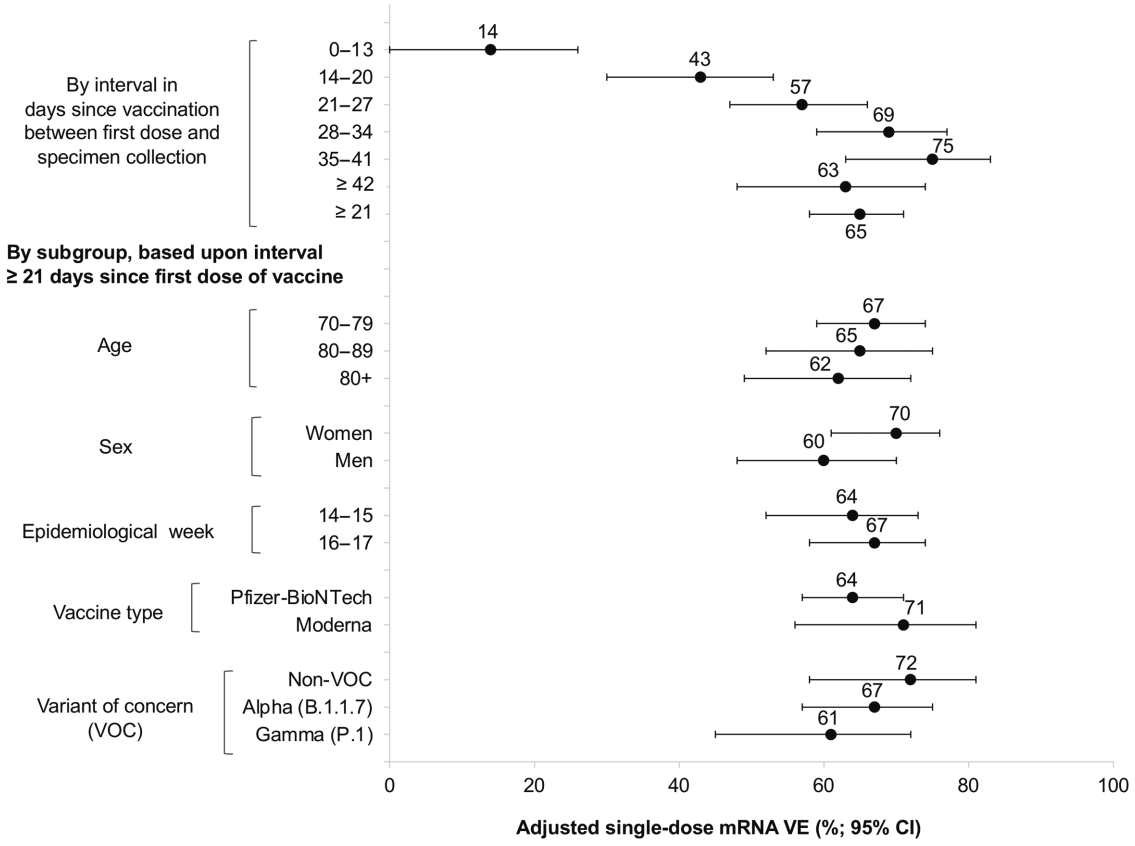

Figure 2. Adjusted VE estimates by interval in days since vaccination and restricted by subgroup, adults ≥ 70 years of age, British Columbia, Canada, weeks 14–17. All vaccine effectiveness estimates are adjusted for age group (70–79, 80–89, 90+ years); sex (men, women); epidemiological week (14, 15, 16, or 17); and health authority (HA) (Fraser HA, Interior HA, Northern HA, Vancouver Coastal HA, Vancouver Island HA). See Supplementary Tables 2–8 for details. VE estimates that are based upon a ≥ 21-day interval between vaccination and specimen collection combine specimens collected 21 or more days since vaccination. Similarly, VE estimates based on a ≥ 42-day interval combine specimens collected 42 or more days since vaccination. Abbreviations: CI, confidence interval; mRNA, messenger RNA; VE, vaccine effectiveness.

than the typical 2-week interval from vaccination to onset date used in clinical trials. Our primary VE estimate of 65% based on RT-PCR detection of infection at ≥ 3 weeks between vaccination and specimen collection may also be an under-estimate. Our findings suggest, however, that a single dose of mRNA vaccine prevented about 2 out of 3 SARS-CoV-2 infections in older adults. Such protection is particularly meaningful considering that it was provided during a period of peak pandemic risk, when VOCs were predominantly contributing to the epidemic in British Columbia.

Our VE estimates were robust in sensitivity and subgroup analyses, varying only by about 10% (absolute) based on sex (10% lower in men) and VOC (11% lower for Gamma vs non-VOC). With overlapping confidence intervals, these comparisons are not definitive but signal the need for further evaluation, notably in younger adults among whom sex differences may be more biologically-mediated [12], and VOC circulation may be more prominent [8]. In British Columbia, where Alpha and Gamma variants have uniquely codominated during a substantial spring wave [8], the finding of their comparable VE in older adults is important. This observation aligns well with immunogenicity findings elsewhere reporting comparable reductions in infection- and vaccine-induced neutralizing antibody for Alpha and Gamma variants [13]. Whereas more severe reductions in immunity or effectiveness have been reported for other VOC such as Beta or Delta [13-15], we had too few detections for their separate VE analysis here. Despite some shared substitutions such as E484K between Gamma and Beta variants, they may not be equal in their potential for vaccine escape. To better correlate molecular markers with immunological and epidemiological measures of vaccine protection, and to inform the need for vaccine update, VE analyses should be stratified as finely as possible by genetic sub-cluster.

Our findings may be compared to other similar studies in older adults although underlying differences (methods, populations, vaccine status and outcome definitions, mix of circulating viruses, etc.) need to be taken into account. Using the TND to assess VE among adults ≥ 70 years in England (but including care-home residents), Bernal et al reported single-dose mRNA VE against symptomatic SARS-CoV-2 infection reaching 61% (95% CI 51–69) by 28–34 days [16], similar to our estimate of 69% (95% CI 59–77) by the same interval.

In a matched case-control study of adults 80–83 years old in England (excluding care-home residents), Mason et al report (in pre-print) mRNA VE against SARS-CoV-2 infection of 55% (95% CI 41–67) by 21–27 days after the first dose [17], also similar to our estimate among adults 80–89 years old of 54% (95% CI 32–70) at that interval. In a recent preprint also from Canada, Chung et al use the TND to assess mRNA VE against symptomatic infection for the population of Ontario with primary analysis based on an interval of ≥ 14 days between vaccination and specimen collection [18]. In subanalysis of adults ≥ 70 years (excluding care-home residents), authors report VE of 40% (95% CI 29–49), which is lower than our estimate of 58% (95% CI 50–64) at ≥ 14 days (not displayed) or our primary analysis of 65% (95% CI 58–71) at ≥ 21 days. Using an interval of 21–27 days and 28–34 days, however, Chung et al report VE of 40% (95% CI 21–54) and 64% (95% CI 46–76), respectively, the latter being more compatible with other estimates above. Of note, the Ontario analysis spanned mid-December to mid-April but as in the province of British Columbia most of their participants, including those ≥ 70 years old, would not have been vaccine-eligible until the tail end of their analysis period, notwithstanding earlier case and control contribution.

Given both time-varying vaccine coverage and disease risk, adjustment for confounding by calendar-time is critical in observational study designs. To address that concern, we restricted our analysis to a narrow window (weeks 14–17) when vaccine coverage and community risk were both high and relatively stable, further adjusting by epidemiological week to address variation. We also explored several approaches for selecting test-negative controls with similar results, likely also reflecting the narrow analysis period we chose. The main limitation of our analysis, as elsewhere, is our reliance on general laboratory submissions and clinical or surveillance data that were originally collected for a different purpose and are subject to missing information and misclassification, as well as selection bias. Although foremost symptom-based, the clinical testing indications for COVID-19 are broad, discretionary and variable. To attempt standardization of the likelihood of test-positivity among sampled specimens we excluded those identified as having been collected from congregate settings (long-term care, assisted or independent living facilities) or for nonclinical screening purposes. Such exclusions, however, may have been incomplete or introduced other unintended biases. We were limited in the covariates we could include in our model and cannot rule out residual bias and confounding. The test-negative design partially, but not fully, standardizes for healthcare seeking behaviors, although other variations in behavior associated with both vaccination and exposure risk could still play a role. As a form of validity check, we assessed VE during the 0–13-day period when little or no vaccine effect is anticipated, confirming negligible VE as expected. For similar reasons, we compared vaccine coverage and other characteristics of our test-negative controls to that of the general source population ≥ 70 years old in British Columbia, and this was reassuringly concordant. Our findings also align well with other observational studies in older adults each of which are, however, subject to similar issues. Because the PLOVER database from which we sampled does not reliably capture symptoms or onset dates, we assessed VE against any infection without symptom or severity specification. VE estimates against more severe outcomes are anticipated to be higher than we report for infection per se [16–18]. Finally, we were limited in our ability to assess VE over the long-term, to compare younger age groups prioritized later for vaccination, or to assess other VOCs such as the Delta variant; however, those analyses are underway.

In conclusion, a single dose of mRNA vaccine reduced the risk of SARS-CoV-2 infection by about two-thirds in community-dwelling adults ≥ 70 years old. Such protection is particularly important because it was observed during a period of peak pandemic risk when VOCs, predominantly Alpha and Gamma variants, together comprised at least 70% of characterized viruses. Substantial single-dose protection in older adults reinforces the option to defer second doses when vaccine supply is scarce and broader first-dose coverage is rapidly needed. Such strategy, however, warrants further evaluation to assess duration of protection over a longer period and against additional VOC.

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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