Adverse outcomes of SARS-CoV-2 infection with delta and omicron variants in vaccinated versus unvaccinated US veterans: retrospective cohort study

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ABSTRACT

OBJECTIVES

To determine the association between covid-19 vaccination types and doses with adverse outcomes of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection during the periods of delta (B.1.617.2) and omicron (B.1.1.529) variant predominance.

DESIGN

Retrospective cohort.

SETTING

US Veterans Affairs healthcare system.

PARTICIPANTS

Adults (≥18 years) who are affiliated to Veterans Affairs with a first documented SARS-CoV-2 infection during the periods of delta (1 July-30 November 2021) or omicron (1 January-30 June 2022) variant predominance. The combined cohorts had a mean age of 59.4 (standard deviation 16.3) and 87% were male.

INTERVENTIONS

Covid-19 vaccination with mRNA vaccines (BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna)) and adenovirus vector vaccine (Ad26.COV2.S (Janssen/Johnson & Johnson)).

MAIN OUTCOME MEASURES

Stay in hospital, intensive care unit admission, use of ventilation, and mortality measured 30 days after a positive test result for SARS-CoV-2.

RESULTS

In the delta period, 95 336 patients had infections with 47.6% having at least one vaccine dose, compared with 184 653 patients in the omicron period, with 72.6% vaccinated. After adjustment for patient demographic and clinical characteristics, in the delta period, two doses of the mRNA vaccines were associated with lower odds of hospital admission (adjusted odds ratio 0.41 (95% confidence interval 0.39 to 0.43)), intensive care unit admission (0.33 (0.31 to 0.36)), ventilation (0.27 (0.24 to 0.30)), and death (0.21 (0.19 to 0.23)), compared with no vaccination. In the omicron period, receipt of two mRNA doses were associated with lower odds of hospital admission (0.60 (0.57 to 0.63)), intensive care unit admission (0.57 (0.53 to 0.62)), ventilation (0.59 (0.51 to 0.67)), and death (0.43 (0.39 to 0.48)). Additionally, a third mRNA dose was associated with lower odds of all outcomes compared with two doses: hospital admission (0.65 (0.63 to 0.69)), intensive care unit admission (0.65 (0.59 to 0.70)), ventilation (0.70 (0.61 to 0.80)), and death (0.51 (0.46 to 0.57)). The Ad26.COV2.S vaccination was associated with better outcomes relative to no vaccination, but higher odds of hospital stay and intensive care unit admission than with two mRNA doses. BNT162b2 was generally associated with worse outcomes than mRNA-1273 (adjusted odds ratios between 0.97 and 1.42).

CONCLUSIONS

In veterans with recent healthcare use and high occurrence of multimorbidity, vaccination was robustly associated with lower odds of 30 day morbidity and mortality compared with no vaccination among patients infected with covid-19. The vaccination type and number of doses had a significant association with outcomes.

WHAT IS KNOWN ON THIS TOPIC

Population based research shows that covid-19 vaccination is effective at reducing risk of infection, admission to hospital, and death

In the period of predominant omicron variant, infections among vaccinated people became more common

The degree to which vaccination type, number of doses, and time since last dose is associated with adverse outcomes among those infected is not as well understood

WHAT THIS STUDY ADDS

All vaccinations were associated with lower odds of admission to hospital or intensive care unit, ventilation use, or death, in 95 336 patients with infections in the delta period and 184 653 in the omicron period

Of the mRNA vaccines, Moderna was associated with better outcomes than Pfizer-BioNTech, and in the omicron period, a third dose of mRNA vaccination was associated with better outcomes than two doses

Introduction

Clinical trials and population studies comparing individuals who are vaccinated or unvaccinated have established covid-19 vaccine effectiveness for preventing infection, hospital admission, and death from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), including against the alpha (B.1.1.7), delta (B.1.617.2), and omicron (B.1.1.529) viral variants.[1-5] However, some studies suggest decreased vaccine effectiveness during the period of delta variant predominance (hereafter, delta period), particularly for preventing infection.[6] Furthermore, during the delta period, the number of breakthrough infections (ie,

infections among vaccinated individuals) increased.[7 8] The omicron variant drove a larger surge in cases in the USA in January and February of 2022 and even greater numbers of breakthrough infections.[9]

Reports suggested that serious illness after SARS-CoV-2 infection is less common in people who are vaccinated than in people who are not vaccinated.[10] However, the difference in severity of clinical outcomes of SARS-CoV-2 by vaccination status has been only minimally characterised, especially according to the predominant viral variant.[11 12] Furthermore, few studies have addressed the effect of third and fourth doses on outcomes among people who were infected. These studies have typically had little adjustment for the many potential confounders that are risk factors for covid-19 related illness severity and also drivers of vaccination decisions. The effect of type of covid-19 vaccine (BNT162b2 (Pfizer-BioNTech), mRNA-1273 (Moderna), or Ad26.COV2.S (Janssen/Johnson & Johnson) (hereafter Janssen)) or time since last vaccination on adverse outcomes after infection with delta or omicron variants also require investigation.

This observational study sought to examine the association of vaccination status, including number and type of vaccine doses received and time since vaccination, with risk of admission to hospital, intensive care unit admission, mechanical ventilation, and death. We studied these outcomes in the 30 days after a positive SARS-CoV-2 test among infected patients of the US Veterans Health Administration. We conducted separate analyses for the periods when the delta and omicron variants were predominant.

Methods

Data source

The US Veterans Health Administration is the largest integrated national healthcare system in the US, with 171 medical centers and 1113 outpatient clinics. The US Veterans Health Administration employs a comprehensive, nationwide electronic health records system, and data from all facilities are transferred to the US Veterans Health Administration's centralized relational database, the Corporate Data Warehouse.[13] The Corporate Data Warehouse includes the covid-19 shared data resource, a set of datasets related to covid-19. It is developed and maintained by the Veterans Affairs Informatics and Computing Infrastructure.[14] We used data from the Corporate Data Warehouse and covid-19 shared data resource last extracted on 28 November 2022. The study was approved by the Institutional Review Boards of Veterans Affairs Puget Sound, Ann Arbor, Durham, Portland, and Palo Alto healthcare systems, which waived the requirement to obtain informed consent because this study was retrospective.

Study design

We designed a retrospective cohort study. Patients were eligible for inclusion on the date of sample collection for their first positive SARS-CoV-2 test. Their 30 days of outcome assessment began on that same date (index). We identified all covid-19 vaccination doses received before the index date for each patient (see definitions below).

We identified all 279 989 adults (≥18 years) who were enrolled with US Veterans Health Administration who had documentation of their first SARS-CoV-2 infection between 1 July-30 November 2021 (delta period) or between 1 January-30 June 2022 (omicron periods). Periods were defined based on tracker data from the Centers for Disease Control and Prevention.[15] We excluded infections that occurred in the calendar month of December 2021, during which omicron replaced delta in the USA. To ensure accuracy of baseline patient characteristics, we excluded 18 835 patients who did not have at least one primary care encounter in the Veterans Affairs healthcare system in the 18 months before index and at least one inpatient or outpatient encounter in the 12 months before index (supplement 4).

We identified all positive SARS-CoV-2 RNA polymerase chain reaction or antigen tests done within US Veterans Health Administration and non-US Veterans Health Administration tests documented in Veterans Affairs records. Such positive tests are identified by the Veterans Affairs National Surveillance Tool and recorded in the covid-19 shared data resource. Positive tests were those that met the Centers for Disease Control and Prevention laboratory standards by human confirmed case review.[14] Reinfections were not included in analysis and only one observation was possible per patient within and across periods. During the study time periods, patients were tested if they had covid-19 symptoms, had known exposure, or they were screened before medical procedures.

Vaccination status

Vaccination status is the primary exposure variable. We combined records of all covid-19 vaccinations from three places. Firstly US Veterans Health Administration data obtained through the covid-19 shared data resource, which document vaccinations administered within Veterans Affairs as well as vaccinations administered outside the US Veterans Health Administration and either reported to the US Veterans Health Administration electronically (eg, from pharmacies like Walgreens, CVS, Walmart; health departments; mass vaccination centers; community healthcare centers; and clinics) or entered in the electronic health records system by US Veterans Health Administration providers using templates. Secondly, community care data, which capture vaccinations administered through community care programs that serve people enrolled with the US Veterans Health Administration. Finally, Centers for Medicare and Medicaid Services claims for vaccinations received through Medicare services (from vaccine approval until 31 July 2022 at the time of extraction).

To ensure that doses that were documented in more than one source were not counted more than once, we treated two vaccine doses as duplicates if they were within seven days of each other. Patients were classified

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Table 1 | Baseline characteristics of all adults with first positive test for severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) during 1 July 2021 to 30 November 2021 (delta period), who have at least one primary care encounter in the previous 18 months, and at least one primary care encounter or inpatient admission in the past 12 months

Characteristics	All patients (n=95 336)	No vaccination (n=49 928)	Partial mRNA (n=2236)	Two doses of mRNA (n=35 994)	Three doses of mRNA (n=1691)	Complete Janssen (n=5064)
Month of infection in 2021:						
July	9928 (10.4)	6149 (12.3)	214 (9.6)	3100 (8.6)	38 (2.2)	389 (7.7)
August	29 849 (31.3)	16 613 (33.3)	773 (34.6)	10 623 (29.5)	153 (9.0)	1522 (30.1)
September	23 897 (25.1)	12 321 (24.7)	611 (27.3)	9333 (25.9)	240 (14.2)	1304 (25.8)
October	15 478 (16.2)	7226 (14.5)	332 (14.8)	6582 (18.3)	409 (24.2)	877 (17.3)
November	16 184 (17.0)	7619 (15.3)	306 (13.7)	6356 (17.7)	851 (50.3)	972 (19.2)
Age, years, mean (SD)	58.8 (16.4)	53.6 (16.0)	57.6 (16.1)	65.7 (14.6)	69.7 (11.9)	58.2 (14.2)
Age, years:						
<50	28 432 (29.8)	20 754 (41.6)	709 (31.7)	5385 (15.0)	116 (6.9)	1361 (26.9)
50 to <65	26 489 (27.8)	14 736 (29.5)	661 (29.6)	8748 (24.3)	297 (17.6)	1910 (37.7)
65 to <80	32 918 (34.5)	12 502 (25.0)	708 (31.7)	16 997 (47.2)	1002 (59.3)	1572 (31.0)
≥80	7497 (7.9)	1936 (3.9)	158 (7.1)	4864 (13.5)	276 (16.3)	221 (4.4)
Male sex	83 982 (88.1)	43 011 (86.1)	1933 (86.4)	32 604 (90.6)	1557 (92.1)	4502 (88.9)
Race:						
White	70 266 (73.7)	36 458 (73.0)	1509 (67.5)	27 012 (75.0)	1332 (78.8)	3656 (72.2)
Black	15 582 (16.3)	8280 (16.6)	513 (22.9)	5605 (15.6)	205 (12.1)	908 (17.9)
Asian	786 (0.8)	371 (0.7)	20 (0.9)	327 (0.9)	13 (0.8)	50 (1.0)
American Indian/Alaska Native	856 (0.9)	446 (0.9)	28 (1.3)	310 (0.9)	21 (1.2)	45 (0.9)
Pacific Islander/Native Hawaiian	914 (1.0)	495 (1.0)	17 (0.8)	338 (0.9)	14 (0.8)	43 (0.8)
Unknown	6932 (7.3)	3878 (7.8)	149 (6.7)	2402 (6.7)	106 (6.3)	362 (7.1)
Ethnicity:						
Non-Hispanic	83 420 (87.5)	43 293 (86.7)	1966 (87.9)	31 857 (88.5)	1521 (89.9)	4422 (87.3)
Hispanic	7455 (7.8)	4095 (8.2)	156 (7.0)	2658 (7.4)	100 (5.9)	403 (8.0)
Unknown	4461 (4.7)	2540 (5.1)	114 (5.1)	1479 (4.1)	70 (4.1)	239 (4.7)
Urban habitation	71 335 (74.8)	36 640 (73.4)	1693 (75.7)	27 815 (77.3)	1311 (77.5)	3563 (70.4)
Geographical region:						
West	22 363 (23.5)	11 735 (23.5)	482 (21.6)	8375 (23.3)	389 (23.0)	1277 (25.2)
Midwest	18 936 (19.9)	9458 (18.9)	340 (15.2)	7604 (21.1)	483 (28.6)	980 (19.4)
Northeast	12 027 (12.6)	5294 (10.6)	233 (10.4)	5403 (15.0)	353 (20.9)	693 (13.7)
South	42 010 (44.1)	23 441 (46.9)	1181 (52.8)	14 612 (40.6)	466 (27.6)	2114 (41.7)
Body mass index, mean (SD):	30.7 (6.5)	30.8 (6.5)	30.5 (6.7)	30.6 (6.4)	29.9 (6.2)	31.3 (6.7)
Body mass index:						
<18.5	950 (1.0)	467 (0.9)	32 (1.4)	391 (1.1)	16 (0.9)	40 (0.8)
18.5 to <25	15 279 (16.0)	7875 (15.8)	395 (17.7)	5862 (16.3)	315 (18.6)	765 (15.1)
25 to <30	30 961 (32.5)	16 122 (32.3)	726 (32.5)	11 839 (32.9)	620 (36.7)	1520 (30.0)
≥30	47 382 (49.7)	24 964 (50.0)	1069 (47.8)	17 697 (49.2)	731 (43.2)	2705 (53.4)
Missing	764 (0.8)	500 (1.0)	14 (0.6)	205 (0.6)	9 (0.5)	34 (0.7)
Charlson Comorbidity Index*:						
0	41 309 (43.3)	26 695 (53.5)	946 (42.3)	11 062 (30.7)	330 (19.5)	2111 (41.7)
1	19 578 (20.5)	10 252 (20.5)	456 (20.4)	7312 (20.3)	305 (18.0)	1163 (23.0)
2	13 398 (14.1)	5974 (12.0)	316 (14.1)	6012 (16.7)	282 (16.7)	739 (14.6)
3	7530 (7.9)	2865 (5.7)	171 (7.6)	3829 (10.6)	222 (13.1)	407 (8.0)
4	5111 (5.4)	1690 (3.4)	133 (5.9)	2813 (7.8)	173 (10.2)	278 (5.5)
5-6	5220 (5.5)	1627 (3.3)	117 (5.2)	3027 (8.4)	210 (12.4)	223 (4.4)
7-8	2264 (2.4)	620 (1.2)	68 (3.0)	1342 (3.7)	119 (7.0)	105 (2.1)
≥9	926 (1.0)	205 (0.4)	29 (1.3)	597 (1.7)	50 (3.0)	38 (0.8)
Care Assessment Need score centile†:						
0-30	39 776 (41.7)	26 780 (53.6)	964 (43.1)	9473 (26.3)	247 (14.6)	2151 (42.5)
31-55	22 106 (23.2)	11 330 (22.7)	438 (19.6)	8567 (23.8)	374 (22.1)	1310 (25.9)
56-75	14 930 (15.7)	5965 (11.9)	328 (14.7)	7392 (20.5)	362 (21.4)	798 (15.8)
76-90	11 705 (12.3)	3792 (7.6)	307 (13.7)	6606 (18.4)	413 (24.4)	529 (10.4)
91-95	907 (1.0)	261 (0.5)	28 (1.3)	527 (1.5)	42 (2.5)	45 (0.9)
96-100	4730 (5.0)	1191 (2.4)	131 (5.9)	2997 (8.3)	212 (12.5)	182 (3.6)
Missing	1182 (1.2)	609 (1.2)	40 (1.8)	432 (1.2)	41 (2.4)	49 (1.0)
Immunosuppressants in prior 90 days:	5693 (6.0)	2063 (4.1)	136 (6.1)	2894 (8.0)	310 (18.3)	267 (5.3)
Smoking:						
Never	36 996 (38.8)	20 119 (40.3)	810 (36.2)	13 373 (37.2)	604 (35.7)	1923 (38.0)
Former	39 182 (41.1)	18 580 (37.2)	826 (36.9)	16 731 (46.5)	841 (49.7)	2036 (40.2)
Current	14 971 (15.7)	8771 (17.6)	486 (21.7)	4564 (12.7)	169 (10.0)	917 (18.1)
Unknown	4187 (4.4)	2458 (4.9)	114 (5.1)	1326 (3.7)	77 (4.6)	188 (3.7)
Comorbidities in the prior two years:						
Alcohol dependence	19 786 (20.8)	10 604 (21.2)	504 (22.5)	7062 (19.6)	298 (17.6)	1223 (24.2)
Asthma	6809 (7.1)	3355 (6.7)	166 (7.4)	2761 (7.7)	140 (8.3)	356 (7.0)
Cancer	16 146 (16.9)	6007 (12.0)	366 (16.4)	8342 (23.2)	580 (34.3)	781 (15.4)

(*Continued*)

Table 1 | Continued

Characteristics	All patients (n=95 336)	No vaccination (n=49 928)	Partial mRNA (n=2236)	Two doses of mRNA (n=35 994)	Three doses of mRNA (n=1691)	Complete Janssen (n=5064)
Cerebrovascular disease	1517 (1.6)	550 (1.1)	45 (2.0)	793 (2.2)	47 (2.8)	75 (1.5)
Chronic kidney disease	11 656 (12.2)	4055 (8.1)	277 (12.4)	6312 (17.5)	394 (23.3)	565 (11.2)
Chronic obstructive pulmonary disease	13 775 (14.4)	5071 (10.2)	375 (16.8)	7122 (19.8)	424 (25.1)	714 (14.1)
Congestive heart failure	6338 (6.6)	2025 (4.1)	198 (8.9)	3584 (10.0)	230 (13.6)	277 (5.5)
Coronary atherosclerotic heart disease	17 374 (18.2)	6324 (12.7)	414 (18.5)	9262 (25.7)	497 (29.4)	795 (15.7)
Dementia	3326 (3.5)	1106 (2.2)	100 (4.5)	1855 (5.2)	107 (6.3)	148 (2.9)
Depression	33 226 (34.9)	17 782 (35.6)	902 (40.3)	11 925 (33.1)	530 (31.3)	1930 (38.1)
Any diabetes	29 043 (30.5)	11 707 (23.4)	674 (30.1)	14 076 (39.1)	744 (44.0)	1699 (33.6)
Drug dependence	4326 (4.5)	2278 (4.6)	199 (8.9)	1433 (4.0)	56 (3.3)	336 (6.6)
Hyperlipidemia	55 713 (58.4)	25 829 (51.7)	1247 (55.8)	24 065 (66.9)	1176 (69.5)	3142 (62.0)
Hypertension	54 735 (57.4)	23 717 (47.5)	1301 (58.2)	25 167 (69.9)	1299 (76.8)	2990 (59.0)
Obstructive sleep apnea	31 482 (33.0)	15 376 (30.8)	734 (32.8)	12 872 (35.8)	616 (36.4)	1734 (34.2)
Peripheral artery disease	8681 (9.1)	2903 (5.8)	211 (9.4)	4839 (13.4)	271 (16.0)	411 (8.1)
Post-traumatic stress disorder	24 805 (26.0)	13 926 (27.9)	652 (29.2)	8372 (23.3)	370 (21.9)	1387 (27.4)
Venous thromboembolism	2221 (2.3)	915 (1.8)	77 (3.4)	1030 (2.9)	70 (4.1)	120 (2.4)

Data are numerator (percentage), unless otherwise specified. mRNA refers to Moderna's mRNA-1273 and Pfizer-BioNTech's BNT162b2 vaccines; Janssen refers to Janssen/Johnson & Johnson's Ad26.COV2.S vaccine. SD=standard deviation.
*Lower number indicates fewer diagnoses.
†Lower number indicates less risk of hospital admission or death based on clinical characteristics.

on the basis of the type and number of vaccine doses received before testing positive for SARS-CoV-2. For no vaccination, patients received no covid-19 vaccine doses or received a single vaccine dose less than 14 days before positive SARS-CoV-2 test. For partial mRNA vaccination, patients received only one dose of mRNA (Pfizer-BioNTech (BNT162b2) or Moderna (mRNA-1273)) more than 14 days before positive SARS-CoV-2 test or received two doses but the second dose was administered within 14 days before positive SARS-CoV-2 test. People were deemed to have had two doses of mRNA if they received two doses of mRNA vaccine at least 14 days before positive SARS-CoV-2 test and had not received a third dose, or less than seven days from third dose. Patients were classified as having three doses of mRNA if they had received three doses of mRNA vaccine at least seven days before positive SARS-CoV-2 test and had not received a fourth dose, or less than seven days from fourth dose. For complete Janssen (Ad26.COV2.S), patients received one dose of this vaccine at least 14 days before positive SARS-CoV-2 test.

We excluded patients with other combinations (eg, ≥four doses mRNA or the adenovirus vector vaccine plus mRNA) because these were uncommon. We also categorized people who received mRNA vaccines as either Pfizer-BioNTech only or Moderna only, on the basis of studies suggested differences in effectiveness between them.[16 17] Instances of mixed mRNA vaccination were rare (during the study period) and excluded from analysis.

In the US Veterans Health Administration system, the two mRNA vaccine types were distributed to facilities to ensure adequate supply based on availability of product and practical considerations (eg, availability of special freezers for Pfizer-BioNTech), but without regard to facility mixture of patients. Facilities typically had only one mRNA type available at a time. Janssen was distributed once the US Food and Drug Administration emergency authorization was granted (27 February 2021). Clinicians did not systematically recommend Janssen for specific patients but patients might have selected Janssen because of a preference for the non-mRNA option or for the fewer doses required. In our analytical period, all facilities administered all three vaccines (Pfizer-BioNTech, Moderna, and Janssen) at some point.

Outcomes

The primary outcomes in the 30 days after the index date were (1) hospital admission, (2) intensive care unit admission, (3) use of mechanical ventilation, and (4) all cause mortality. Deaths occurring both within and outside of the Veterans Affairs are comprehensively captured in the Corporate Data Warehouse from various sources including Veterans Affairs inpatient files, Veterans Affairs Beneficiary Identification and Records Locator System, Social Security Administration files, and the Department of Defence.[18] Data from the Centers for Medicare and Medicaid Services included hospital admissions but did not provide information about intensive care unit admissions and ventilation; these outcomes were thus drawn from the US Veterans Health Administration records only. The reason for hospital admission is not recorded, so we could not determine which were designated as covid-19 related. However, planned procedures were cancelled for patients who tested positive for SARS-CoV-2, therefore infections identified through screening before procedures would be unlikely to be followed by hospital admission due to unrelated procedures. Additionally, patients who were admitted to hospital before the index date were not considered at risk for this outcome.

Baseline characteristics

We ascertained sociodemographic, geographical, and clinical characteristics for all Veteran patients of the Veterans Affairs healthcare system meeting inclusion for the two years before index date. We selected

Table 2 | Baseline characteristics of all adults with first positive test for severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) during 1 January 2022 to 30 June 2022 (omicron period), who have at least one primary care encounter in the previous 18 months, and at least one primary care encounter or inpatient admission in the past 12 months

Characteristics	All patients (n=184 653)	No vaccination (n=50 552)	Partial mRNA (n=4278)	Two doses of mRNA (n=56 911)	Three doses of mRNA (n=56 115)	Complete Janssen (n=8419)
Month of infection in 2022:						
January	107 596 (58.3)	32 905 (65.1)	2685 (62.8)	37 858 (66.5)	26 145 (46.6)	5825 (69.2)
February	22 764 (12.3)	7101 (14.0)	535 (12.5)	6624 (11.6)	6888 (12.3)	1023 (12.2)
March	6542 (3.5)	1712 (3.4)	150 (3.5)	1699 (3.0)	2458 (4.4)	262 (3.1)
April	6931 (3.8)	1306 (2.6)	121 (2.8)	1489 (2.6)	3374 (6.0)	201 (2.4)
May	17 377 (9.4)	3112 (6.2)	318 (7.4)	3910 (6.9)	7836 (14.0)	452 (5.4)
June	23 443 (12.7)	4416 (8.7)	469 (11.0)	5331 (9.4)	9414 (16.8)	656 (7.8)
Age (years), mean (SD)	59.7 (16.2)	54.5 (16.5)	55.7 (16.8)	57.4 (16.3)	66.4 (13.6)	55.4 (15.2)
Age (years):						
<50	50 905 (27.6)	20 063 (39.7)	1602 (37.4)	18 575 (32.6)	6835 (12.2)	2925 (34.7)
50 to <65	53 560 (29.0)	14 895 (29.5)	1247 (29.1)	17 597 (30.9)	14 545 (25.9)	3071 (36.5)
65 to <80	64 595 (35.0)	13 032 (25.8)	1138 (26.6)	16 626 (29.2)	27 599 (49.2)	2047 (24.3)
≥80	15 593 (8.4)	2562 (5.1)	291 (6.8)	4113 (7.2)	7136 (12.7)	376 (4.5)
Male sex	160 158 (86.7)	43 246 (85.5)	3581 (83.7)	48 051 (84.4)	50 330 (89.7)	7352 (87.3)
Race:						
White	125 262 (67.8)	35 404 (70.0)	2605 (60.9)	37 747 (66.3)	37 858 (67.5)	5957 (70.8)
Black	37 810 (20.5)	9287 (18.4)	1106 (25.9)	12 185 (21.4)	12 028 (21.4)	1459 (17.3)
Asian	2925 (1.6)	499 (1.0)	70 (1.6)	983 (1.7)	1087 (1.9)	118 (1.4)
American Indian/Alaska Native	1666 (0.9)	490 (1.0)	37 (0.9)	547 (1.0)	449 (0.8)	77 (0.9)
Pacific Islander/Native Hawaiian	2065 (1.1)	512 (1.0)	50 (1.2)	683 (1.2)	636 (1.1)	88 (1.0)
Unknown	14 925 (8.1)	4360 (8.6)	410 (9.6)	4766 (8.4)	4057 (7.2)	720 (8.6)
Ethnicity:						
Non-Hispanic	155 261 (84.1)	42 773 (84.6)	3562 (83.3)	47 234 (83.0)	47 621 (84.9)	7094 (84.3)
Hispanic	18 159 (9.8)	4373 (8.7)	365 (8.5)	5991 (10.5)	5750 (10.2)	749 (8.9)
Unknown	11 233 (6.1)	3406 (6.7)	351 (8.2)	3686 (6.5)	2744 (4.9)	576 (6.8)
Urban habitation	143 315 (77.6)	36 935 (73.1)	3212 (75.1)	44 626 (78.4)	45 801 (81.6)	5998 (71.2)
Geographical region:						
West	47 019 (25.5)	12 288 (24.3)	1041 (24.3)	14 811 (26.0)	14 256 (25.4)	2298 (27.3)
Midwest	32 791 (17.8)	9798 (19.4)	638 (14.9)	9117 (16.0)	10 243 (18.3)	1561 (18.5)
Northeast	28 739 (15.6)	6720 (13.3)	594 (13.9)	8294 (14.6)	10 362 (18.5)	1191 (14.1)
South	76 104 (41.2)	21 746 (43.0)	2005 (46.9)	24 689 (43.4)	21 254 (37.9)	3369 (40.0)
Body mass index, mean (SD)	30.3 (6.4)	30.3 (6.5)	29.8 (6.1)	30.7 (6.6)	30.0 (6.0)	30.9 (6.6)
Body mass index:						
<18.5	2199 (1.2)	703 (1.4)	67 (1.6)	674 (1.2)	544 (1.0)	103 (1.2)
18.5 to <25	32 368 (17.5)	9128 (18.1)	826 (19.3)	9344 (16.4)	10 126 (18.0)	1343 (16.0)
25 to <30	61 994 (33.6)	16 675 (33.0)	1359 (31.8)	18 363 (32.3)	19 958 (35.6)	2649 (31.5)
≥30	86 780 (47.0)	23 575 (46.6)	1971 (46.1)	28 109 (49.4)	25 237 (45.0)	4258 (50.6)
Missing	1312 (0.7)	471 (0.9)	55 (1.3)	421 (0.7)	250 (0.4)	66 (0.8)
Charlson Comorbidity Index*:						
0	76 476 (41.4)	25 989 (51.4)	2058 (48.1)	25 259 (44.4)	16 740 (29.8)	4006 (47.6)
1	37 383 (20.2)	10 225 (20.2)	881 (20.6)	11 711 (20.6)	11 156 (19.9)	1767 (21.0)
2	26 349 (14.3)	6174 (12.2)	543 (12.7)	7754 (13.6)	9367 (16.7)	1103 (13.1)
3	15 207 (8.2)	3099 (6.1)	288 (6.7)	4270 (7.5)	6048 (10.8)	587 (7.0)
4	10 211 (5.5)	2008 (4.0)	170 (4.0)	2821 (5.0)	4213 (7.5)	360 (4.3)
5-6	11 295 (6.1)	1952 (3.9)	199 (4.7)	3108 (5.5)	4878 (8.7)	379 (4.5)
7-8	5098 (2.8)	768 (1.5)	99 (2.3)	1324 (2.3)	2371 (4.2)	157 (1.9)
≥9	2634 (1.4)	337 (0.7)	40 (0.9)	664 (1.2)	1342 (2.4)	60 (0.7)
Care Assessment Need score centile†:						
0-30	72 848 (39.5)	25 048 (49.5)	2000 (46.8)	25 721 (45.2)	14 096 (25.1)	4110 (48.8)
31-55	42 627 (23.1)	11 269 (22.3)	867 (20.3)	12 296 (21.6)	14 172 (25.3)	1910 (22.7)
56-75	29 109 (15.8)	6419 (12.7)	537 (12.6)	7862 (13.8)	11 415 (20.3)	1058 (12.6)
76-90	23 809 (12.9)	4648 (9.2)	466 (10.9)	6374 (11.2)	9968 (17.8)	775 (9.2)
91-95	2034 (1.1)	377 (0.7)	43 (1.0)	569 (1.0)	854 (1.5)	73 (0.9)
96-100	11 314 (6.1)	1839 (3.6)	245 (5.7)	3190 (5.6)	4916 (8.8)	354 (4.2)
Missing	2912 (1.6)	952 (1.9)	120 (2.8)	899 (1.6)	694 (1.2)	139 (1.7)
Immunosuppressants in prior 90 days	13 032 (7.1)	2439 (4.8)	235 (5.5)	3207 (5.6)	5873 (10.5)	408 (4.8)
Smoking:						
Never	74 423 (40.3)	19 258 (38.1)	1709 (39.9)	23 776 (41.8)	23 071 (41.1)	3156 (37.5)
Former	71 501 (38.7)	17 651 (34.9)	1421 (33.2)	20 904 (36.7)	24 802 (44.2)	3052 (36.3)
Current	30 432 (16.5)	10 706 (21.2)	867 (20.3)	9686 (17.0)	6333 (11.3)	1842 (21.9)
Unknown	8297 (4.5)	2937 (5.8)	281 (6.6)	2545 (4.5)	1909 (3.4)	369 (4.4)
Comorbidities in the prior two years:						
Alcohol dependence	39 679 (21.5)	11 257 (22.3)	1043 (24.4)	12 649 (22.2)	10 914 (19.4)	2081 (24.7)
Asthma	14 246 (7.7)	3581 (7.1)	328 (7.7)	4419 (7.8)	4602 (8.2)	618 (7.3)

(*Continued*)

Table 2 | Continued

Characteristics	All patients (n=184 653)	No vaccination (n=50 552)	Partial mRNA (n=4278)	Two doses of mRNA (n=56 911)	Three doses of mRNA (n=56 115)	Complete Janssen (n=8419)
Cancer	26 399 (14.3)	4937 (9.8)	448 (10.5)	6872 (12.1)	11 547 (20.6)	803 (9.5)
Cerebrovascular disease	3671 (2.0)	733 (1.4)	77 (1.8)	1058 (1.9)	1449 (2.6)	134 (1.6)
Chronic kidney disease	23 926 (13.0)	4558 (9.0)	430 (10.1)	6687 (11.7)	9891 (17.6)	848 (10.1)
Chronic obstructive pulmonary disease	26 971 (14.6)	5873 (11.6)	514 (12.0)	7844 (13.8)	10 154 (18.1)	1080 (12.8)
Congestive heart failure	13 775 (7.5)	2575 (5.1)	284 (6.6)	4005 (7.0)	5521 (9.8)	547 (6.5)
Coronary atherosclerotic heart disease	34 723 (18.8)	6837 (13.5)	605 (14.1)	9775 (17.2)	14 141 (25.2)	1230 (14.6)
Dementia	7775 (4.2)	1456 (2.9)	208 (4.9)	2463 (4.3)	2934 (5.2)	255 (3.0)
Depression	68 150 (36.9)	18 773 (37.1)	1771 (41.4)	22 179 (39.0)	19 122 (34.1)	3359 (39.9)
Any diabetes	56 451 (30.6)	11 742 (23.2)	1098 (25.7)	16 362 (28.8)	21 726 (38.7)	2315 (27.5)
Drug dependence	9603 (5.2)	2917 (5.8)	353 (8.3)	3091 (5.4)	2221 (4.0)	584 (6.9)
Hyperlipidemia	108 281 (58.6)	25 514 (50.5)	2111 (49.3)	32 149 (56.5)	38 072 (67.8)	4662 (55.4)
Hypertension	108 802 (58.9)	24 565 (48.6)	2256 (52.7)	31 925 (56.1)	39 670 (70.7)	4445 (52.8)
Obstructive sleep apnea	62 478 (33.8)	14 955 (29.6)	1308 (30.6)	19 480 (34.2)	20 902 (37.2)	2731 (32.4)
Peripheral artery disease	18 112 (9.8)	3430 (6.8)	290 (6.8)	5117 (9.0)	7437 (13.3)	627 (7.4)
Post-traumatic stress disorder	51 197 (27.7)	14 813 (29.3)	1313 (30.7)	16 390 (28.8)	13 956 (24.9)	2523 (30.0)
Venous thromboembolism	4775 (2.6)	1055 (2.1)	123 (2.9)	1315 (2.3)	1799 (3.2)	181 (2.1)

Data are numerator (percentage). mRNA refers to Moderna's mRNA-1273 and Pfizer-BioNTech's BNT162b2 vaccines; Janssen refers to Janssen/Johnson & Johnson's Ad26.COV2.S vaccine.
SD=standard deviation.
*Lower number indicates fewer diagnoses.
†Lower number indicates less risk of hospital admission or death based on clinical.

30 baseline characteristics that were potentially associated with likelihood of vaccination and outcomes as confounders, described in Supplement 1. We used the patients' Charlson Comorbidity Index[19] and their Care Assessment Need Scores[20] as two cumulative measures of comorbidity burden and healthcare utilisation. Specific comorbid conditions were selected as covariates above and beyond summary measures of comorbidities if they were likely to be associated with both outcomes and vaccine choice or access and not uncommon (>2% of patients). The Veterans Affairs Centralized Interactive Phenomics Resource provided the codes from the tenth edition of the International Statistical Classification of Diseases and Related Health Problems that were used to define each comorbid condition and these were coded as present versus absent. Body mass index was also included and was based on the height and weight recorded in the electronic health records system. We obtained smoking status from the covid-19 shared data resource. We also generated an indicator of one or more prescriptions for an immunosuppressive medication in the previous 90 days (supplement 2). Supplement 13 contains an analysis of the relative effect of adjusting for each covariate on the effect estimates.

Measures of covid-19 treatments

For descriptive purposes, we included Veterans Affairs data on receipt of covid-19 pharmacotherapies, although these variables were not included in multivariable modelling as they occurred after baseline and could induce problems, such as immortal time. From pharmacy records, we identified covid-19 specific inpatient and outpatient pharmacotherapies available during the study period.

Missing data

Key information was not available for some variables included in analysis, such as race, body mass index, and smoking status. These missing data were assigned an unknown category in categorical variables. For most of the measures, such as diagnoses and treatments, variables were coded as present in the records versus not present and thus without missing data.

Statistical analysis

We used multivariable logistic regression models with a fixed effect for region to determine the association between vaccination status and each outcome. All modelling adjusted for the 30 patient characteristics. We used no vaccination or two doses mRNA as a

Table 3 | Count of 30 day outcomes by vaccination group and SARS-CoV-2 era

Outcomes	All patients	No vaccination	Partial mRNA	Two doses of mRNA	Three doses of mRNA	Complete Janssen
Delta period (1 July-30 November 2021)						
Hospital admission	12 496 (13.1)	6950 (13.9)	295 (13.2)	4445 (12.3)	242 (14.3)	510 (10.1)
Ventilator use	1835 (1.9)	1265 (2.5)	35 (1.6)	447 (1.2)	28 (1.7)	52 (1.0)
Intensive care unit admission	4218 (4.4)	2629 (5.3)	79 (3.5)	1238 (3.4)	93 (5.5)	161 (3.2)
Death	4018 (4.2)	2605 (5.2)	79 (3.5)	1127 (3.1)	60 (3.5)	137 (2.7)
Omicron period (1 January-30 June 2022)						
Hospital admission	17 383 (9.4)	5337 (10.6)	400 (9.4)	4928 (8.7)	5182 (9.2)	715 (8.5)
Ventilator use	1524 (0.8)	539 (1.1)	35 (0.8)	422 (0.7)	408 (0.7)	70 (0.8)
Intensive care unit admission	4524 (2.5)	1542 (3.1)	100 (2.3)	1274 (2.2)	1220 (2.2)	203 (2.4)
Death	3158 (1.7)	1278 (2.5)	92 (2.2)	898 (1.6)	689 (1.2)	125 (1.5)

Data are numerator (percentage). mRNA refers to Moderna's mRNA-1273 and Pfizer-BioNTech's BNT162b2 vaccines; Janssen refers to Janssen/Johnson & Johnson's Ad26.COV2.S vaccine.

Table 4 | Unadjusted and adjusted associations between vaccination group and 30 day outcomes of SARS-CoV-2 infections that occurred from 1 July-30 November 2021 (delta period) among patients in the US Veterans Health Administration system. Data are odds ratio (OR) and 95% confidence intervals, unless otherwise specified as rate

	Hospital admission			ICU admission			Ventilation			Death		
	Rate*	Crude OR	Adjusted OR†	Rate*	Crude OR	Adjusted OR†	Rate*	Crude OR	Adjusted OR†	Rate*	Crude OR	Adjusted OR†
Reference category: no vaccination‡												
No vaccination (n=49 928)	162	1	1	56	1	1	26	1	1	54	1	1
Partial (n=2236)	151	0.94 (0.83 to 1.06)	0.60‡ (0.53 to 0.69)	37	0.66‡ (0.52 to 0.82)	0.44‡ (0.35 to 0.55)	16	0.61‡ (0.43 to 0.84)	0.43‡ (0.30 to 0.60)	36	0.67‡ (0.53 to 0.83)	0.38‡ (0.30 to 0.49)
Two doses mRNA (n=35 994)	140	0.87‡ (0.84 to 0.91)	0.41 (0.39 to 0.43)	36	0.64‡ (0.60 to 0.69)	0.33‡ (0.31 to 0.36)	13	0.48‡ (0.43 to 0.54)	0.27‡ (0.24 to 0.30)	32	0.59‡ (0.55 to 0.63)	0.21‡ (0.19 to 0.23)
Three doses mRNA (n=1691)	165	1.03 (0.90 to 1.19)	0.39‡ (0.33 to 0.45)	58	1.05 (0.84 to 1.29)	0.46‡ (0.37 to 0.58)	17	0.65 (0.43 to 0.93)	0.31‡ (0.21 to 0.45)	36	0.67‡ (0.51 to 0.86)	0.20‡ (0.15 to 0.26)
Complete Janssen (n=5064)	112	0.69‡ (0.63 to 0.76)	0.51‡ (0.46 to 0.56)	33	0.59‡ (0.50 to 0.69)	0.45‡ (0.38 to 0.53)	10	0.40‡ (0.30 to 0.52)	0.31‡ (0.23 to 0.40)	27	0.51‡ (0.42 to 0.60)	0.35‡ (0.29 to 0.42)
Reference category: two doses of mRNA‡												
No vaccination (n=49 928)	162	1.15‡ (1.10 to 1.19)	2.42‡ (2.31 to 2.54)	56	1.56‡ (1.46 to 1.67)	3.00‡ (2.78 to 3.23)	26	2.07‡ (1.86 to 2.31)	3.77‡ (3.36 to 4.23)	54	1.70‡ (1.59 to 1.83)	4.78‡ (4.41 to 5.19)
Partial (n=2236)	151	1.08 (0.95 to 1.22)	1.46‡ (1.27 to 1.67)	37	1.03 (0.81 to 1.29)	1.32 (1.04 to 1.67)	16	1.26 (0.88 to 1.76)	1.63‡ (1.13 to 2.28)	36	1.13 (0.89 to 1.42)	1.84‡ (1.43 to 2.33)
Two doses mRNA (n=35 994)	140	1	1	36	1	1	13	1	1	32	1	1
Three doses mRNA (n=1691)	165	1.19 (1.03 to 1.36)	0.94 (0.81 to 1.09)	58	1.63‡ (1.31 to 2.02)	1.39‡ (1.11 to 1.73)	17	1.34 (0.89 to 1.93)	1.17 (0.78 to 1.70)	36	1.14 (0.86 to 1.47)	0.95 (0.72 to 1.24)
Complete Janssen (n=5064)	112	0.80‡ (0.72 to 0.88)	1.23‡ (1.11 to 1.36)	33	0.92 (0.78 to 1.09)	1.35‡ (1.13 to 1.60)	10	0.83 (0.61 to 1.09)	1.15 (0.85 to 1.53)	27	0.86 (0.72 to 1.03)	1.69‡ (1.40 to 2.03)
Comparison of two doses of Pfizer v Moderna vaccines												
Moderna (n=17 063)	131	1	1	34	1	1	11	1	1	34	1	1
Pfizer (n=18 877)	148	1.13‡ (1.06 to 1.20)	1.25‡ (1.17 to 1.34)	38	1.13 (1.01 to 1.27)	1.19‡ (1.06 to 1.34)	14	1.35‡ (1.12 to 1.63)	1.42‡ (1.17 to 1.73)	30	0.89 (0.79 to 1.00)	1.07 (0.95 to 1.21)
Comparison of different intervals since last vaccination§												
Two doses mRNA:												
7-90 days prior (n=1368)	112	1	1	22	1	1	10	1	1	18	1	1
91-150 days prior (n=7289)	112	1.00 (0.83 to 1.22)	0.84 (0.69 to 1.03)	36	1.68‡ (1.16 to 2.53)	1.41 (0.97 to 2.14)	14	1.41 (0.82 to 2.64)	1.14 (0.66 to 2.15)	20	1.09 (0.72 to 1.71)	0.86 (0.56 to 1.38)
151-270 days prior (n=26 157)	148	1.33‡ (1.11 to 1.59)	0.97 (0.80 to 1.18)	36	1.66‡ (1.17 to 2.47)	1.35 (0.94 to 2.01)	13	1.32 (0.79 to 2.42)	1.05 (0.62 to 1.94)	35	1.90‡ (1.30 to 2.91)	1.05 (0.71 to 1.65)

ICU=Intensive care unit.
*Rate is calculated per 1000 patient at risk months (up to one month per patient).
†Adjusted by multivariable logistic regression for 30 baseline characteristics listed in table 1. The characteristics were modelled for adjustment as shown in supplementary table 1.
‡Reflects a p<0.0125, a correction for four multiple comparisons of the primary models to p<0.05.
§Categories selected based on distribution, with longer periods not included due to small sample size.

Table 5 | Unadjusted and adjusted association between vaccination group and 30 day outcomes of SARS-CoV-2 infections that occurred from 1 January 2022 to 30 June 2022 (omicron period) among patients in the US Veterans Health Administration system. Data are odds ratio (OR) and 95% confidence intervals, unless otherwise specified as rate

	Hospital admission			ICU admission			Ventilation			Death		
	Rate*	Crude OR	Adjusted OR†	Rate*	Crude OR	Adjusted OR†	Rate*	Crude OR	Adjusted OR†	Rate*	Crude OR	Adjusted OR†
Reference category: no vaccination												
No vaccination (n=50 552)	118	1	1	32	1	1	11	1	1	26	1	1
Partial (n=4278)	103	0.87 (0.78 to 0.97)	0.66‡ (0.58 to 0.74)	24	0.76‡ (0.62 to 0.93)	0.60‡ (0.48 to 0.73)	8	0.77 (0.53 to 1.06)	0.69 (0.48 to 0.96)	22	0.85 (0.68 to 1.04)	0.65‡ (0.52 to 0.82)
Two doses mRNA (n=56 911)	94	0.80‡ (0.77 to 0.84)	0.60‡ (0.57 to 0.63)	23	0.73‡ (0.68 to 0.78)	0.57‡ (0.53 to 0.62)	8	0.69‡ (0.61 to 0.79)	0.59‡ (0.51 to 0.67)	16	0.62‡ (0.57 to 0.67)	0.43‡ (0.39 to 0.48)
Three doses mRNA (n=56 115)	101	0.86‡ (0.83 to 0.90)	0.39‡ (0.38 to 0.41)	22	0.71‡ (0.65 to 0.76)	0.37‡ (0.34 to 0.40)	7	0.68‡ (0.60 to 0.77)	0.41‡ (0.36 to 0.47)	12	0.48‡ (0.44 to 0.53)	0.22‡ (0.20 to 0.25)
Complete Janssen (n=8419)	92	0.79‡ (0.72 to 0.85)	0.70‡ (0.64 to 0.76)	25	0.79‡ (0.68 to 0.91)	0.71‡ (0.61 to 0.83)	8	0.78 (0.60 to 0.99)	0.74 (0.57 to 0.94)	15	0.58‡ (0.48 to 0.70)	0.55‡ (0.45 to 0.66)
Reference category: two doses of mRNA												
No vaccination (n=50 552)	118	1.24‡ (1.20 to 1.30)	1.66‡ (1.59 to 1.74)	32	1.37‡ (1.27 to 1.48)	1.76‡ (1.62 to 1.90)	11	1.44‡ (1.27 to 1.64)	1.71‡ (1.50 to 1.95)	26	1.62‡ (1.48 to 1.76)	2.31‡ (2.10 to 2.53)
Partial (n=4278)	103	1.09 (0.98 to 1.21)	1.09 (0.97 to 1.23)	24	1.05 (0.85 to 1.28)	1.05 (0.84 to 1.29)	8	1.10 (0.77 to 1.54)	1.17 (0.81 to 1.64)	22	1.37‡ (1.10 to 1.69)	1.51‡ (1.19 to 1.89)
Two doses mRNA (n=56 911)	94	1	1	23	1	1	8	1	1	16	1	1
Three doses mRNA (n=56 115)	101	1.07‡ (1.03 to 1.12)	0.65‡ (0.63 to 0.69)	22	0.97 (0.90 to 1.05)	0.65‡ (0.59 to 0.70)	7	0.98 (0.86 to 1.12)	0.70‡ (0.61 to 0.80)	12	0.78‡ (0.70 to 0.86)	0.51‡ (0.46 to 0.57)
Complete Janssen (n=8419)	92	0.98 (0.90 to 1.06)	1.16‡ (1.06 to 1.27)	25	1.08 (0.93 to 1.25)	1.25‡ (1.07 to 1.46)	8	1.12 (0.86 to 1.44)	1.26 (0.97 to 1.62)	15	0.94 (0.78 to 1.13)	1.26 (1.03 to 1.53)
Comparison of Pfizer v Moderna vaccines												
Two doses of Moderna (n=28 230)	90	1	1	21	1	1	7	1	1	17	1	1
Two doses of Pfizer (n=28 548)	99	1.10‡ (1.04 to 1.17)	1.34‡ (1.26 to 1.43)	24	1.14 (1.02 to 1.27)	1.32‡ (1.17 to 1.48)	8	1.25 (1.03 to 1.52)	1.39‡ (1.15 to 1.70)	15	0.92 (0.80 to 1.05)	1.16 (1.01 to 1.33)
Three doses of Moderna (n=25 457)	91	1	1	21	1	1	7	1	1	13	1	1
Three doses of Pfizer (n=27 875)	109	1.21‡ (1.14 to 1.28)	1.33‡ (1.25 to 1.42)	24	1.16 (1.03 to 1.30)	1.21‡ (1.07 to 1.36)	8	1.19 (0.97 to 1.46)	1.22 (0.99 to 1.49)	12	0.91 (0.78 to 1.06)	0.97 (0.83 to 1.14)
Comparison of different intervals since last vaccination§												
Two doses of mRNA:												
7-150 days prior (n=5721)	73	1	1	18	1	1	6	1	1	11	1	1
151-270 days prior (n=14 948)	66	0.90 (0.80 to 1.02)	1.02 (0.89 to 1.17)	17	0.93 (0.74 to 1.18)	1.06 (0.83 to 1.35)	6	1.00 (0.68 to 1.49)	1.08 (0.73 to 1.62)	10	0.93 (0.69 to 1.27)	1.14 (0.84 to 1.57)
271-365 days prior (n=27 260)	108	1.47‡ (1.32 to 1.65)	1.04 (0.92 to 1.17)	27	1.50‡ (1.22 to 1.86)	1.11 (0.89 to 1.38)	9	1.39 (0.99 to 2.03)	1.05 (0.74 to 1.53)	22	2.05‡ (1.59 to 2.71)	(1.15 0.87 to 1.53)
Three doses mRNA:												
7-90 days prior (n=22 127)	78	1	1	18	1	1	6	1	1	10	1	1
91-150 days prior (n=15 161)	115	1.48‡ (1.38 to 1.60)	1.16‡ (1.07 to 1.25)	27	1.48‡ (1.28 to 1.70)	1.17 (1.01 to 1.35)	9	1.49‡ (1.17 to 1.88)	1.18 (0.93 to 1.51)	16	1.55‡ (1.29 to 1.86)	1.31‡ (1.09 to 1.58)

ICU=Intensive care unit.
*Rate is calculated per 1000 patient at risk months (up to one month per patient).
†Adjusted by multivariable logistic regression for 30 baseline characteristics listed in table 1. The characteristics were modelled for adjustment as shown in supplementary table 1.
‡Reflects a p<0.0125, a correction for four multiple comparisons of the primary models to p<0.05.
§Categories selected based on distribution, with longer periods not included due to small sample sizes.

reference in separate models. We generated separate models for the delta and omicron periods. We further tested whether outcomes varied by type of mRNA vaccine received (Pfizer-BioNTech *v* Moderna) and by time interval since last vaccination (0-90 days, 91-150 days, 151-270 days, and 271-365 days), among people who were vaccinated only. Only a relatively small number of patients had received a third dose during the delta period, therefore, we only stratified for three versus two doses for these models in the omicron period.

Patients were not considered at risk for admission to hospital or intensive care unit, or ventilation if they were using that service at the time of their index date (eg, an admission to hospital that began before, and crossed over, the date of SARS-CoV-2 detection). Patients in such scenarios were excluded from modelling for outcomes for which they were not at risk. We examined four outcomes so we applied a correction of p=0.05/4 in interpreting p values for our primary models to account for multiple comparisons. We note that comparisons between models should be limited due to the differing reference groups.

We conducted several sensitivity and secondary analyses. We estimated Cox proportional hazards models for all outcomes as an alternative modelling strategy, censoring on date of death for non-death outcomes. We also used the primary modelling strategy to compare people with more than two mRNA vaccines to people with the initial two dose series of mRNA vaccines completed at least six months prior (ie, eligible for another dose). We generated cumulative incidence curves and descriptive statistics of days since last dose by outcome and vaccination group. We generated adjusted risk differences from estimates of the marginal probabilities from our adjusted models and further generated confidence intervals using bootstrapping.[21]

Patient and public involvement

This study is from the Veterans Affairs Covid-19 Observational Research Collaboratory, a research consortium that uses mixed methods to study covid-19 outcomes. From this consortium, we used ongoing qualitative interviews with veterans who have had covid-19, which helped to inform our research questions. We will disseminate findings through materials intended for Veterans and other patient groups, with assistance from a Veteran patient engagement group.

Results

In total, 95 336 US Veterans Health Administration patients had a qualifying SARS-CoV-2 positive test in the delta period and 184 653 patients did in the omicron period (table 1 and table 2). The demographic characteristics were similar to the US Veterans Health Administration patient population[22] in terms of being disproportionately non-Hispanic white, male, and older, although Black individuals are over represented in this sample, compared with the US population. Patients were more likely to have been vaccinated if they had an infection in the omicron period than in the delta period (134 101 (72.6%) of 184 653 *v* 45 408 (47.6%) of 95 336), and more had received a third mRNA dose by the omicron period (56 115 (30.4%) of 184 653 *v* 1691 (1.8%) of 95 336). During both periods, patients who were unvaccinated had more characteristics that are associated with lower risk of severe outcomes than did patients who were vaccinated, including lower Charlson Comorbidity Index and Care Assessment Need scores (table 1 and table 2). This finding indicates that patients' likelihood of receiving vaccination was affected by their risk for severe outcomes. Use of covid-19 treatment with drugs was rare in both periods across all vaccination groups (supplement 3).

The percentage of patients who had adverse outcomes of admission to hospital, ventilation use, intensive care unit admission, or death was lower in the omicron period than in the delta period overall and within each of the subgroups of adverse events (table 3). However, we observed similar patterns for vaccination status and outcomes across the two time periods (table 4 and table 5, supplement 9, and 12). Specifically, all vaccination types (including one dose of an mRNA vaccine) were associated with a lower risk of all adverse outcomes, compared with no vaccination, after accounting for baseline differences in clinical and demographic characteristics. Findings from Cox Proportional Hazards models were similar (supplement 10). For all primary models, χ^2 tests for the fixed effect for region indicated significant variability between regions in the association of vaccination group on the four outcomes (supplement 7).

In the delta period, receiving a partial mRNA vaccination was associated with higher odds of all outcomes except intensive care unit admission compared with two mRNA doses after multiple comparisons correction (adjusted odds ratios between 1.46 and 1.84; table 4). A third dose did not have a consistent pattern of association across outcomes compared with two doses. Receipt of the Janssen vaccine was associated with higher odds of admission to hospital (adjusted odds ratios 1.23 (95% confidence interval 1.11 to 1.36)), intensive care unit admission (1.35 (1.13 to 1.60)), and death (1.69 (1.40 to 2.03)), compared with two doses of mRNA vaccines, although lower odds of all outcomes compared with being unvaccinated (adjusted odd ratios between 0.31 and 0.51 (table 4)).

In the omicron period, results were largely similar to the delta period, but a consistent pattern emerged showing a benefit of a third dose of mRNA vaccination (table 5); although, direct comparisons between periods are limited because the comparison groups are composed of different patients. Specifically, a third dose was associated with lower odds of hospital admission (adjusted odds ratio 0.65 (95% confidence interval 0.63 to 0.99)), intensive care unit admission (0.65 (0.59 to 0.70)), ventilation use (0.70 (0.61 to 0.80)), and death (0.51 (0.46 to 0.57)) compared with

two doses. This finding persisted in the sensitivity analyses that excluded patients who were less than 180 days after their second dose, and thus not yet eligible for a third dose (supplement 11).

Compared with two doses of Moderna, prior vaccination with two doses of Pfizer was associated with higher odds of hospital admission, intensive care unit admission, and ventilation use in both delta and omicron periods (table 4 and table 5). Also, three doses of Pfizer was associated with higher odds of hospital admission (adjusted odds ratio 1.33 (95% confidence interval 1.25 to 1.42)) and intensive care unit admission (1.21 (1.07 to 1.36)) than three doses of Moderna in the omicron period.

Among people who received two doses of a mRNA vaccine, a longer time interval since last vaccination did not appear to be associated with worse outcomes after adjustment for baseline characteristics, even when this time extended as long as 271-365 days since second dose vaccination (table 4 and table 5). Among people who received three doses of mRNA vaccination, increasing time since last vaccination from 0-90 days to 91-150 days was associated with higher odds of hospital admission (adjusted odds ratio 1.16 (95% confidence interval 1.07 to 1.25)) and death (1.31 (1.09 to 1.58)) but not intensive care unit admission or ventilation in the omicron period.

Discussion

Principal findings

In US Veterans who tested positive for SARs-CoV-2 during periods of predominant delta and omicron variant circulation, vaccination was associated with a significantly reduced risk of severe and fatal outcomes. This finding was consistently true across all doses of mRNA vaccination examined (one to three doses), as well as for the advenovirus vector by Janssen, although the different vaccination types were not equivalent. These findings extend an earlier study of US veterans who had infections during January-October 2021, which found that vaccination broadly was associated with lower risk of mortality among people who were infected.[23] The findings support the continued importance of vaccination as a key tool in reducing morbidity and mortality from covid-19, even as treatment with drugs become more widespread in use. Important context to these findings is that the population using US Veterans Health Administration services have many risk factors for poor outcomes of SARS-CoV-2 infection because they are predominantly male, older, and have a high prevalence of multimorbidity. Although this study elucidates the role of vaccines among particularly susceptible populations, results might not generalise to populations who are less at risk.

A third mRNA vaccine dose was associated with a lower risk of all outcomes of infection (admission to hospital or the intensive care unit, use of ventilation, and death) in the omicron period compared with two doses, but not as clearly in the delta period. The scarcity of a protective effect in the delta period might be due to residual confounding. Specifically, third doses were uncommon in this period. Our descriptive data show that uptake was fastest for patients at the high levels of risk for adverse outcomes of infection. This difference in uptake likely extended to ways that we could not measure. Alternatively, differences between variants, such as the lower pathogenicity and severity of the omicron variant,[24 25] could explain this finding. Residual confounding related to which patients received third doses earliest after approval might also have affected the comparison between more recent and less recent third doses during the omicron period.

Comparison with other studies

This study adds important vaccine-specific information to an emerging literature on the benefits of covid-19 vaccination. Among healthcare workers, two (adjusted odds ratio of 0.25) or three (0.16) doses of mRNA vaccination was associated with lower odds of persistent symptoms of covid-19 past acute illness (known as long covid) compared with being unvaccinated.[26] In another studies of veterans affairs, prior vaccination was associated with lower probability of many types of persistent symptoms, such as coagulation and other hematological symptoms, musculoskeletal, and pulmonary.[23]

Patients who had received two doses of the Pfizer-BioNTech vaccine had worse outcomes than did people who had received two doses of the Moderna vaccine in both periods. These results are consistent with previous studies, suggesting that primary vaccination with Moderna is more effective than primary vaccination with Pfizer-BioNTech.[16 17 27] Each dose of Moderna's mRNA-1273 contains more than three times the dose of mRNA than Pfizer-BioNTech's BNT162b2 (100 µg versus 30 µg), which might elicit greater or longer lasting immune responses. Other differences include the specific mRNA sequence used, potential differences in tolerability, the composition of liquid microspheres, and the ratio of lipids to mRNA. Whether these differences in outcomes between the two mRNA vaccines persist after a third dose in the omicron period is still unclear. We found that people who had received three doses of Pfizer vaccine had significantly higher odds of being admitted to hospital and the intensive care unit than did recipients of three doses of Moderna in the omicron period. Some studies reported that the third dose effectiveness against infection of Moderna was slightly higher than Pfizer-BioNTech,[28 29] but others did not agree.[30] Further work might identify whether the ideal spacing between booster doses varies between mRNA vaccine types.

We found little evidence of the effect of primary mRNA vaccination in preventing adverse outcomes after infection waning over time in either period. Even people who received their second mRNA vaccine 271-365 days before infection did not appear to have worse outcomes than did those who received their second dose 0-150 days before becoming infected. The exception was that we did find that risk of hospital admission and death (but not intensive care

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unit admission or ventilation) appeared to wane for patients who had received three mRNA vaccine doses when comparing those whose last dose was 91-150 day before infection to those whose last dose was 7-90 days before infection. Prior studies have showed declining vaccine effectiveness over time.[31-36] However, these studies have estimated vaccine effectiveness among individuals who were infected and those who were not, which combines the effect of reduced susceptibility to infection with reduced risk of worse outcomes if infected. By contrast, we examined the association of vaccine status with outcomes among only people who had been infected. Our findings suggest that protection from poor outcomes, once infected, might wane slower than protection from infection.

Strengths and limitations of this study

This study benefited from a large national sample of a population at high risk for poor outcomes of covid-19 illness. The study also had several key limitations. Direct comparisons between the delta and omicron periods are limited. Our veteran population was mainly male, with high proportions of multimorbidity. The ethnic and socioeconomic diversity in our population allowed a more robust assessment of under-represented groups in research, including people who are at a high risk to poor outcomes. We focused on 30 day outcomes to minimize including events unrelated to infection, but protracted deaths were not assessed. We were not able to measure some outcomes related to admission to hospital that occurred outside of the Veterans Affairs system, although deaths were ascertained regardless of location. The sample did not include individuals who had SARS-CoV-2 infection who were not tested or documented in the Veterans Affairs system, and home testing became increasingly common nationally during this time.[37] A substantial number of infections might be missed as a result, particularly those resulting in no or mild symptoms or among patients otherwise not engaging in medical care, and the effect of vaccination on outcomes might be different for infections not recorded in medical records. Because vaccination has a protective effect against documented infection,[1] people who become infected who were vaccinated might be more susceptible to infection and poor outcomes, including in ways not measured (eg, due to genetic factors).[38]

Conclusions

We found that breakthrough SARS-CoV-2 infections were of generally lower severity and less likely to result in death than infections among unvaccinated individuals after accounting for many risk factors for poor outcomes. The findings support the importance of vaccination as a strategy in mitigating the harms of covid-19 beyond its role in preventing infection. Although all doses and types of vaccination were associated with better outcomes than being unvaccinated, data from the omicron period of infections suggest the largest benefit came from a third dose of mRNA vaccinations and from Moderna over Pfizer-BioNTech vaccines.

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Ethical approval: The study was approved by the Institutional Review Boards of Veterans Affairs Puget Sound, Ann Arbor, Durham, Portland and Palo Alto healthcare systems, which waived the requirement to obtain informed consent because this was a retrospective study.

Data sharing: Data used in the study are available to researchers through the Department of Veterans Affairs. See Method section for details of data systems and Appendix for statistical code.

The lead author (ASBB) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Dissemination to participants and related patient and public communities: We will disseminate findings through materials intended for Veterans and other patient groups, with assistance from a Veteran patient engagement group.

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Web appendix: Online appendix