

Vaccine Effectiveness of 3 Versus 2 Doses of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) mRNA Vaccines in a High-Risk National Population

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Background. Knowledge of the vaccine effectiveness (VE) of a third or booster vaccine dose in preventing SARS-CoV-2 infection or its consequences is critical in developing recommendations for their use. We determined relative VE of 3 vs 2 doses of an mRNA vaccine in preventing symptomatic SARS-CoV-2 infection, hospitalization, and severe/critical disease.

Methods. Among veterans who had received 2 doses of an mRNA vaccine by 30 April 2021, we identified those who received a third dose of the same vaccine between 22 September and 24 November 2021 and 1:1 matched controls who had not received their third dose by then. Using Cox proportional hazards model, we calculated adjusted hazards ratios for symptomatic infection, hospitalization, and intensive care unit (ICU) admission or death after SARS-CoV-2-positive test.

Results. Among 2 321 366 veterans who received 2 doses of Pfizer BNT-162b2 or Moderna mRNA-1273 vaccine by 30 April 2021, we matched 395 686 persons who received a third dose of the same vaccine between 22 September and 24 November 2021 to controls who did not receive a third dose. Adjusted HRs (95% CI) were .15 (.11–.21) for symptomatic infection and .18 (.13–.26) for hospitalizations for 3 vs 2 doses, corresponding to relative VE of 85% and 82%. Five ICU admissions or deaths were observed (4 among recipients of 2 doses). There was no difference in VE between BNT162b2 versus mRNA-1273 recipients.

Conclusions. A third dose of a SARS-CoV-2 mRNA vaccine is associated with high VE against symptomatic infection, hospitalization, and critical disease in the pre-Omicron era.

Keywords. SARS-CoV-2; booster vaccination; vaccine effectiveness; Veterans; mRNA vaccines.

Several vaccines against the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection are now available and are highly effective in preventing asymptomatic and symptomatic infection; moderate, severe, or critical disease; and death [1–6]. However, vaccine effectiveness (VE) wanes over time, particularly against asymptomatic infection [7, 8]. Persons who receive a third dose of the vaccine 5 or more months after the second dose have a lower risk of infection and infection-related outcomes compared with those who receive only 2 doses [9–11]. Vaccine effectiveness of a booster dose has been studied primarily in Israel, where the third dose was authorized before other countries. These studies often lack data on key comorbidities and represent a population that is demographically different from the population in the United States. In a just published report from the United States, the adjusted

odds ratio for 3 vaccine doses of an mRNA vaccine versus 2 doses was 0.16 for the Delta variant for symptomatic infection, corresponding to an 84% VE in preventing symptomatic infection [12].

Veterans enrolled in the Department of Veterans Affairs Healthcare System (VA) in the United States represent a high-risk national population due to older age and a high burden of comorbidities compared with the national population [13, 14]. Despite these differences, VE among veterans who received 2 doses of an mRNA vaccine remains high [5, 15]. We sought to determine the effectiveness of a third dose of the same mRNA vaccine 5 or more months after the second dose in preventing documented infection, moderate disease, or severe/critical disease in the national VA population.

METHODS

Study Population and Participants

The data sources used for this study have been previously described [5, 14]. Briefly, we used the VA COVID-19 Shared Data Resource for the current study, which was created by the VA in response to the SARS-CoV-2/coronavirus disease 2019 (COVID-19) pandemic and contains information on all

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veterans with a confirmed laboratory diagnosis of SARS-CoV-2 infection within the VA and those who tested outside the VA with a VA clinical note confirming the diagnosis. Updated regularly, the VA COVID-19 Shared Data Resource contains extensive demographic, clinical, pharmacologic, laboratory, vital signs, and clinical outcomes information, which is derived from multiple validated sources including the Corporate Data Warehouse and the VA electronic medical records.

For the current study, we identified veterans in the VA COVID-19 Shared Data Resource who had received 2 doses of an mRNA vaccine (either BNT162b2 [Pfizer] or mRNA-1273 [Moderna]) by 30 April 2021 and had at least 2 primary care appointments in the preceding 18 months of vaccine rollout, because these individuals are more likely to receive care through the VA. We excluded those who had died, had a positive nasopharyngeal swab polymerase chain reaction (PCR) result for SARS-CoV-2, or received a third dose of the vaccine before 22 September 2021, the date of US Food and Drug Administration (FDA) approval of boosters. The 22 September 2021 date also provided at least a 4.5-month interval between the second and the third dose for those who received the third dose. We also excluded those persons who received a different vaccine for the second dose. For each person thus identified, we identified cases who received a third dose of the same vaccine between 22 September 2021 and 24 November 2021 and matched them 1:1 without replacement on the date 14 days following their third dose to a control who had not yet received their third dose on or before that date (defined as the time of matching). Both members of a pair were considered to be at risk until the event of interest or one of the following censoring events occurred: the control received the third dose, death, or the end of the study period. Upon one of these events, both members of a pair were removed from the risk set. Controls were also matched on the following factors: age (10-year blocks), sex, race (as White, Black or other race), Charlson comorbidity index (as Charlson score ≤ 2 vs > 2), vaccine type, calendar week of second vaccine dose, and geographic site of second vaccine dose administration. The Charlson comorbidity index is a validated and widely used score that identifies persons at the highest risk for mortality over a period of time based on the presence and severity of comorbidities [16, 17]. For vaccination site, we used the VA facility where the second dose of the vaccine was administered to account for geographic variation in vaccination, testing patterns, and regional differences in community transmission. Data retrieved included demographic characteristics, clinical diagnoses, presence of symptoms at presentation, anthropometric measurements, and select laboratory results. Comorbidities were defined according to the definitions used in the VA Corporate Data Warehouse, which uses the *International Classification of Diseases* (Ninth or Tenth Revision, as appropriate) for classifying comorbidities [18–20]. These definitions have been used in numerous previous publications related to

SARS-CoV-2 infection [5, 18–24]. Baseline diagnoses included all diagnoses recorded in the 2 years before the index date.

Outcomes

We assessed 3 outcomes from 22 September 2021 to 24 November 2021: symptomatic infection (defined as the presence of symptoms consistent with flulike illness and a PCR-positive swab), hospitalization with COVID-19, and intensive care unit (ICU) admission or fatal case of COVID-19 (the subset of those hospitalized and required admission to the ICU or died within 28 days of SARS-COV-2–positive test results).

Statistical Analyses

Using an unadjusted Poisson regression accounting for follow-up time, we estimated the incidence rate/10 000 person-weeks by various baseline characteristics among those with and without the third vaccine dose. Adjusted hazard ratios (HR_{adj}) comparing 3 doses with 2 doses for each outcome (and 95% confidence intervals [CIs]) were estimated using Cox proportional hazards models adjusted for all variables used for matching except for the time of matching. Vaccine effectiveness was calculated as $1 - HR_{adj}$. Where P values were used to compare variables, a 2-sided P value of less than .05 was considered statistically significant.

We used Kaplan-Meier curves to demonstrate the probability of remaining event-free for each group. Test of equality among strata was determined by using log-rank P values, with a $P < .05$ considered statistically significant.

Ethical Approval

The study was approved by the Institutional Review Board at VA Pittsburgh Healthcare System with a waiver of informed consent requirement.

RESULTS

We identified a total of 2 321 366 persons who had received 2 doses of either the BNT162b2 or the mRNA-1273 vaccine by 30 April 2021, had at least 2 primary care appointments at the VA, and had not previously tested positive. Of these, we excluded 125 611 total persons who had a documented infection (19 704), died (33 962), or had received a third dose of a vaccine (91 903) between 20 April 2021 and 22 September 2021. Of the remaining 2 195 755, we also excluded 30 648 for receiving a heterologous booster during our study period, leaving 2 165 107 as our final cohort prior to matching. Among the persons thus identified, we matched 395 686 persons who received a third dose of the same vaccine between 22 September and 24 November 2021 and 1:1 matched controls who did not receive a third dose of the vaccine (Figure 1).

The median age for both groups was 73 years (interquartile range [IQR], 66–77 years), 94% were male, 72% were White, and 19% were Black (Table 1). The median Charlson

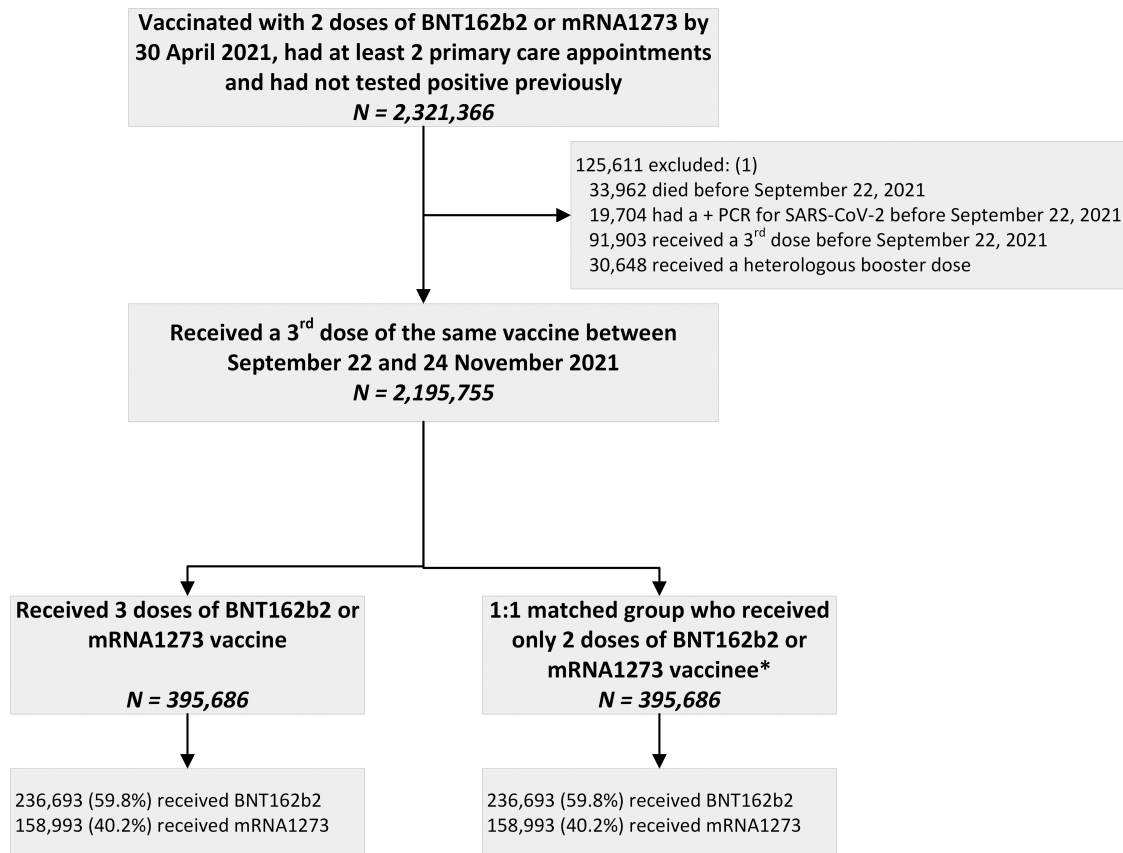


Figure 1. Study flow sheet. (1) The sum of the excluded conditions does not add up to this number since some excluded individuals had more than 1 exclusion criteria. (2) 1:1 matched group without a third dose (matched on age [10-year blocks], sex, race, BMI, Charlson comorbidity index, vaccine type for doses 1 and 2, calendar week of second vaccine dose, VA station of second dose of vaccine). Abbreviations: BMI, body mass index; PCR, polymerase chain reaction; SARS-Cov-2, severe acute respiratory syndrome coronavirus 2; VA, Department of Veterans Affairs Healthcare System.

comorbidity index was 1 (IQR, 0–3). The BNT162b2 vaccine was administered to 236 693 (60%) and the mRNA-1273 vaccine was administered to 158 993 (40%) in each group. Persons administered the BNT162b2 vaccine were followed for a total of approximately 807 248 person-weeks, while those administered mRNA-1273 were followed for a total of 241 658 person-weeks

Table 1. Baseline Characteristics of Persons Who Received 3 and 2 Doses of an mRNA Vaccine

Characteristics	3 Doses (n = 395 686)	2 Doses (n = 395 686)
Age, median (IQR), y	73 (66,77)	73 (67,77)
Male sex, n (%)	373 840 (94%)	373 840 (94%)
Race, n (%)		
White	284 789 (72%)	284 789 (72%)
Black	76 526 (19%)	76 526 (19%)
Other	34 371 (8.7%)	34 371 (8.7%)
Charlson comorbidity index, median (IQR)	1 (0–3)	1 (0–3)
Vaccination type, n (%)		
BNT-162b2	236 693 (60%)	236 693 (60%)
mRNA1273	158 993 (40%)	158 993 (40%)

Abbreviation: IQR, interquartile range.

(Table 2). Incidence rate point estimates for symptomatic infection and hospitalization per 10 000 person-weeks were consistently lower for individuals receiving 3 doses compared with those who received only 2 doses. Only 5 individuals experienced ICU admission or death; all 5 had received the BNT162b2 vaccine and 4 had received only 2 doses. Further analyses on ICU admission or death outcomes are not reported due to low incidence. The VE (95% CI) regardless of vaccination type was .85 (.79–.89) for symptomatic infection and .82 (.77–.87) for hospitalizations (Table 2). The number of events, incidence rate per 1000 person-days, and the VEs for BNT162b2 and mRNA-1273 vaccines are also provided in Table 2.

Incidence rates per 10 000 person-weeks and the hazard ratios for those with 3 versus 2 doses by age, race, and Charlson comorbidity index subgroups are also provided in Table 2. Vaccine effectiveness for recipients of 3 doses compared with those who received only 2 doses remained consistently high among various strata of age, race, and Charlson comorbidity index (Table 2).

Kaplan-Meier curves demonstrated that the probability of remaining free of symptomatic infection and hospitalization

Table 2. Estimated Comparative Effectiveness of the Third Dose of BNT162b2 and mRNA-1273 Vaccines

	Total Person Weeks of Follow Up ^a	Number of events		Incidence rate per 10,000 person weeks (95% CI) ^b		Hazard Ratio (95% CI) ^b	VE 3 vs. 2 Doses
		3 Doses	2 Doses	3 Doses	2 Doses		VE % (95% CI)
All persons							
Symptomatic infection	1 048 907	85	443	.81 (.66,1)	4.22 (3.85,4.64)	.15 (.11,.21)	85 (79,89)
Hospitalization	1 048 907	23	101	.22 (.15,.33)	.96 (.79,1.17)	.18 (.13,.26)	82 (77,87)
BNT162b2							
Symptomatic infection	807 248.3	68	338	.84 (.66,1.07)	4.19 (3.76,4.66)	.16 (.12,.22)	84 (78,88)
Hospitalization	807 248.3	21	74	.26 (.17,.4)	.92 (.73,1.15)	.23 (.15,.35)	77 (65,85)
mRNA1273							
Symptomatic infection	241 658.3	17	105	.70 (.44,1.13)	4.34 (3.59,5.26)	.13 (.1,.17)	87 (83,90)
Hospitalization	241 658.3	2	27	.08 (.02,.33)	1.12 (.77,1.63)	.06 (.05,.07)	94 (93,95)
By subgroups							
Age <70 years							
Symptomatic infection	335 269.6	25	152	.75 (.51,1.11)	4.53 (3.87,5.31)	.14 (.11,.18)	86 (82,89)
Hospitalization	335 269.6	5	17	.15 (.06,.36)	.51 (.32,.82)	.25 (.15,.41)	75 (59,85)
Age ≥70 years							
Symptomatic infection	713 637	60	291	.84 (.65,1.08)	4.08 (3.64,4.57)	.16 (0.12,0.22)	84 (78,88)
Hospitalization	713 637	18	84	.25 (.16,.40)	1.18 (.95,1.46)	.17 (0.12,0.23)	83 (77,88)
Race White							
Symptomatic infection	753 132.6	62	349	.82 (.64,1.06)	4.63 (4.17,5.15)	.14 (.11,.19)	86 (81,89)
Hospitalization	753 132.6	14	78	.19 (.11,.31)	1.04 (.83,1.29)	.14 (.11,.18)	86 (82,89)
Race Black							
Symptomatic infection	204 840.6	15	65	.73 (.44,1.21)	3.17 (2.49,4.05)	.20 (.13,.29)	80 (71,87)
Hospitalization	204 840.6	6	19	.29 (.13,.65)	0.93 (.59,1.45)	.27 (.16,.47)	73 (53,84)
Charlson comorbidity index ≤2							
Symptomatic infection	753 342.9	37	243	.49 (.36,.68)	3.23 (2.84,3.66)	.12 (.09,.15)	88 (85,91)
Hospitalization	753 342.9	8	32	.11 (.05,.21)	0.42 (.30,.60)	.19 (.13,.27)	81 (73,87)
Charlson comorbidity index >2							
Symptomatic infection	295 563.7	48	200	1.62 (1.22,2.16)	6.77 (5.89,7.77)	.20 (.14,.30)	80 (70,86)
Hospitalization	295 563.7	15	69	.51 (.31,.84)	2.33 (1.84,2.96)	.18 (.13,.25)	82 (75,87)

^aWeeks of follow up are identical between comparison groups.

^bIncidence rates estimated from Poisson regression model; hazard ratios from cox proportional hazards model.

VE, vaccine effectiveness

was significantly higher among those who received 3 doses compared with those who received only 2 doses of the vaccine (log-rank $P < .001$ for both) (Figure 2). There was no difference among recipients of BNT162b2 compared with the mRNA-1273 vaccine for documented infection (log-rank $P = .40$) or hospitalization (log-rank $P = .08$) (Figure 3).

DISCUSSION

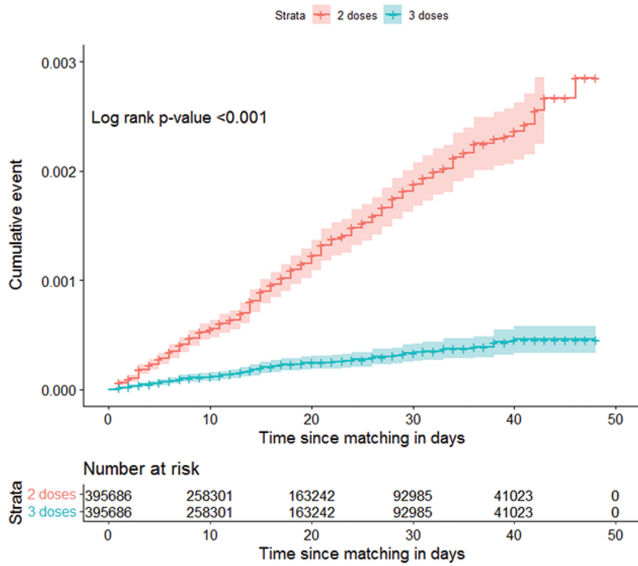
In this large national retrospective study, we demonstrate that a third dose of an mRNA vaccine is highly effective in preventing PCR-confirmed symptomatic infection, acute care hospitalization, and severe/critical disease over a short-term follow-up.

There is strong evidence that immunity wanes over time after 2 doses of an mRNA vaccine [7, 8]. In key studies, VE dropped to less than 25% against confirmed infection, and to less than 60% against severe/critical disease, after 6 months of receiving the second dose [7]. A third dose of the vaccine 5 or more months after the second dose is associated with a sharp increase in the antibody levels and reduced risk of

symptomatic and severe infection and mortality [10, 11, 25]. Previous VE studies of a third dose of the vaccine are often limited by a lack of information on comorbidities, or are in a demographically different population than the United States. We found that the overall VE was 85% against documented infection, and 82% against moderate disease (hospitalization). There were no severe/critical disease events among those who received 3 doses. Our study provides robust estimates of incidence and effectiveness in a large national population at a particularly high risk of infection and adverse outcomes after infection. Our study groups are also well matched demographically and clinically to provide assurance regarding the results.

Among population subgroups, we found the VE against symptomatic infection to be consistently above 80% among those younger or older than 70 years, among Whites and Blacks, among those with a body mass index of less or more than 30 kg/m², and among those with a Charlson comorbidity index score of less or more than 2. Infection among older persons, those with higher a body mass index, and those with a higher burden of comorbidities

Panel A: symptomatic infection, 2 vs. 3 doses



Panel B: hospitalization, 2 vs. 3 doses

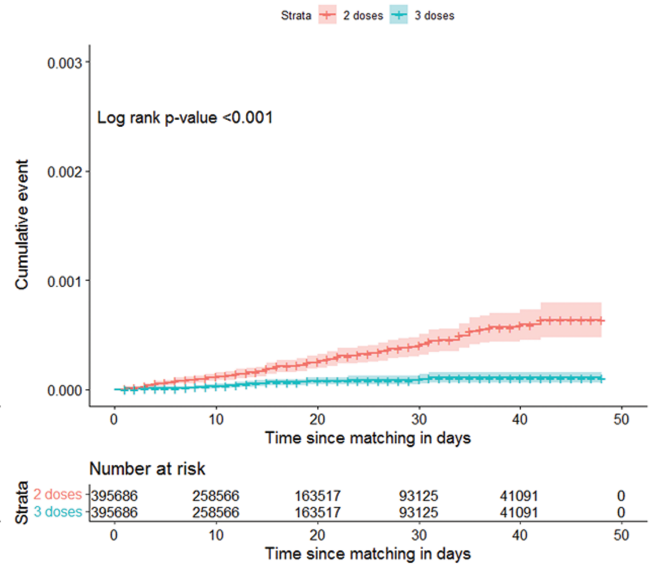


Figure 2. Kaplan-Meier curves demonstrating the probability of remaining event-free over time among recipients of 3 or 2 doses of an mRNA vaccine, for symptomatic infection (A, left) and hospitalization (B, right) outcomes. There were no COVID-19–related ICU or death events among recipients of 3 doses. Abbreviations: COVID-19, coronavirus disease 2019; ICU, intensive care unit.

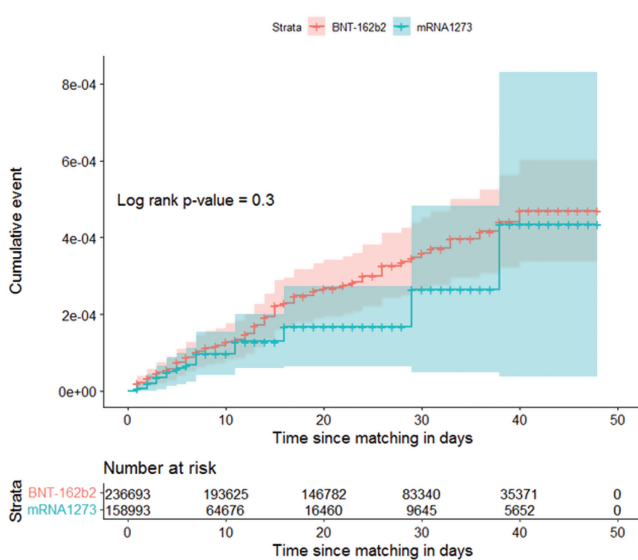
has been associated with poor clinical outcomes [22, 26]. Our study provides assurance regarding the effectiveness of a third dose in preventing infection among these high-risk strata.

Several previous studies have suggested higher VE with the mRNA-1273 vaccine compared with the BNT162b2 vaccine [15, 27]. Various reasons have been suggested for these differences, including difference in dose and interval between the first and

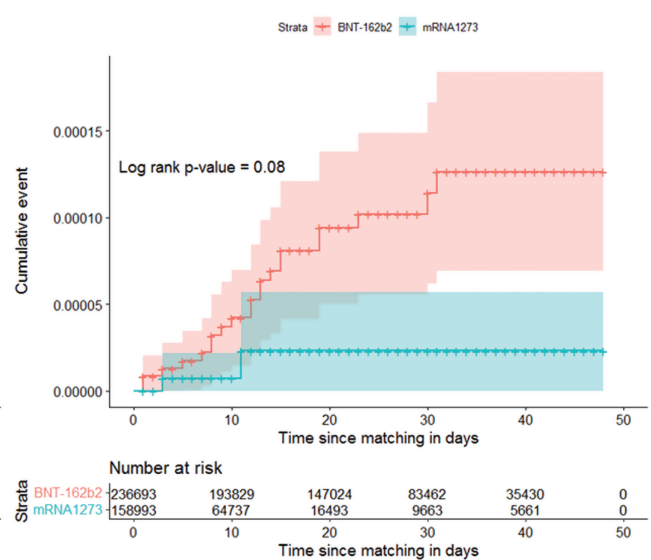
second dose of the vaccine. Whether inherent differences between the 2 types of vaccines play any part is not known. In our study, we did not find any difference in VE against symptomatic infection or hospitalization between the 2 vaccines.

The strengths of our study include a large national population with validated data extracted over the duration of the pandemic. We used established methods to construct the cohort and the

Panel A: symptomatic infection, BNT162b2 vs. mRNA1273



Panel B: hospitalization, BNT162b2 vs. mRNA1273



Note: There were no COVID-related ICU or death events among recipients of three doses.

Figure 3. Kaplan-Meier curves demonstrating the probability of remaining event-free over time among recipients of 3 doses of BNT162b2 or mRNA-1273 vaccines, for symptomatic infection (A, left) and hospitalization (B, right) outcomes. There were no COVID-19–related ICU or death events among recipients of 3 doses. Abbreviations: COVID-19, coronavirus disease 2019; ICU, intensive care unit.

comparison groups, and to determine the risk of outcome events. Several limitations also need to be noted when interpreting our data. We retrospectively analyzed existing data, with the associated limitations inherent in such analyses. The most notable limitation is the lack of information on VE against the Omicron variant, which was not in circulation during the study period. The overwhelming variant during the study period was the Delta variant [28]. We accounted for the geographic and temporal variations in testing and immunization pattern by matching the groups for testing facility and time of vaccination. Finally, the follow-up time after the third dose was short and longer-term effectiveness of a third dose needs to be determined in longer-term studies.

In conclusion, a third dose of an mRNA vaccine is highly effective in preventing symptomatic infection as well as acute care hospitalizations in the short term compared with a 2-dose regimen. Whether the effectiveness of a 3-dose regimen will be long-lasting and the effect of the introduction of the Omicron variant in this high-risk population need further study.

Notes

Author Contributions. Study concept and study design and drafting of the manuscript: A. A. B. Data acquisition: F. B. M. and P. Y. Data analysis: V. B. T., F. B. M., P. Y., and A. A. B. Critical revision of the manuscript for important intellectual content and final approval of the article: All authors. A. A. B. and F. B. M. had complete access to data at all times and accept the responsibility of the integrity of this article.

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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.

Data availability. This study used data created and maintained by the Veterans Health Administration, Department of Veterans Affairs. These data are freely available to approved individuals upon fulfilling the specified requirements.

Role of sponsors and affiliate institutions.

- Design and conduct of the study: None
- Collection, management, analysis, and interpretation of the data: Data used in this study were obtained from the Department of Veterans Affairs COVID-19 Shared Data Resource, which had no role in study design, analysis, interpretation, or publication of the results.
- Preparation, review, or approval of the manuscript: None
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