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Effectiveness of mRNA COVID-19 Vaccines against Omicron and Delta Variants among US Veterans

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Summary box:

- Early reports show lower estimated vaccine effectiveness (VE) against Omicron infection for both 2-doses and 3-doses of COVID-19 vaccines. We estimated the VE against infection, hospitalization and death among US Veterans for either 2-doses or 3-doses of mRNA vaccines during periods of Omicron and Delta variant dominance.
- We found the mRNA vaccine boosters provided a level of protection against Omicron like that of 2-dose against Delta, with VE at 64%, 89%, and 94% against infection, hospitalization, and death, respectively.

Abstract (words: 300)

Objectives: To estimate effectiveness of mRNA booster doses against 2-dose vaccinations during periods of Delta and Omicron dominance.

Design: We conducted a matched test-negative case-control study to estimate VE of three and two doses of mRNA vaccines against infection (regardless of symptoms). We then conducted a matched case-control study to estimate VE against COVID-19-related hospitalization and death, where controls were selected from the tested population (positive or negative).

Setting: Veterans Health Administration (VHA)

Participants: Electronic health record data from 114640 Veterans who had a SARS-CoV-2 test during November 2021-January 2022 were utilized. Patients were largely 65 years or older (52%), male (88%), and non-Hispanic white (59%).

Main outcome measures: First positive result for a SARS-CoV-2 polymerase chain reaction (PCR) or antigen test.

Results: Against infection, booster doses had higher VE - 64% (95% confidence interval [CI], 63 to 65) - than 2-dose VE (12%; 95% CI, 10 to 15) during the Omicron period. For the Delta period, estimated VE against infection was 90% (95% CI, 88 to 92) among boosted vaccinees, and was higher than VE among 2-dose vaccinees [54% (95% CI, 50 to 57)]. Against hospitalization, booster dose VE was 89% (95% CI, 88 to 91) during Omicron and 94% (95% CI, 90 to 96) during Delta; the 2-dose VE was 63% (95% CI, 58 to 67) during Omicron and 75% (95% CI, 69 to 80) during Delta. Against death, estimated VE with a booster dose was 94% (95% CI, 90 to 96) during Omicron and 96% (95% CI, 87 to 99) during Delta, while the 2-dose VE was 77% (95% CI, 67 to 83) during Omicron and 92% (95% CI, 83 to 96) during Delta.

Conclusions: A mRNA vaccine booster is more effective against infection, hospitalization, and death than 2-dose vaccination among an older male population with comorbidities.

INTRODUCTION

We previously reported[1,2] the effectiveness of COVID-19 mRNA vaccines against infection, hospitalization, and mortality among Veterans Health Administration (VHA)-enrolled Veterans through September 2021, when the major circulating variants in the United States included Alpha, Beta, and Delta. We found estimated vaccine effectiveness to remain high in the first three months after vaccination and to decrease significantly after 5 months.[2] With the rise of the Omicron variant in December 2021-January 2022, we updated our estimates of vaccine effectiveness (VE) to measure continued effectiveness of both mRNA vaccines in a population including the entire U.S. and included the booster (3-dose) vaccination.

Starting in September 2021, the Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices recommended a booster dose of COVID-19 vaccines to help increase protection against SARS-CoV-2.[5,6,7,8,9] As of early March 2022, the VHA had over 4 million fully vaccinated Veterans (2-dose of mRNA or 1-dose of Johnson & Johnson's Janssen COVID-19 vaccine) and over 1.6 million Veterans had received an mRNA booster.[10] As of March 2022, the VHA reported more than 613,000 COVID-19 cases and 21,309 confirmed deaths.[10]

Early reports[11,12,13,15] showed lower VEs against infection for the fully vaccinated (2-dose series) and even for those who received a booster (3-dose) during the Omicron period, but VE against hospitalization[14] remained high during both periods. These early reports on the Omicron variant were regional in the U.S., focused on one of the mRNA vaccines not both or were from outside the U.S. We sought to estimate VE against infection, hospitalization, and mortality for mRNA vaccines authorized in the U.S. (Pfizer-BioNTech and Moderna), for the fully vaccinated (2-dose) and those who received a booster (3-dose) of mRNA vaccines during the Delta and

Omicron dominant periods[16] in the US Veteran population, which includes individuals across the U.S. with underlying health conditions and diverse socio-economic backgrounds.

METHODS

We followed the Strengthening the Reporting of Observational Studies in Epidemiology reporting guideline.

Data Source

We used electronic medical records and COVID-19 laboratory test data from the VHA Corporate Data Warehouse (CDW) to define infection irrespective of symptoms. The VHA CDW holds electronic medical records for about 9 million U.S. Veterans who use the VHA's network of 1,293 health care facilities, including hospitals and outpatient clinics.[29] Using CDC variant tracking data[16], we presumed Omicron SARS-CoV-2 infections those tested positive during January 2022 and Delta those tested positive in November 2021. Because December 2021 represented an overlap of both variants, we excluded infections occurred during this month. As Medicare claims were available only up to August 2021, we used them to find COVID-19 diagnoses, vaccinations, and hospitalizations prior to the study period to exclude patients with prior history of COVID-19 and to augment our vaccination records. Since this population of Veterans was largely over 65 years old, we supplemented CDW data with available Medicare data as Veterans may use Medicare to provide healthcare services even if we found frequent users of VHA. We used VHA CDW records to determine date of death.

Study Design

To estimate VE against infection, we conducted a matched test negative case-control study (Table 1). The study population included Veterans ages ≥18 years residing in a US state or Washington, D.C., tested for SARS-CoV-2 by PCR (98%) or antigen (2%) testing at a VHA

facility during the study period (November 2021 (Delta predominance) or January 2022 (Omicron predominance)). We required patients to have enrolment in the VHA and at least one inpatient/outpatient encounter at a VHA facility during the 2 years before the study period and be tested within the VA at an outpatient clinic or emergency room or within one day of hospitalization. As we wanted to study a COVID-19 naïve population, we used VHA records to exclude patients with a known prior history of COVID-19, defined as a VHA diagnosis code or positive antigen/PCR lab test prior to the study period. For those with dual Medicare enrolment, we also excluded patients with any claim with a COVID-19 diagnosis code prior to the study period up until August 2021 (the latest available date for Medicare data). We excluded Johnson & Johnson's Janssen vaccinees at the date of vaccination, thus excluding their subsequent tests from the analysis. We also censored vaccinees with more than 3 doses of any vaccine at the date of their fourth vaccination. Veterans who tested positive (regardless of symptoms) were considered cases, and those who tested negative, controls. For patients with multiple tests, those negative tests within 10 days of a positive test were excluded (positive tests were kept and negative tests were excluded). We matched each case with up to 4 controls based on Health and Human Service (HHS) geographic region and SARS-CoV-2 laboratory tests within 3 weeks of the case specimen collection date as both are measures of local disease burden. Demographic characteristics of the matched population were described by reporting the frequency and proportion for categorical variables and the mean (SD) for continuous variables (Table1). Standardized mean differences[27] were used to describe differences in characteristics between cases and controls. For estimated VE against hospitalization and death, we utilized a matched case-control design. Cases were those who tested positive and were hospitalized or died within 30 days of the positive COVID-19 test. Controls were those not hospitalized or who did not die

within 30 days of their SARS-CoV-2 tests, irrespective of test results. Any patient with dual Medicare-VHA enrolment who had a claim for COVID-related hospitalization prior to the study period was already excluded, thus ineligible to be a control.

To better inform our interpretation of VE against hospitalization and mortality in the two time periods, we conducted a sub-analysis in which we assessed VE against COVID-related hospitalization and death among those already infected, restricting our hospitalization and mortality analysis to patients with a positive test. Cases were defined as before, and controls were those who were not hospitalized or who did not die within 30 days of a positive test. We also compared average length-of-stay (LOS) and rates of intensive care unit (ICU) admission among those hospitalized in the Delta and Omicron periods.

Exposure

We defined 2-dose vaccination as receipt of two doses of an mRNA COVID-19 vaccine, and booster vaccination as receipt of a third doses of an mRNA vaccine (about 95% of mRNA 3rd doses occurred approximately six months after a 2nd dose). We designated exposure to the two-dose regimen or a booster from 14 days following vaccination, excluding events in days 0-13. We designated patients as unvaccinated if they had no record of vaccination in either VHA CDW or in Medicare.

Statistical Analysis

We used conditional logistic regression to calculate odds ratios (ORs) with 95% confidence intervals (CI) for the association between positive SARS-CoV-2 testing and 2 or 3 doses of mRNA COVID-19 vaccine during Delta and Omicron periods. In the model, we included number of mRNA vaccine doses (2 or 3) as the primary explanatory variable, an indicator variable for SARS-CoV-2 presumed variant (Delta or Omicron) based on test date, and their

interaction terms. We estimated the association between SARS-CoV-2 infections and number of mRNA vaccine doses by the OR, adjusting for age (continuous), race, rurality, VHA benefits priority, and comorbid conditions (cancer, congestive heart failure, hypertension, immunocompromising conditions, obesity, and diabetes). Confounders were determined based on prior study[1,2] and known factors associated with SARS-CoV-2[28]. We also used conditional logistic regression to analyze VE against hospitalizations and death.

Severity of disease was determined by average length of stay (LOS) in days between admission date and discharge date for overall COVID-19-related hospitalizations and average LOS in an intensive care unit (ICU) during a hospitalization related to COVID-19.

All tests were two-tailed, and we chose 0.05 as the level of statistical significance. We performed data analysis using SAS 9.4 (SAS Institute, Cary, North Carolina).

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

RESULTS

Study Population

In November 2021 (Delta period) there were 4,134 positive SARS-CoV-2 tests (cases), and 170,316 negative tests (controls). After matching, 4,134 cases and 16,536 controls remained (see Table 1 for baseline characteristics and Figure 1 for attrition); 2,300 (56%) cases and 3,951 (24%) controls were unvaccinated at the time of testing. In January 2022 (Omicron period) there were 32,983 positive tests (cases) and 263,780 negative tests (controls). After matching, 32,983 cases and 126,363 controls remained. At the time of testing, 13,153 (40%) cases and 29,110

(23%) controls remained unvaccinated. During both periods, cases tended to be non-Hispanic white, have a lower CCI score and younger than controls. Patients included in this study were largely 65 years or older (94447, 52%), male (158395, 88%), and non-Hispanic white (105437, 59%).

Table 1. Baseline Characteristics of Matched Study Subjects

	Delta			Omicron		
	Case (4134)	Control (16536)	SMD^	Case (32983)	Control (126363)	SMD^
Number of mRNA vaccines, No. (%)						
0	2300 (56)	3951 (24)	68.6	13153 (40)	29110 (23)	36.9
2	1627 (39)	8035 (49)	18.7	11983 (36%)	35400 (28%)	17.9
3	141 (3)	4221 (26)	66.2	6960 (21)	58953 (47)	56.1
Vaccine manufacturer, No. (%)						
Moderna	1057 (26)	7120 (43)	37.5	9935 (30)	50921 (40)	21.4
Pfizer-BioNTech	777 (19)	5465 (33)	33.0	9890 (30)	46283 (37)	14.1
No Vaccine Recorded	2300 (56)	3951 (24)	68.6	13153 (40)	29110 (23)	36.9
Age, years, No. (%)						
18 to 44	904 (22)	114 (1)	71.0	7828 (24%)	8966 (7)	47.4
45 to 64	1417 (34)	6091 (37)	5.3	12884 (39)	47365 (37)	3.2
65 to 74	1110 (27)	6381 (39)	25.2	7738 (23)	41715 (33)	21.3
75 to 84	537 (13)	2871 (17)	12.2	3584 (11)	21345 (17)	17.5
85+	166 (4)	1079 (7)	11.2	949 (3%)	6972 (6)	13.2
Race, No. (%)						
Black	494 (12)	4636 (28)	41.1	8523 (26)	37049 (29)	7.8
Hispanic	193 (5)	601 (4)	5.2	1973 (6)	7425 (6)	0.4
White	3193 (77)	10139 (61)	35.0	20038 (61)	72067 (57)	7.6
other	254 (6)	1160 (7)	3.5	2449 (7)	9822 (8)	1.3
Sex, No. (%)						
Female	420 (10)	1656 (10)	0.5	4419 (13)	15126 (12)	4.3
Male	3714 (90)	14880 (90)	0.5	28564 (87)	111237 (88)	4.3
Quan's CCI						
Mean (SD)	0.8 (1.5)	1.6 (2.1)	44.2	0.8 (1.5)	1.3 (1.9)	31.8
Median (Q1-Q3)	0 (0-1)	1 (0-2)		0 (0-1)	1 (0-2)	

Abbreviations: Quan's CCI, Charlson comorbidity index, Quan's version[26]
See Supplemental Table 1 (Young-Xu et al.)[1] for definitions of variables in this table
^Standardized mean difference of 10 or greater was used to identify imbalance between cases and controls[27]

Vaccine Effectiveness against infection

For those with 2-dose mRNA vaccine, VE was 54% (95% CI, 50 to 57) for Delta and 12% (95% CI, 10 to 15) for Omicron. VE for those who received an mRNA vaccine booster was 90% (95% CI, 88 to 92) in the Delta period and 64% (95% CI, 63 to 65) in the Omicron period (Table 2). For the Delta period, the median time from the 2nd dose to the SARS-CoV-2 test date was 241 days (note: 6 months were suggested in the FDA guideline regarding a booster) and 35 days from the 3rd dose. As is expected this median time from 2nd dose of vaccination increased for the Omicron period to 289 days and 72 days from the 3rd dose.

Table 2. Estimated Vaccine Effectiveness Against Laboratory Confirmed SARS-CoV-2 Infection by Dose and Variant

Variant	VE (95% CI)	VE Interval (14+ days after vaccination)
Omicron	12% (10, 15)	*2nd* dose
Omicron	64% (63, 65)	3rd dose
Delta	54% (50, 57)	*2nd* dose
Delta	90% (88, 92)	3rd dose
Above numbers exclude Johnson & Johnson's Janssen vaccines as of the date of the Johnson & Johnson's Janssen vaccine. 2nd and 3rd doses are for mRNA vaccines compared to no vaccination in the indicated period beginning 14 days after vaccination. Tests occurring in 0-13 days after vaccination were excluded.		
Cases and controls were matched 1:4 on HHS region and date. The adjusted variables include the following: age (continuous), body mass index, cancer, congestive heart failure, chronic kidney disease, chronic obstructive pulmonary disease, diabetes mellitus, hypertension, immunocompromised, priority level, race/ethnicity, and rurality.		

Hospitalization and Death

VE against COVID-related hospitalization for those who received 2-dose mRNA vaccine was 75% (95% CI, 69 to 80) in the Delta period and 63% (95% CI, 58 to 67) in the Omicron period (Table 3). VE against COVID-related hospitalization for those who received an mRNA vaccine booster was 94% (95% CI, 90 to 96) in the Delta period –higher than the 2-dose VE, and 89% (95% CI, 88 to 91) in the Omicron period – (Table 3). In a sub-analysis restricted to those with a

positive COVID-19 test in the study period, we evaluated VE against progression to hospitalization among the infected only, we found that VE for booster against COVID-related hospitalization was 53% (95% CI, 12 to 75) in the Delta period – not statistically different from the 2-dose VE, and 78% (95% CI, 74 to 81) in the Omicron period – almost twice higher than the 2-dose VE (Table S1). Among Omicron-associated hospitalizations (regardless of vaccination status), the length of stay (LOS) averaged 6.5 days (95% CI, 6.2 to 6.7 days), compared to 7.2 days (95% CI, 6.6 to 7.8) among Delta-associated hospitalizations. 11.3% (95% CI, 8.8 to 13.8%) of hospitalizations during the Delta period resulted in ICU admission; in contrast, 8.3% (95% CI, 7.2 to 9.5%) of COVID-related hospitalizations during the Omicron period resulted in ICU admission (Figure 2).

Table 3. Estimated Vaccine Effectiveness Against COVID-19-related Hospitalization and Death by Dose and Variant

VE Interval (14+ days after vaccination)		VE (95% CI)
Hospitalization		
Omicron	2nd dose	63% (58, 67)
Omicron	3rd dose	89% (88, 91)
Delta	2nd dose	75% (69, 80)
Delta	3rd dose	94% (90, 96)
Death		
Omicron	2nd dose	77% (67, 83)
Omicron	3rd dose	94% (90, 96)
Delta	2nd dose	92% (83, 96)
Delta	3rd dose	96% (87, 99)
Above numbers exclude Johnson & Johnson's Janssen vaccines as of the date of the Johnson & Johnson's Janssen vaccine. 2nd and 3rd doses are for mRNA vaccines compared to no vaccination in the indicated period beginning 14 days after vaccination. Tests occurring in 0-13 days after vaccination were excluded.		
Cases and controls were matched 1:4 (max) without replacement on HHS and lab test date within three weeks. The adjusted variables include the following: age (continuous), body mass index, cancer, congestive heart failure, chronic kidney disease, chronic obstructive pulmonary disease, diabetes mellitus, hypertension, immunocompromised, priority level, race/ethnicity, and rurality.		

For those who received 2 doses of mRNA vaccines, VE against death was 92% (95% CI, 85 to 97) during Delta period and 77% (95% CI, 67 to 83) during Omicron period. VE against death for those who received an mRNA vaccine booster was 96% (95% CI, 87 to 99) – no difference from the 2-dose VE - during the Delta period, and 94% (95% CI, 90 to 96) –higher than the 2-dose VE - during the Omicron period.

DISCUSSION

Our study shows that Veterans who received an mRNA vaccine booster were highly protected against COVID-related outcomes, particularly hospitalization and death, during both the Delta and Omicron periods. These findings largely align with other VE studies of Omicron[11,12,13,14,15,17]. Also, among Veterans tested positive for COVID-19, irrespective of vaccination, those infected during the Omicron period were less likely to be hospitalized and, if hospitalized, had shorter lengths of stay and lower likelihood of ICU admission.

We found that the booster dose significantly increased protection against infection, regardless of symptoms, providing 90% VE against Delta and 64% against Omicron (Table 2) than the 2-dose regimen. These results were generally aligned with published findings. Early results from Southern California[12] showed that booster doses improved VE against infection when compared to 2-doses during both the Delta and Omicron periods. Similarly, a study from Israel focusing specifically on the Pfizer mRNA vaccine during the Delta period, estimated that a booster vaccination reduced the rate of confirmed infection as compared to those who did not receive a booster as to bring the vaccine efficacy up to a that reported against the Alpha variant.[18]

Although we found moderate VE against hospitalization after 2-dose vaccination (Table 3), the booster dose significantly improved VE against hospitalization during the Delta and Omicron

periods. For hospitalization, the booster dose increased the VE from 75% to 94% against Delta and from 63% to 89 % against Omicron. Estimated VE of the booster dose against mortality was high during both Delta and Omicron periods: 94% for Omicron and 96% for Delta. These estimates of high VE against mortality resembled the reduced risk of mortality reported elsewhere in the U.S.[20]

A study from South Africa that focused on two-doses of the Pfizer vaccine found an estimated VE against hospitalization of 93% (95% CI, 90 to 94) during the Delta period and 70% (95% CI, 62 to 76) during the Omicron period.[11] While we found a similar drop in effectiveness from the Delta to the Omicron period, our VE estimates were lower for both periods. Waning protection over time and differences in populations may contribute to the disagreement in our findings. For example, studies of hospitalized U.S. Veterans pre-dating the Omicron period showed an estimated VE of 86.8% (95% CI, 80.4-91.1) for full vaccination (including mRNA and Johnson & Johnson's Janssen),[3] 86.1% (95% CI, 77.7 to 91.3) for 2 doses of Moderna and 75.1% (95% CI, 64.6 to 82.4) for 2 doses of Pfizer-BioNTech.[4]

Our supplementary cases-only analysis showed that the booster vaccination was still highly effective against hospitalization among vaccine breakthrough cases in both the Omicron and Delta periods, with a higher point estimate for the Omicron period (Table S2). This is consistent with a study from the U.K. showing reduced risk of hospitalization among those infected with the Omicron variant compared to the Delta variant.[30]

Our results highlight the value of booster doses for protection against infection and, more importantly, against hospitalization and death. They also revealed distinctive features of the two variants, and lower severity of illness for the Omicron variant as compared to the Delta variant.

STRENGTHS AND LIMITATIONS

Strengths of this study include a large, diverse population and near real-time access to medical records. The VHA population offers insight into populations often underrepresented in US studies: racial minorities with a wide range of socio-economic backgrounds. Also, the VHA Veteran population is older (47% above 65), [25] sicker, [24] and predominantly male (90% male).[25] Although data on symptomatic versus asymptomatic infection and reasons for SARS-CoV-2 testing were infrequently recorded, in a random sample of Veterans who tested positive and had a detailed record, 26% reported no symptoms (Table S2). Possible misclassification of vaccination status and missing hospitalization records are of concerns because Veterans could go elsewhere for vaccination and hospitalization. For Veterans enrolled in Medicare, we checked records through August 2021 (latest available Medicare data) for COVID-19 vaccination, diagnoses, and related hospitalizations. We also limited the study population to Veterans who routinely sought care at the VHA to minimize misclassification. We assessed patient vaccination status as of November 2021 and January 2022. Other studies, including one of our own, have examined waning mRNA vaccine effectiveness against infection,[2,21,22,23] so we did not labor further on this topic. Nevertheless, Veterans with underlying conditions and health seeking behaviors may have been vaccinated earlier, thus increased their likelihood of having reduced immunity.

Sequencing data were not available for individual SARS-CoV-2 laboratory tests, so we defined variant periods based on estimated variant proportions in the U.S. by the CDC. To reduce misclassification, we excluded December 2021 when Delta and Omicron variants shared dominance, analyzing November 2021 (when Delta was almost 100% dominant) and January 2022 (when Omicron was 90%-100% dominant) separately.[16] In a future study we plan to use individual sequencing data after they become available in the VHA.

CONCLUSION

In November 2021, the CDC expanded the booster recommendation to everyone 18 and older 6 months after their second mRNA dose or 2 months after receiving Johnson & Johnson's Janssen vaccine.[7] At that time, 2-dose mRNA vaccine effectiveness among our study population of VHA Veterans were 54%, 75%, and 92% against COVID-19 infection, hospitalization, and death due to the Delta variant, respectively. Our findings indicate that mRNA vaccine boosters were very effective against severe COVID-related outcomes during both Delta and Omicron periods. Moreover, the booster vaccination reduced the likelihood of hospitalization among infected patients. Overall, the mRNA vaccine boosters provided a level of protection against Omicron like that of 2-dose against Delta, with VE at 64%, 89%, and 94% against infection, hospitalization, and death, respectively. We can witness the impact of the mRNA vaccine boosters as case numbers continue to drop and the surge of the Omicron variant abates across the United States.

Ethics Approval Statement

The study (Reference number: 1593089) was approved by the institutional review board (IRB) of the Department of Veterans Affairs Medical Center in White River Junction, Vermont, which waived the requirement for informed consent due to impracticality and low risk of the study.

Contributorship: YYX, HIS, CK, and VCM conceptualised and designed the study. YYX, EP, GZ, JS, AB, and CK conducted data analysis. All the authors reviewed titles, abstract, and full-text papers for eligibility. YYX and GZ drafted the paper, and all authors reviewed drafts and approved the final version. YYX is the guarantor of the paper.

Disclaimer: This article represents the authors' best judgement and should not bind or obligate the VA, the FDA, or any other institution.

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Data availability statement: Data may be obtained from a third party and are not publicly available. The data that support the findings of this study are available upon reasonable request from the respective health data stewardship entities.

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Figure 1. Attrition

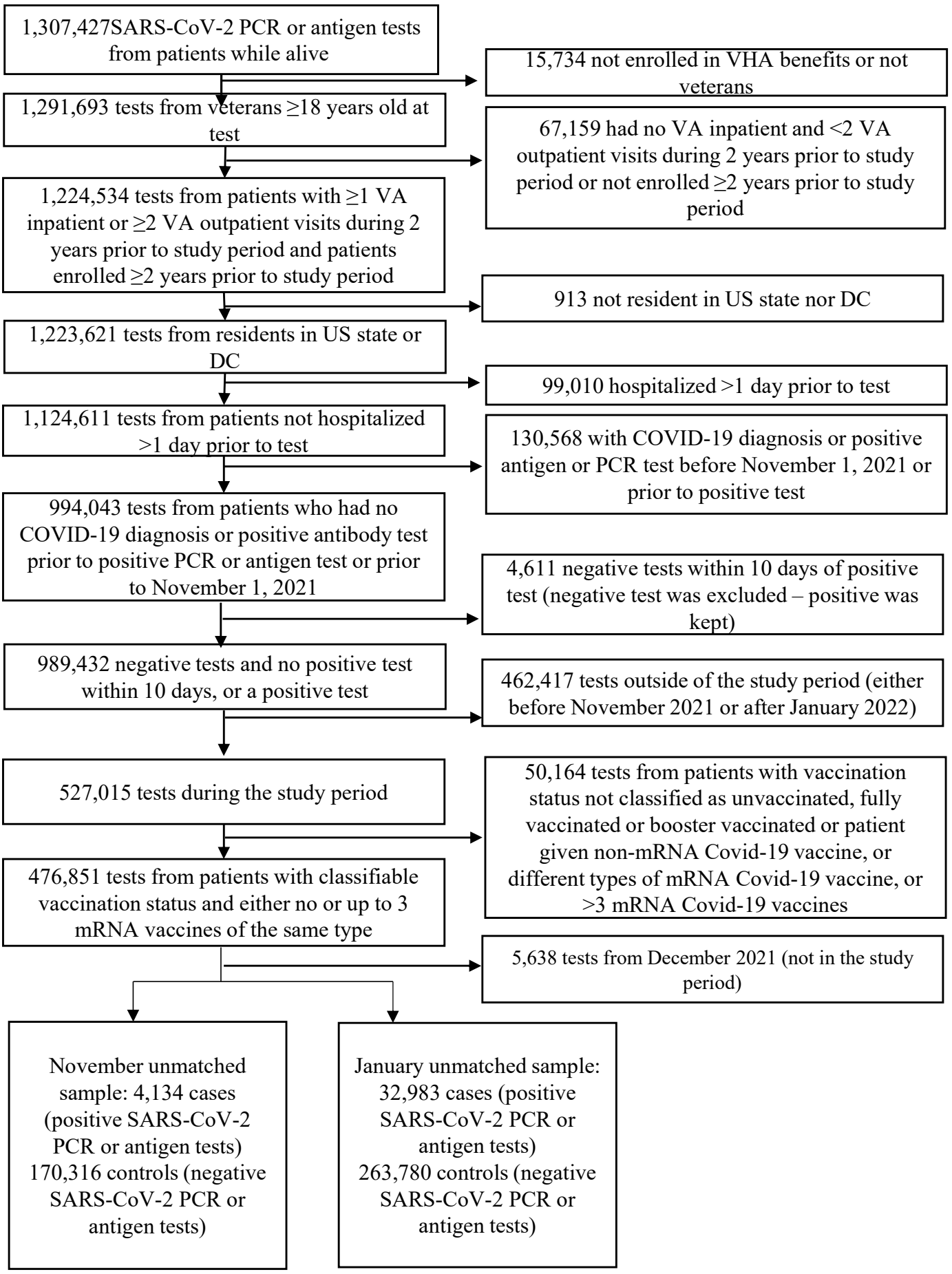
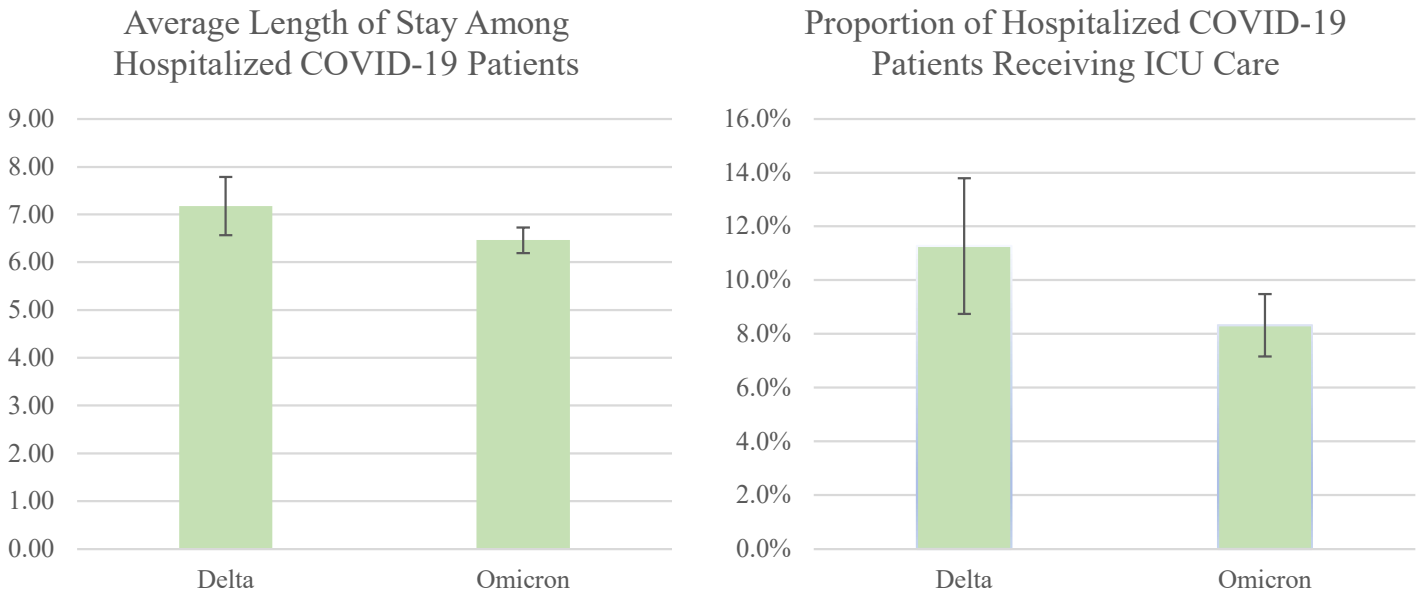


Figure 2. Average Hospital Length-of-Stay* and Intensive Care Unit Use during Delta and Omicron Periods



* Number of days between admission and discharge dates

Supplemental Materials Legend

1. Table S1. Estimated Vaccine Effectiveness Against COVID-19-related Hospitalization and Death Among Patients with a Positive Test
2. Table S2. Reasons for Testing and Symptoms

Table S1. Estimated Vaccine Effectiveness Against COVID-19-related Hospitalization and Death Among Patients with a Positive Test by Dose and Variant

VE Interval (14+ days after vaccination)		VE (95% CI)
Hospitalization		
Omicron	2nd dose	55% (49, 60)
Omicron	3rd dose	78% (74, 81)
Delta	2nd dose	59% (48, 68)
Delta	3rd dose	53% (12, 75)
Death		
Omicron	2nd dose	61% (47, 72)
Omicron	3rd dose	85% (77, 91)
Delta	2nd dose	81% (67, 89)
Delta	3rd dose	62% (-25, 88)
Above numbers exclude Johnson & Johnson's Janssen vaccines as of the date of the Johnson & Johnson's Janssen vaccine. 2nd and 3rd doses are for mRNA vaccines compared to no vaccination in the indicated period beginning 14 days after vaccination. Tests occurring in 0-13 days after vaccination were excluded.		
Cases and controls were matched 1:4 (max) without replacement on HHS and lab test date within three weeks. The adjusted variables include the following: age (continuous), body mass index, cancer, congestive heart failure, chronic kidney disease, chronic obstructive pulmonary disease, diabetes mellitus, hypertension, immunocompromised, priority level, race/ethnicity, and rurality.		

Table S2. Reasons for Testing and Symptoms in A Random Sample of COVID-19 Tests

	Frequency	Percent
Reason for Testing Recorded (n=1421)		
Exposure	574	40%
Screening	847	60%
Positive Tests (n=606)		
Asymptomatic	160	26%
Symptomatic	346	57%
Unknown	100	17%
Total Sample (n=10000)		
Records indicating asymptomatic/symptomatic/reason for testing	1958	20%
Unknown	8042	80%
Exposure: ICD-10-CM code Z20.822; Screening: ICD-10-CM code Z11.52; up to 1 day before and including the date of the SARS-CoV-2 test		

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1,5
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	7
Objectives	3	State specific objectives, including any prespecified hypotheses	7-8
Methods			
Study design	4	Present key elements of study design early in the paper	9
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	8-9
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	9-10, 9
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8-10
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8
Bias	9	Describe any efforts to address potential sources of bias	10-11
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	10-11
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	10-11
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	11-12, figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	Table 1, page 12-13
Outcome data	15*	Report numbers of outcome events or summary measures over time	12-13

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	
Generalisability	21	Discuss the generalisability (external validity) of the study results	
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Effectiveness of mRNA COVID-19 Vaccines against Omicron and Delta Variants in a matched test-negative case-control study among US Veterans

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Effectiveness of mRNA COVID-19 Vaccines against Omicron and Delta Variants in a matched test-negative case-control study among US Veterans

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Subtitle: Covid-19 booster Vaccines among Veterans

Key words: COVID-19; SARS-CoV-2; Delta; Omicron; Veterans; mRNA vaccine; vaccine effectiveness

Abstract (words now: 284, suggested limit:300)

Objectives: To estimate effectiveness of mRNA booster doses during periods of Delta and Omicron variant dominance.

Design: We conducted a matched test-negative case-control study to estimate VE of three and two doses of mRNA vaccines against infection (regardless of symptoms), and against COVID-19-related hospitalization and death.

Setting: Veterans Health Administration (VHA)

Participants: We used electronic health record data from 114,640 Veterans who had a SARS-CoV-2 test during November 2021-January 2022. Patients were largely 65 years or older (52%), male (88%), and non-Hispanic white (59%).

Main outcome measures: First positive result for a SARS-CoV-2 polymerase chain reaction (PCR) or antigen test.

Results: Against infection, booster doses had higher estimated VE –[64% (95% confidence interval [CI], 63 to 65)] than 2-dose vaccination [12% (95% CI, 10 to 15)] during the Omicron period. For the Delta period, VE against infection was 90% (95% CI, 88 to 92) among boosted vaccinees, higher than VE among 2-dose vaccinees [54% (95% CI, 50 to 57)]. Against hospitalization, booster dose VE was 89% (95% CI, 88 to 91) during Omicron and 94% (95% CI, 90 to 96) during Delta; 2-dose VE was 63% (95% CI, 58 to 67) during Omicron and 75% (95% CI, 69 to 80) during Delta. Against death, VE with a booster dose was 94% (95% CI, 90 to 96) during Omicron and 96% (95% CI, 87 to 99) during Delta.

Conclusions: Among an older, mostly male, population with comorbidities, we found that an mRNA vaccine booster was highly effective against infection, hospitalization, and death. Although the effectiveness of booster vaccination against infection was moderately higher against Delta than against the Omicron SARS-CoV2 variant, effectiveness against severe disease and death was similarly high against both variants.

Strengths and limitations of this study

- This study included a large, diverse population of US Veterans and near real-time access to medical records
- We used a test-negative case control approach to implicitly account for differences in health seeking behaviors between cases and non-cases
- By restricting participation to individuals who had used the VA health system in the past two years and were also tested for COVID-19 in the VA system, we increased our confidence that participants were active users of the VA health care system for vaccination, medical office visits and hospitalizations. Nonetheless, some misclassification of vaccination status and missing hospitalization records (for Veterans seeking care outside of the VHA) was still possible
- Symptoms and reason for SARS-CoV-2 testing were infrequently coded
- Sequencing data were not yet available for individual SARS-CoV-2 laboratory tests, so we defined dominant circulation periods for each SARS-CoV2 variant of interest based on CDC estimates of variant circulation in the U.S.

INTRODUCTION

In March 2020, the World Health Organization (WHO) declared coronavirus 19 (COVID-19), the disease caused by SARS-CoV-2, a pandemic.[1] By December 2020, the United States (U.S.) Food and Drug Administration (FDA) issued Emergency Use Authorizations (EUA) for two mRNA vaccines, based on the spike glycoprotein of the Wuhan strain of the SARS-CoV-2 virus, for the prevention of COVID-19. [2] [3]

Despite early reports on the effectiveness of these vaccines [4] [5] [6] [7] [8, 9] and persistence of anti-SARS-Cov-2 antibodies following vaccination [10], frequent mutations have increasingly challenged the effectiveness of these vaccines [11] [12]. In July 2021, a new, more infectious variant, B.1.617.2 (Delta) became the most dominant variant in the United States [13]. In November 2021, another variant, B.1.1.529 (Omicron) was identified in the United States and became the dominant variant by mid-December. Although the Omicron variant is more infectious than Delta, it is considered less deadly [14]. However, the number of mutations in Omicron's spike protein, compared to the Wuhan strain, is larger than for Delta, raising questions regarding the effectiveness of the FDA-authorized vaccines against Omicron [15].

We previously reported [9] [11] the effectiveness of COVID-19 mRNA vaccines against infection, hospitalization, and mortality among Veterans Health Administration (VHA)-enrolled Veterans through September 2021, when the major circulating variants in the United States included Alpha, Beta, and Delta. We found estimated vaccine effectiveness to remain high in the first three months after vaccination and to decrease significantly after 5 months [11]. With the rise of the Omicron variant in December 2021-January 2022 and the lengthening time from vaccination with the 2-dose primary series, we updated our estimates of vaccine effectiveness

(VE) to measure continued effectiveness of both mRNA vaccines in a population including the entire U.S. and included VE estimates for the booster (3-dose) vaccination.

Starting in September 2021, the Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices recommended a booster dose of COVID-19 vaccine to increase protection. [16] [17] As of early March 2022, the VHA had over 4 million fully vaccinated Veterans (2-dose of mRNA or 1-dose of Johnson & Johnson's Janssen COVID-19 vaccine) and over 1.6 million Veterans had received an mRNA booster [18]. As of March 2022, the VHA reported more than 613,000 COVID-19 cases and 21,309 confirmed deaths [18].

Early reports [19] [20] [21] [22] showed lower VEs against infection for the fully vaccinated (2-dose series) and even for those who received a booster (3-dose) during the Omicron period, but VE against hospitalization [23] remained high during both periods. These early reports on the Omicron variant were regional in the U.S., focused on one of the mRNA vaccines not both or were from outside the U.S. We sought to estimate VE against infection, hospitalization, and mortality for mRNA vaccines authorized in the U.S. (Pfizer-BioNTech and Moderna), for the fully vaccinated (2-dose) and those who received a booster (3-dose) of mRNA vaccines during the Delta and Omicron dominant periods [13] in the US Veteran population, which includes individuals across the U.S. with underlying health conditions and diverse socio-economic backgrounds.

METHODS

The study was approved by the institutional review board (IRB) of the Department of Veterans Affairs Medical Center in White River Junction, Vermont, which waived the requirement for informed consent. We followed the Strengthening the Reporting of Observational Studies in Epidemiology reporting guideline.

Patient and Public Involvement statement

Neither patients nor the public were involved in this study.

Data Source

We used electronic medical records and COVID-19 laboratory test data from the VHA Corporate Data Warehouse (CDW) to define infection irrespective of symptoms. The VHA CDW holds electronic medical records for about 9 million U.S. Veterans who use the VHA's network of 1,293 health care facilities, including hospitals and outpatient clinics [24]. Using CDC variant tracking data [13], we presumed positive tests during January 2022 were Omicron SARS-CoV-2 infections and those positive during November 2021 were Delta. Because December 2021 represented an overlap of both variants, we excluded positive tests from that month. As Medicare claims were available only up to August 2021, we used them to find COVID-19 diagnoses, vaccinations, and hospitalizations prior to the study period to exclude patients with prior history of COVID-19 and to augment our vaccination records. Since this population of Veterans was largely over 65 years old, we supplemented CDW data with available Medicare data as Veterans may use Medicare to provide healthcare services even if we found frequent users of VHA. We used VHA CDW records to determine date of death and hospitalizations with admission diagnosis related to COVID-19.

Study Design

To estimate VE against infection, we conducted a matched test negative case-control study.

Inclusion criteria: 1) Tested at the VHA for SARS-CoV-2 via antigen or PCR; 2) Enrolled in VHA benefits for 2+ years and a Veteran; 3) Met VHA use criteria of 1 inpatient or 2 outpatient visits during the 2 years prior to study period; 4) Resident of U.S. state or DC 5) Exposed in the community (excluded those hospitalized >1 day prior to test); 6) 18 years old or older at the time

of the test with valid demographic data (excluded those with missing sex or date-of-birth); 7) COVID-19 naïve (excluded those with a positive test or diagnosis code in VHA or Medicare prior to the study period); 8) Veterans with positive tests during the study period were included as cases; 9) Veterans with negative tests during the study period were included as controls; 10) The test occurred during the study period (November 2021 (Delta predominance) or January 2022 (Omicron predominance)); 11) Classifiable vaccination status: 0 to 3 doses of mRNA vaccination. Exclusions: 1) Negative tests taken within 10 days following a positive test; and 2) Veterans vaccinated with Janssen vaccine.

We matched each case (positive tests) with up to 4 controls (negative tests) based on Health and Human Service (HHS) geographic region and SARS-CoV-2 laboratory tests within 3 weeks of the case specimen collection date as both are measures of local disease burden. Demographic characteristics of the matched population were described by reporting the frequency and proportion for categorical variables and the mean (SD) for continuous variables. Standardized mean differences (SMD) [25] were used to describe differences in characteristics between cases and controls. For estimated VE against hospitalization and death, we utilized a matched case-control design. Depending on the analysis, cases were those hospitalized or were those who died within 30 days of the positive COVID-19 test. Controls were those not hospitalized or who did not die within 30 days of their SARS-CoV-2 tests, irrespective of test results. Any patient with dual Medicare-VHA enrolment who had a claim for COVID-related hospitalization prior to the study period was already excluded, thus ineligible to be a control. Hospitalizations were defined as a hospital admission diagnosis related to COVID-19 after a positive SARS-CoV-2 test.

To better inform our interpretation of VE against hospitalization and mortality in the two time periods, we conducted a sub-analysis in which we assessed VE against COVID-related

hospitalization and death among those already infected, restricting our hospitalization and mortality analysis to patients with a positive test. Cases were defined as before, and controls were those who were not hospitalized or who did not die within 30 days of a positive test. We also compared average length-of-stay (LOS) and rates of intensive care unit (ICU) admission among those hospitalized in the Delta and Omicron periods.

Exposure

We defined 2-dose vaccination as receipt of two doses of an mRNA COVID-19 vaccine, and booster vaccination as receipt of a third doses of an mRNA vaccine (about 95% of mRNA 3rd doses occurred approximately six months after a 2nd dose). We designated exposure to the two-dose regimen or a booster from 14 days following vaccination, excluding events in days 0-13. We designated patients as unvaccinated if they had no record of vaccination in either VHA CDW or in Medicare.

Statistical Analysis

We used conditional logistic regression to calculate odds ratios (ORs) with 95% confidence intervals (CI) for the association between positive SARS-CoV-2 testing and 2 or 3 doses of mRNA COVID-19 vaccine during Delta and Omicron periods. In the model, we included number of mRNA vaccine doses (2 or 3) as the primary explanatory variable, an indicator variable for SARS-CoV-2 presumed variant (Delta or Omicron) based on test date, and their interaction terms. We estimated the association between SARS-CoV-2 infections and number of mRNA vaccine doses by the OR, adjusting for age (continuous), race, rurality, VHA benefits priority, and comorbid conditions (cancer, congestive heart failure, hypertension, immunocompromising conditions, obesity, and diabetes). Confounders were determined based on prior study [9] [11] and known factors associated with SARS-CoV-2 [26]. We also used

conditional logistic regression to analyze VE against hospitalizations and death. Due to sample size and scope of the study, we did not analyze one dose of mRNA vaccine.

Severity of disease was determined by average length of stay (LOS) in days between admission date and discharge date for overall COVID-19-related hospitalizations and average LOS in an intensive care unit (ICU) during a hospitalization related to COVID-19.

All tests were two-tailed, and we chose 0.05 as the level of statistical significance. We performed data analysis using SAS 9.4 (SAS Institute, Cary, North Carolina).

RESULTS

Study Population

In November 2021 (Delta period) there were 4,134 positive SARS-CoV-2 tests (cases), and 170,316 negative tests (controls) (Figure 1). After matching, 4,134 cases and 16,536 controls remained (see Table 1 for baseline characteristics); 2,300 (56%) cases and 3,951 (24%) controls were unvaccinated at the time of testing. In January 2022 (Omicron period) there were 32,983 positive tests (cases) and 263,780 negative tests (controls). After matching, 32,983 cases and 126,363 controls remained. At the time of testing, 13,153 (40%) cases and 29,110 (23%) controls remained unvaccinated. During both periods, cases tended to have a lower CCI score and to be younger than controls. Patients included in this study were largely 65 years or older (94,447, 52%), male (158,395, 88%), and non-Hispanic white (105,437, 59%). The cases in both the Delta and Omicron periods had similar proportions of comorbid conditions at baseline, while the controls during the Delta period had a slightly higher proportion of comorbid conditions (Table 1). Reasons for testing and presence of symptoms from a random sample of individuals who presented for testing are displayed in Table S1.

Table 1. Baseline Characteristics of Matched Study Subjects

	Delta			Omicron		
	Case (4134)	Control (16536)	SMD^	Case (32983)	Control (126363)	SMD^
Number of mRNA vaccines, No. (%)						
0	2300 (56)	3951 (24)	68.6	13153 (40)	29110 (23)	36.9
1	66 (2)	329 (2)	3.0	887 (3)	2900 (2)	2.5
2	1627 (39)	8035 (49)	18.7	11983 (36)	35400 (28)	17.9
3	141 (3)	4221 (26)	66.2	6960 (21)	58953 (47)	56.1
Vaccine manufacturer for first dose, No. (%)						
Moderna	1057 (26)	7120 (43)	37.5	9935 (30)	50921 (40)	21.4
Pfizer-BioNTech	777 (19)	5465 (33)	33.0	9890 (30)	46283 (37)	14.1
Janssen	0	0	0	<11	49 (0)	S
No Vaccine Recorded	2300 (56)	3951 (24)	68.6	13153 (40)	29110 (23)	36.9
Age, years, No. (%)						
18 to 44	904 (22)	114 (1)	71.0	7828 (24)	8966 (7)	47.4
45 to 64	1417 (34)	6091 (37)	5.3	12884 (39)	47365 (37)	3.2
65 to 74	1110 (27)	6381 (39)	25.2	7738 (23)	41715 (33)	21.3
75 to 84	537 (13)	2871 (17)	12.2	3584 (11)	21345 (17)	17.5
85+	166 (4)	1079 (7)	11.2	949 (3)	6972 (6)	13.2
Race/Ethnicity, No. (%)						
Black, non-Hispanic	494 (12)	4636 (28)	41.1	8523 (26)	37049 (29)	7.8
Hispanic, any race	193 (5)	601 (4)	5.2	1973 (6)	7425 (6)	0.4
White, non-Hispanic	3193 (77)	10139 (61)	35.0	20038 (61)	72067 (57)	7.6
other	254 (6)	1160 (7)	3.5	2449 (7)	9822 (8)	1.3
Sex, No. (%)						
Female	420 (10)	1656 (10)	0.5	4419 (13)	15126 (12)	4.3
Male	3714 (90)	14880 (90)	0.5	28564 (87)	111237 (88)	4.3
Quan's CCI						
Mean (SD)	0.8 (1.5)	1.6 (2.1)	44.2	0.8 (1.5)	1.3 (1.9)	31.8
Median (Q1-Q3)	0 (0-1)	1 (0-2)		0 (0-1)	1 (0-2)	
Comorbid conditions						
Cancer	180 (4)	1296 (8)	14.6	1387 (4)	8542 (7)	11.2
Congestive heart failure	202 (5)	1574 (10)	18.0	1420 (4)	9495 (8)	13.6
Hypertension	1314 (32)	7783 (47)	31.7	10333 (31)	53387 (42)	22.8
Obesity	391 (9)	1770 (11)	4.1	2851 (9)	12452 (10)	4.2
Diabetes without complications	608 (15)	2941 (18)	8.4	4529 (14)	21207 (17)	8.5
Diabetes with complications	279 (7)	2230 (13)	22.5	2075 (6)	13970 (11)	17.0
Immunocompromising conditions	463 (11)	3229 (20)	23.2	3464 (11)	20904 (17)	17.7

Abbreviations: Quan's CCI, Charlson comorbidity index, Quan's version, S, suppressed due to small numbers, SD, standard deviation, Q1-Q3, quartiles 1 to 3[26]

See Supplemental Table 1 (Young-Xu et al.)[1] for definitions of variables in this table

^Standardized mean difference of 10 or greater was used to identify imbalance between cases and controls[27]

Vaccine Effectiveness against infection

For those with 2-dose mRNA vaccine, VE was 54% (95% CI, 50 to 57) for Delta and 12% (95% CI, 10 to 15) for Omicron. VE for those who received an mRNA vaccine booster was 90% (95% CI, 88 to 92) in the Delta period and 64% (95% CI, 63 to 65) in the Omicron period (Table 2). For the Delta period, the median time from the 2nd dose to the SARS-CoV-2 test date was 241 days and 35 days from the 3rd dose. As is expected this median time from 2nd dose of vaccination increased for the Omicron period to 289 days and 72 days from the 3rd dose.

Table 2. Estimated Vaccine Effectiveness Against Laboratory Confirmed SARS-CoV-2 Infection by Dose and Variant

Variant	Number of doses versus unvaccinated	Adjusted VE (95% CI)^
Omicron	*2nd* dose (cases: 24136, controls: 79953)	12% (10, 15)
Omicron	3rd dose (cases: 19839, controls: 69182	64% (63, 65)
Delta	*2nd* dose (cases: 3878, controls: 15576)	54% (50, 57)
Delta	3rd dose (cases: 2342, controls: 9395)	90% (88, 92)
Above numbers exclude Johnson & Johnson's Janssen vaccines as of the date of the Johnson & Johnson's Janssen vaccine. 2nd and 3rd doses are for mRNA vaccines compared to no vaccination in the indicated variant predominant period beginning 14 days after vaccination. Tests occurring in 0-13 days after vaccination were excluded.		
^Cases and controls were matched 1:4 on HHS region and date. The adjusted variables include the following: age (continuous), body mass index (missing, normal <26, overweight/obese ≥26), cancer, congestive heart failure, chronic kidney disease, chronic obstructive pulmonary disease, diabetes mellitus, hypertension, immunocompromised, priority level, race/ethnicity, and rurality.		

Hospitalization and Death

VE against COVID-related hospitalization for those who received 2-dose mRNA vaccine was 75% (95% CI, 69 to 80) in the Delta period and 63% (95% CI, 58 to 67) in the Omicron period (Table 3). VE against COVID-related hospitalization for those who received an mRNA vaccine

booster was 94% (95% CI, 90 to 96) in the Delta period, higher than the 2-dose VE, and 89% (95% CI, 88 to 91) in the Omicron period (Table 3). In a sub-analysis restricted to those with a positive COVID-19 test in the study period, we evaluated VE against progression to hospitalization among the infected only, we found that VE for booster against COVID-related hospitalization was 53% (95% CI, 12 to 75) in the Delta period – not statistically different from the 2-dose VE, and 78% (95% CI, 74 to 81) in the Omicron period – almost twice higher than the 2-dose VE (Table S2). Among Omicron-associated hospitalizations (regardless of vaccination status), the length of stay (LOS) averaged 6.5 days (95% CI, 6.2 to 6.7 days), compared to 7.2 days (95% CI, 6.6 to 7.8) among Delta-associated hospitalizations. 11.3% (95% CI, 8.8 to 13.8%) of hospitalizations during the Delta period resulted in ICU admission; in contrast, 8.3% (95% CI, 7.2 to 9.5%) of COVID-related hospitalizations during the Omicron period resulted in ICU admission (Figure 2).

Table 3. Estimated Vaccine Effectiveness Against COVID-19-related Hospitalization and Death by Dose and Variant

Variant	Number of doses versus unvaccinated	Adjusted VE (95% CI)^
Hospitalization		
Omicron	2nd dose (cases: 1746, controls: 6964)	63% (58, 67)
Omicron	3rd dose (cases: 1403, controls: 5611)	89% (88, 91)
Delta	2nd dose (cases: 570, controls: 2282)	75% (69, 80)
Delta	3rd dose (cases: 381, controls: 1532)	94% (90, 96)
Death		
Omicron	2nd dose (cases: 322, controls: 1285)	77% (67, 83)
Omicron	3rd dose (cases: 267, controls: 1066)	94% (90, 96)
Delta	2nd dose (cases: 109, controls: 431)	92% (83, 96)
Delta	3rd dose (cases: 89, controls: 354)	96% (87, 99)
Above numbers exclude Johnson & Johnson's Janssen vaccines as of the date of the Johnson & Johnson's Janssen vaccine. 2nd and 3rd doses are for mRNA vaccines compared to no vaccination in the indicated variant predominant period beginning 14 days after vaccination. Tests occurring in 0-13 days after vaccination were excluded.		

^Cases and controls were matched 1:4 (max) without replacement on HHS and lab test date within three weeks. The adjusted variables include the following: age (continuous), body mass index (missing, normal <26, overweight ≥26), cancer, congestive heart failure, chronic kidney disease, chronic obstructive pulmonary disease, diabetes mellitus, hypertension, immunocompromised, priority level, race/ethnicity, and rurality.

For those who received 2 doses of mRNA vaccines, VE against death was 92% (95% CI, 85 to 97) during Delta period and 77% (95% CI, 67 to 83) during Omicron period. VE against death for those who received an mRNA vaccine booster was 96% (95% CI, 87 to 99), and no different from the 2-dose VE, during the Delta period, and was 94% (95% CI, 90 to 96), higher than the 2-dose VE, during the Omicron period.

DISCUSSION

Our study shows that Veterans who received an mRNA vaccine booster were highly protected against COVID-related outcomes, particularly hospitalization and death, during both the Delta and Omicron periods. These findings largely align with other VE studies of Omicron [19] [20] [21] [23] [22] [27]. Also, among Veterans tested positive for COVID-19, irrespective of vaccination, those infected during the Omicron period were less likely than those infected during the Delta period to be hospitalized and, if hospitalized, had shorter lengths of stay and lower likelihood of ICU admission.

We found that the booster dose significantly increased protection against infection, regardless of symptoms, providing higher protection than the 2-dose regimen during both variant predominant periods. However, VE of the booster does against Delta was consistently higher than that against Omicron. These results were generally aligned with published findings. Early results from Southern California [20] showed that booster doses improved VE against infection when compared to 2-doses during both the Delta and Omicron periods. Similarly, a study from Israel

focusing specifically on the Pfizer mRNA vaccine during the Delta period, estimated that a booster vaccination reduced the rate of confirmed infection as compared to those who did not receive a booster, bringing the VE up to that reported against the Alpha variant [28].

Although we found moderate VE against hospitalization after 2-dose vaccination, the booster dose significantly improved VE against hospitalization during the Delta and Omicron periods. Estimated VE of the booster dose against mortality was high during both Delta and Omicron periods. These estimates of high VE against mortality resembled the reduced risk of mortality reported elsewhere in the U.S. [29]

A study from South Africa that focused on two-doses of the Pfizer vaccine found an estimated VE against hospitalization of 93% (95% CI, 90 to 94) during the Delta period and 70% (95% CI, 62 to 76) during the Omicron period [19]. While we found a similar drop in effectiveness from the Delta to the Omicron period, our VE estimates were lower for both periods. Waning protection over time and differences in populations may contribute to the discrepancy in our findings.

Our supplementary cases-only analysis showed that the booster vaccination was still highly effective against hospitalization among vaccine breakthrough cases in both the Omicron and Delta periods, with a higher point estimate for the Omicron period (Table S2). This is consistent with a study from the U.K. showing reduced risk of hospitalization among those infected with the Omicron variant compared to the Delta variant [30].

Our results highlight the value of booster doses for protection against infection and, more importantly, against hospitalization and death. They also revealed distinctive features of the two variants, and lower severity of illness for the Omicron variant as compared to the Delta variant.

STRENGTHS AND LIMITATIONS

Strengths of this study include a large, diverse population and near real-time access to medical records. The VHA population offers insight into populations often underrepresented in US studies: racial minorities with a wide range of socio-economic backgrounds. Also, the VHA Veteran population is older (47% above 65) [31], sicker [32], and predominantly male (90% male) [31].

Although data on symptomatic versus asymptomatic infection and reasons for SARS-CoV-2 testing were infrequently recorded, in a random sample of Veterans who tested positive and had a detailed record, about a quarter reported no symptoms. Possible misclassification of vaccination status and missing hospitalization records are of concerns because Veterans could go elsewhere for vaccination and hospitalization. For Veterans enrolled in Medicare, we checked records through August 2021 (latest available Medicare data) for COVID-19 vaccination, diagnoses, and related hospitalizations. We also limited the study population to Veterans who routinely sought care at the VHA to minimize misclassification. We assessed patient vaccination status as of November 2021 and January 2022. Other studies, including one of our own, have examined waning mRNA vaccine effectiveness against infection [11] [33] [34], so we did not labor further on this topic. Nevertheless, Veterans with underlying conditions and health seeking behaviors may have been vaccinated earlier, thus increased their likelihood of having reduced immunity.

Sequencing data were not available for individual SARS-CoV-2 laboratory tests, so we defined variant periods based on estimated variant proportions in the U.S. by the CDC. To reduce misclassification, we excluded December 2021 when Delta and Omicron variants shared dominance, analyzing November 2021 (when Delta was almost 100% dominant) and January

2022 (when Omicron was 90%-100% dominant) separately [13]. In a future study we plan to use individual sequencing data after they become available in the VHA.

CONCLUSION

In November 2021, the CDC expanded the booster recommendation to everyone 18 and older 6 months after their second mRNA dose or 2 months after receiving Johnson & Johnson's Janssen vaccine.[7] At that time, 2-dose mRNA vaccine effectiveness among our study population of VHA Veterans were 54%, 75%, and 92% against COVID-19 infection, hospitalization, and death due to the Delta variant, respectively. Our findings indicate that mRNA vaccine boosters were very effective against severe COVID-related outcomes during both Delta and Omicron periods among a predominantly male population. Moreover, the booster vaccination reduced the likelihood of hospitalization among infected patients. Overall, the mRNA vaccine boosters provided a level of protection against Omicron like that of 2-dose against Delta, with VE at 64%, 89%, and 94% against infection, hospitalization, and death, respectively. We can witness the impact of the mRNA vaccine boosters as case numbers continue to drop and the surge of the Omicron variant abates across the United States.

Figure Legend/Caption

Figure 1. Attrition

Figure 2. Average Hospital Length-of-Stay and Intensive Care Unit Use during Delta and Omicron Periods

Ethics Approval Statement

The study (Reference number: 1593089) was approved by the institutional review board (IRB) of the department of Veterans Affairs Medical Center in White River Junction, Vermont, which waived the requirement for informed consent dur to impracticality and low risk of the study.

Contributorship: YYX, HSI, CK, and VCM conceptualized and designed the study. YYX, EIP, GMZ, JS, ASB, and CK conducted data analysis. YYX, GMZ, HIS, CK, EIP, JS, ASB, MH, DOB, MCR, STB, and VCM reviewed titles, abstract, and full-text papers for eligibility. YYX and GZ drafted the paper, and YYX, GMZ, HIS, CK, EIP, JS, ASB, MH, DOB, MCR, STB, and VCM reviewed drafts and approved the final version. YYX is the guarantor of the paper.

Disclaimer: This article represents the authors' best judgement and should not bind or obligate the VA, FDA, or any other institution.

Competing interests: YYX, EIP, GMZ, JS, ASB, and CK acknowledge having received funding from Pfizer for other research projects other than this one.

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Data availability statement: Data may be obtained from a third part and are not publicly available. The data that support the findings of this study are available upon reasonable request from the respective health data stewardship entities.

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Figure 1. Attrition

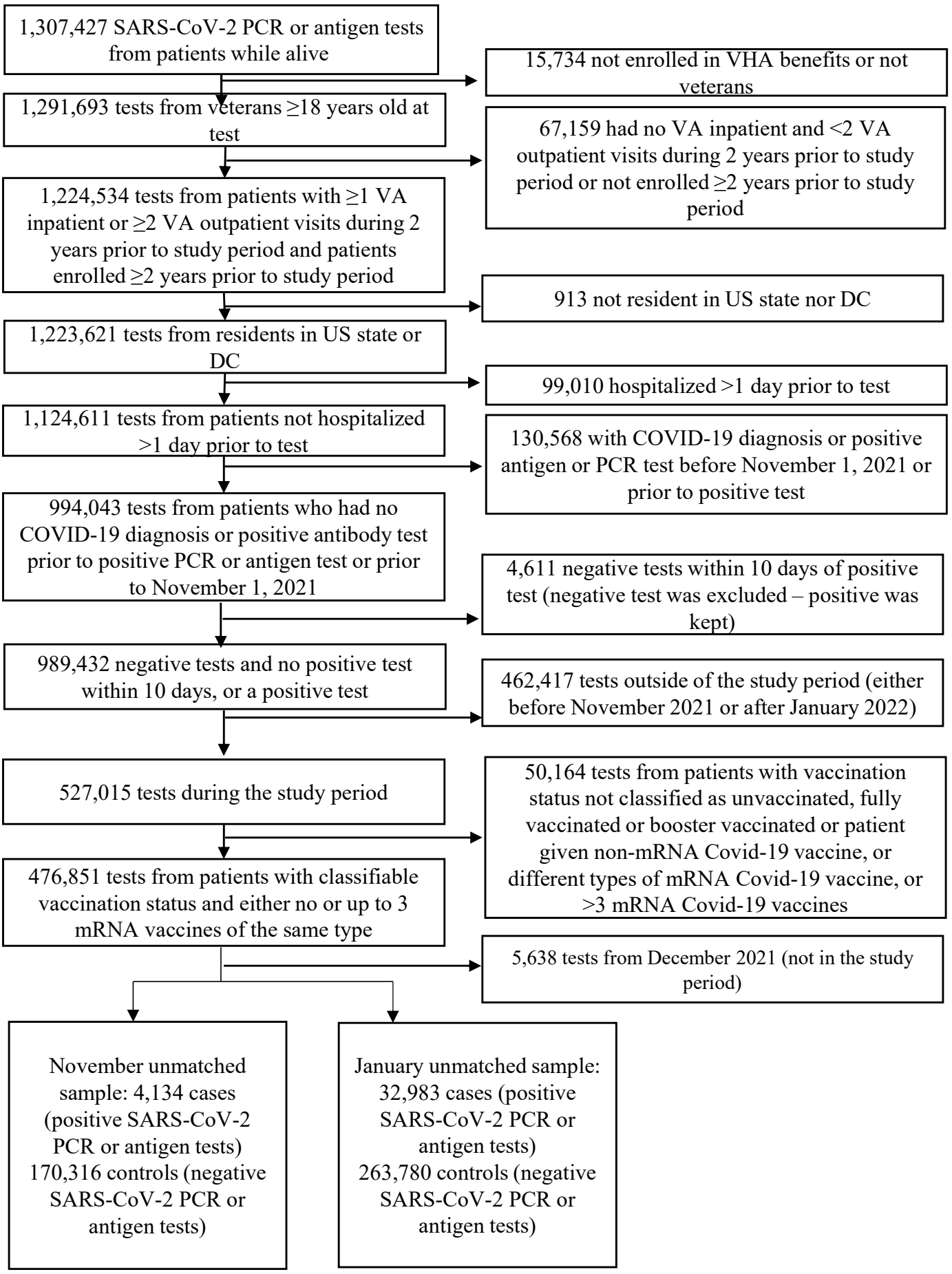
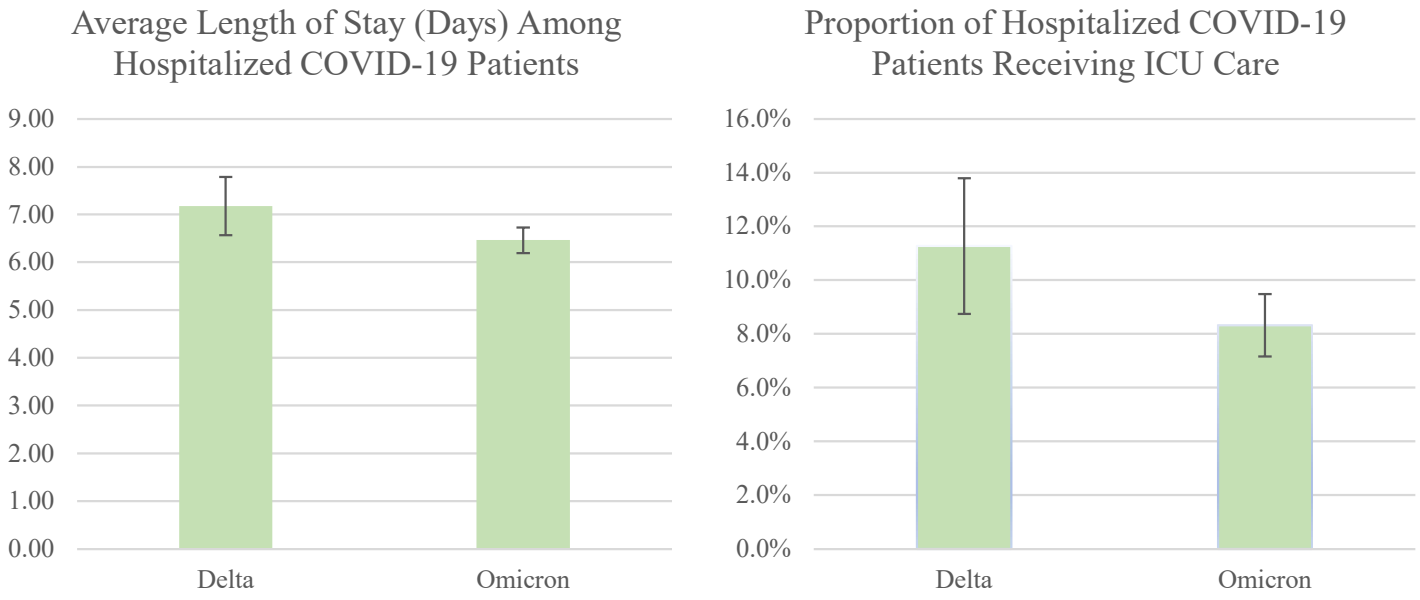


Figure 2. Average Hospital Length-of-Stay* and Intensive Care Unit Use during Delta and Omicron Periods



* Number of days between admission and discharge dates

Supplemental Materials Legend

1. Table S1. Reasons for Testing and Symptoms
2. Table S2. Estimated Vaccine Effectiveness Against COVID-19-related Hospitalization and Death Among Patients with a Positive Test
3. List S3. of Inclusion and Exclusion Criteria

Table S1. Reasons for Testing and Symptoms in A Random Sample of COVID-19 Tests

	Frequency	Percent
Reason for Testing Recorded (n=1421)		
Exposure	574	40%
Screening	847	60%
Positive Tests (n=606)		
Asymptomatic	160	26%
Symptomatic	346	57%
Unknown	100	17%
Total Sample (n=10000)		
Records indicating asymptomatic/symptomatic/reason for testing	1958	20%
Unknown	8042	80%
Exposure: ICD-10-CM code Z20.822; Screening: ICD-10-CM code Z11.52; up to 1 day before and including the date of the SARS-CoV-2 test		

Table S2. Estimated Vaccine Effectiveness Against COVID-19-related Hospitalization and Death Among Patients with a Positive Test by Dose and Variant

Variant	Number of doses versus unvaccinated	Adjusted VE (95% CI)^
Hospitalization		
Omicron	*2nd* dose (cases:1746, controls: 6715)	55% (49, 60)
Omicron	3rd dose (cases: 1403, controls: 5209)	78% (74, 81)
Delta	*2nd* dose (cases: 570, controls: 1912)	59% (48, 68)
Delta	3rd dose (cases: 381, controls: 986)	53% (12, 75)
Death		
Omicron	*2nd* dose (cases: 322, controls: 1286)	61% (47, 72)
Omicron	3rd dose (cases: 267, controls: 1062)	85% (77, 91)
Delta	*2nd* dose (cases: 109, controls: 434)	81% (67, 89)
Delta	3rd dose(cases: 89, controls: 352)	62% (-25, 88)
Above numbers exclude Johnson & Johnson's Janssen vaccines as of the date of the Johnson & Johnson's Janssen vaccine. 2nd and 3rd doses are for mRNA vaccines compared to no vaccination in the indicated period beginning 14 days after vaccination. Tests occurring in 0-13 days after vaccination were excluded.		
^Cases and controls were matched 1:4 (max) without replacement on HHS and lab test date within three weeks. The adjusted variables include the following: age (continuous), body mass index, cancer, congestive heart failure, chronic kidney disease, chronic obstructive pulmonary disease, diabetes mellitus, hypertension, immunocompromised, priority level, race/ethnicity, and rurality.		

List 1. Inclusion and Exclusion Criteria

Inclusion criteria:

- Tested at the VHA for SARS-CoV-2 via antigen or PCR
- Enrolled in VHA benefits for 2+ years and a Veteran
- Met VHA use criteria of 1 inpatient or 2 outpatient visits during the 2 years prior to study period
- Resident of U.S. state or DC
- Exposed in the community (excluded those hospitalized >1 day prior to test)
- 18 years old or older at the time of the test with valid demographic data (excluded those with missing sex or date-of-birth)
- COVID-19 naïve (excluded those with a positive test or diagnosis code in VHA or Medicare prior to the study period)
- Veterans with positive tests during the study period were included as cases
- Veterans with negative tests during the study period were included as controls
- The test occurred during the study period (November 2021 (Delta predominance) or January 2022 (Omicron predominance))
- Classifiable vaccination status:
  - 0 to 3 doses of mRNA vaccination

Exclusions:

- Negative tests taken within 10 days following a positive test
- Veterans vaccinated with Janssen vaccine

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1	Lines 1-2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3-4	Lines 64-88
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6-7	Lines 119-130
Objectives	3	State specific objectives, including any prespecified hypotheses	7	Lines 142-147
Methods				
Study design	4	Present key elements of study design early in the paper	8	Lines 170-171
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	8	Lines 155-168
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	8-9	Lines 172-183
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	9-10	Lines 184-203
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	10-11	Lines 205- 223

Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8-9	Lines 155-164, 186-190
Bias	9	Describe any efforts to address potential sources of bias	8	Lines 164-168
Study size	10	Explain how the study size was arrived at		Figure 1

Continued on next page

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	10-11	Lines 217-220
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	10-11	Lines 212-221, lines 227-228
		(*b*) Describe any methods used to examine subgroups and interactions	11	Lines 221-223
		(*c*) Explain how missing data were addressed	9	Lines 175-176, Table 2, Table 3
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	8-9	Lines 170-171, lines 184-186
		(*e*) Describe any sensitivity analyses	10	lines 197-203
Results				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	11	See Figure 1 Attrition Lines 231-236
		(b) Give reasons for non-participation at each stage		See Figure 1 Attrition
		(c) Consider use of a flow diagram		See Figure 1 Attrition
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	11-12	See Table 1 Lines 236-242
		(b) Indicate number of participants with missing data for each variable of interest		Table 1
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)		N/A
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time		N/A
		Case-control study—Report numbers in each exposure category, or summary measures of exposure		See Table 1, Table 2, Table 3
		Cross-sectional study—Report numbers of outcome events or summary measures		N/A
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10-11 12	Lines 217-220 See Tables 2-3 Lines 245-247
		(*b*) Report category boundaries when continuous variables were categorized		Table 2-3
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period		N/A

Continued on next page

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses		Table 3 Table S2 and Figure 2
Discussion				
Key results	18	Summarise key results with reference to study objectives	13	Lines 273-279
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15 5	Lines 314-332 Lines 98-104
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14	Lines 305-307
Generalisability	21	Discuss the generalisability (external validity) of the study results	4 15	Lines 84-88 Lines 311-313
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	17	Lines 360-361

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.