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MAJOR ARTICLE

Protection from COVID-19 mrna vaccination and prior SARS-cov-2 infection against COVID-19–associated encounters in adults during Delta and Omicron predominance

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[2]Partners contributing data on medical events and estimated dates of Omicron predominance were in Indiana (December 26), Oregon (December 24), Texas (December 16), Utah (December 24), and Washington (December 24).
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***Background*:** Data assessing protection conferred from COVID-19 mRNA vaccination and/or prior SARS-CoV-2 infection during Delta and Omicron predominance periods in the U.S. are limited.

***Methods*:** This cohort study included persons ≥18 years who had ≥1 healthcare encounter across four health systems and had been tested for SARS-CoV-2 before August 26, 2021. COVID-19 mRNA vaccination and prior SARS-CoV-2 infection defined the exposure. Cox regression estimated hazard ratios (HRs) for the Delta and Omicron periods; protection was calculated as (1-HR)x100%.

***Results*:** Compared to unvaccinated and previously uninfected persons, during Delta predominance, protection against COVID-19-associated hospitalizations was high for those 2- or 3-dose vaccinated and previously infected, 3-dose vaccinated alone, and prior infection alone (range:91%-97%, with overlapping 95% confidence intervals (95%CIs)); during Omicron predominance, estimates were lower (range:77%-90%). Protection against COVID-19-associated emergency department/urgent care (ED/UC) encounters during Delta predominance was high for those exposure groups (range:86%-93%); during Omicron predominance, protection remained high for those 3-dose vaccinated with or without a prior infection (76% (95%CI=67%-83%) and 71% (95%CI=67%-73%), respectively).

***Conclusions*:** COVID-19 mRNA vaccination and/or prior SARS-CoV-2 infection provided protection against COVID-19-associated hospitalizations and ED/UC encounters regardless of variant. Staying up-to-date with COVID-19 vaccination still provides protection against severe COVID-19 disease, regardless of prior infection.

Key words: COVID-19 vaccination; prior SARS-CoV-2 infection; protection; COVID-19-associated hospitalizations; Omicron variant

INTRODUCTION

Prior SARS-CoV-2 infection or COVID-19 vaccination provides protection against subsequent moderate and severe COVID-19 disease (1-6). The SARS-CoV-2 B.1.1.529 (Omicron) variant emerged in the United States in mid-December 2021 and resulted in high reinfection and breakthrough infection rates (7, 8). Studies have examined the protection induced from prior infection and/or vaccination against laboratory-confirmed SARS-CoV-2 infections (1, 9-11) and COVID-19–associated hospitalizations during Omicron predominance (10-12). However, data evaluating the protective effect of vaccination and/or prior infection in both the Delta and Omicron predominance periods in the United States are limited.

The Centers for Disease Control and Prevention (CDC), in collaboration with nine U.S. healthcare systems and research centers with integrated medical, laboratory, and vaccination records, established the VISION Network to assess COVID-19 vaccine effectiveness. Our objective for this analysis was to assess and compare the protection conferred from COVID-19 mRNA vaccination and/or prior SARS-CoV-2 infection against laboratory-confirmed COVID-19–associated emergency department/urgent care (ED/UC) encounters and hospitalizations in adults during periods of Delta and Omicron predominance.

METHODS

Study Population and Design

Within the VISION Network[1], four sites (BSWH, IH, KPNW, and RG) contributed longitudinal data to construct a patient cohort of adults aged ≥18 years who had ≥1 healthcare encounter in the year prior to August 26, 2021. For IH and KPNW, adults were also required to have active membership in the system's health plan during the study period.

The study period during Delta predominance began August 26, 2021, 14 days after the first U.S. recommendation for a third mRNA COVID-19 primary vaccine dose in immunocompromised persons (13). The dates when the Omicron variant became predominant were determined for each study site beginning on the date that the Omicron variant accounted for >50% of sequenced isolates in each medical facility's state and in national genomic surveillance[2] (5). Within each variant predominance period, two cohorts were created to differentiate follow-up time up until the occurrence of a COVID-19–associated ED/UC encounter or hospitalization. Follow-up for the Omicron analysis continued through June 13, 2022, the last date of data extraction. Patients were followed until the occurrence of a COVID-19–associated ED/UC encounter or hospitalization, death, end of the study period, or receipt of a fourth mRNA vaccine dose,

whichever occurred first. For those who had received one mRNA dose at the start of the study or when the Omicron variant became predominant and later received a second mRNA dose, follow-up started two weeks after receipt of the second dose.

We limited the analysis to patients who had ≥1 SARS-CoV-2 test (regardless of result) before August 26, 2021. Immunocompromised patients were identified by previously published diagnosis codes (14).

Outcomes

The outcomes were ED/UC encounters and hospitalizations with a COVID-19–like illness diagnosis and a positive molecular test for SARS-CoV-2 within 14 days before or 72 hours after the medical encounter (6).

Exposure variable

Our six-level time-varying exposure variable was defined based on both COVID-19 vaccination status and prior SARS-CoV-2 infection (Table S1). Vaccination status was obtained via electronic health records (EHRs) and state immunization registries. Prior infection for each variant predominance period was ascertained from test results documented in EHRs, and linked records with the state health department and public health testing sites (including retail pharmacies) for one site (RG), using rapid antigen or molecular assays. The index test date was defined as the date of specimen collection associated with the most recent positive SARS-CoV-2 test result within the 14 days prior to the COVID-19-associated ED/UC encounter or hospitalization, or the date of the encounter if testing only occurred after the admission or encounter date. Adults were considered unvaccinated if no COVID-19 vaccine doses were documented, 2-dose mRNA vaccinated if the second dose of an mRNA vaccine (BNT162b2 or mRNA-1273) was received ≥14 days before the index test date, and 3-dose mRNA vaccinated if the third dose of an mRNA vaccine was received ≥7 days before the index test date (15). For each vaccination status, separate exposure levels were created to distinguish between those with and without a documented prior infection. Adults were considered to have a prior infection if the earliest prior positive SARS-CoV-2 test result occurred ≥90 days before the index test date during either Delta or Omicron predominance; persons who had a positive test <90 days before the index date did not start contributing person-time until the 90th day after the positive result (16). Adults were considered to not have a documented prior infection if they had been tested since March 1, 2020 and had no documented positive test results during the study period. Recipients of Ad26.COV2 (Janssen [Johnson & Johnson]) and persons who were not classified into any of the six-level exposure levels (e.g., persons who only had one mRNA dose documented during the entire study period) were excluded.

Statistical analysis

Patients' characteristics were compared across exposure groups; a standardized mean difference of >0.2 was considered noteworthy (17). Kaplan-Meier estimates (18) graphically displayed the cumulative incidence of COVID-19-associated ED/UC encounters and hospitalizations for each variant predominance period.

Hazard ratios comparing the exposure groups with respect to COVID-19–associated ED/UC encounters and hospitalizations were estimated using Cox proportional hazards models adjusting for age, sex, race/ethnicity, total number of underlying conditions, and geographic region *a priori*. The adjusted hazard ratios (aHR) compared the reference group (unvaccinated adults without a documented prior infection) with each of the other five exposure groups defined by vaccination and prior infection; each comparison was estimated separately. We calculated measures of protection using (1-aHR)x100%, analogous to vaccine effectiveness.

Three secondary analyses were conducted. First, to account for the timing since the most recent immunizing event (i.e., prior infection or last vaccine dose), we distinguished the exposure groups between outcomes that occurred <150 or ≥150 days since the most recent immunizing event (Table S1). Second, we refined exposure groups to account for the order of immunizing events (Table S1). Persons with infections that occurred in between mRNA doses were excluded from this analysis. Third, we limited our main analysis to patients without immunocompromising conditions. All analyses were conducted using SAS software version 9.4 (Cary, NC). This study was reviewed and approved by the Westat, Inc. institutional review board, to which participating sites cede review.[3]

RESULTS

Participant characteristics

After applying the eligibility criteria from the four contributing sites (Figure S1), 1,303,547 and 1,303,559 adults were included in the cohort followed until a COVID-19-associated ED/UC encounter or hospitalization, respectively, during Delta predominance; within both cohorts, most were women (61%), aged 18–49 years (50%), and non-Hispanic White (71%); 58% had underlying conditions, and 11%-12% had immunocompromising conditions (Tables 1-2). Among persons with immunocompromising conditions, 22% were 3-dose mRNA vaccinated. Characteristics of the 1,442,026 and 1,442,080 adults followed until a COVID-19-associated ED/UC encounter or hospitalization, respectively, during Omicron predominance were similar (Figure S2, Tables 3-4). Among persons with immunocompromising conditions, 34% were 3-dose mRNA vaccinated.

Exposure status

Within both cohorts followed during Delta predominance, 41% adults were unvaccinated, 43% had received two mRNA doses, and 16% had received three mRNA doses; 18% had a documented SARS-CoV-2 infection ≥90 days before the index date of the COVID-19-associated encounter. Distributions of vaccination and prior infection statuses were similar within both cohorts during Omicron predominance, though the proportions of 2-dose mRNA vaccinated adults decreased to 30% and of 3-dose mRNA vaccinated adults increased to 26%. Month of the index test dates associated with COVID-19–associated ED/UC encounters and hospitalizations varied across exposure groups during Delta predominance (Tables 1-2, respectively), though the distribution of month of index test dates for all encounters during Omicron predominance was more similar across exposure groups, with higher proportions in January 2022 (Tables 3-4).

Protection against COVID-19–associated Emergency Department and Urgent Care Encounters

During Delta predominance, cumulative incidence of COVID-19–associated ED/UC encounters gradually increased over time. Incidence was consistently highest among unvaccinated adults without a documented prior infection and lowest for 2- or 3-dose mRNA vaccinated adults with a prior infection (Figure S3). Compared to unvaccinated adults without a documented prior infection, protection against COVID-19–associated ED/UC encounters was high and similar for those 2- or 3-dose mRNA vaccinated with a prior infection, and 3-dose mRNA vaccinated alone (range: 91%–98%, with overlapping 95% confidence intervals (CIs)), though point estimates for those 2- or 3-dose vaccinated and previously infected were higher at 94% and 98%, respectively (Figure 1). 2-dose mRNA vaccinated adults without a prior infection had lower protection at 72% (95%CI=70%–74%), with a median time from the second dose to the encounter of 259 days (Table 1).

Since the beginning of Omicron predominance, cumulative incidence quickly peaked by 40 days and plateaued for the remaining follow-up period. Incidence was consistently highest for unvaccinated or 2-dose mRNA vaccinated adults without a prior infection and lowest for 3-dose mRNA vaccinated adults with or without a prior infection. Within each exposure group, cumulative incidence of ED/UC encounters was higher during Omicron predominance relative to Delta predominance (Figure S3). Compared to unvaccinated adults without a documented prior infection, protection from 3-dose mRNA vaccination with a documented prior infection remained high at 76% (95%CI=71%–80%). Lower protection was observed from 3-dose mRNA doses without a prior infection (66% (95%CI=64%–69%), 2 mRNA doses with a prior infection (62% (95%CI=58%–66%)), and prior infection alone (37% (95%CI=31%–41%)). Protection was lowest for those 2-dose mRNA vaccination without a documented prior infection (18% (95%CI=14%–22%)), with a median time from the second dose to the encounter of 258 days (Table 3). Within each exposure group, protection was lower during Omicron predominance

compared to Delta predominance, though the decline in protection was smallest for those 3-dose mRNA vaccinated (Figure 1).

Protection against COVID-19–associated Hospitalizations

During Delta predominance, cumulative incidence of COVID-19-associated hospitalizations was lower relative to COVID-19–associated ED/UC encounters within the same period, though trends were otherwise similar (Figure S4). Compared to unvaccinated adults without a documented prior infection, protection against COVID-19–associated hospitalizations was high and similar for those 2- or 3-dose mRNA vaccinated with a prior infection, 3-dose mRNA vaccinated alone, and prior infection alone (range: 91%–96%), though point estimates for those 2- or 3-dose vaccinated with a previous infection were higher at 96% and 95%, respectively (Figure 2). Protection was lower for those only 2-dose mRNA vaccinated at 73% (95%CI=70%–75%), with a median time from the second dose to the hospitalization of 258 days (Table 2).

During Omicron predominance, cumulative incidence of COVID-19–associated hospitalizations were lower relative to Delta predominance, yet still peaked by 50 days since Omicron predominance began and then plateaued. Incidence remained highest for the unvaccinated adults with no documented prior infection and lowest for adults who were 3-dose mRNA vaccinated with a prior infection (Figure S4). Protection was similar for those 2- or 3-dose mRNA vaccinated and previously infected, 3-dose vaccinated alone, and prior infection alone (range: 76%–90%, with overlapping 95% CIs), though the point estimate for those 3-dose vaccinated with a prior infection was highest at 90% (Figure 2). Protection was lowest for those 2-dose mRNA vaccination without a documented prior infection (39% (95%CI=33%–44%)), with a median time from the second dose to the encounter of 282 days (Table 1). Within each exposure group, protection was lower during Omicron predominance compared to Delta predominance, though the decline in protection was smallest for those 3-dose mRNA vaccinated (Figure 2).

Secondary analyses

In a secondary analysis differentiating time since the last immunizing event, protection against COVID-19–associated ED/UC encounters and hospitalizations during Delta predominance was higher for those 2-dose mRNA vaccinated alone when the encounter occurred <150 days since second dose receipt compared to when the encounter occurred ≥150 days since second dose receipt (Tables S2-S3). Similarly, higher protection against COVID-19–associated ED/UC encounters and hospitalizations during Omicron predominance was observed for those 3-dose mRNA vaccinated alone with more recent second dose receipt compared to more distal receipt (Tables S2-S3). Protection against COVID-19–associated ED/UC encounters during Omicron predominance was also higher for those only previously infected with more recent infection and for those 3-dose mRNA vaccinated with a documented prior infection with more

recent immunizing event (each respectively compared to more distal events) (Table S2). Otherwise, during both variant predominance periods, protection against COVID-19–associated ED/UC encounters and hospitalizations was similar for those 2-dose mRNA vaccinated with a documented prior infection regardless of when the last immunizing event occurred (Table S2-S3).

In another secondary analysis differentiating the order of immunizing events, protection against COVID-19–associated ED/UC encounters during Omicron predominance was higher in those 2-dose mRNA vaccinated and were subsequently infected compared to those infected who subsequently received two mRNA doses. Otherwise, protection was similar whether the infection occurred before or after receipt of two or three mRNA doses (Table S2). Protection against COVID-19–associated hospitalizations during Omicron predominance was similar whether the infection occurred before or after receipt of two mRNA doses (Table S3).

In a final secondary analysis excluding immunocompromised patients, protection against COVID-19–associated ED/UC encounters and hospitalizations during both variant predominant periods were overall similar to that in the main analysis (Tables S2-S3).

DISCUSSION

Within a cohort of over 1.2 million adults across four health systems, unvaccinated persons without a documented prior infection were at highest risk for COVID-19–associated ED/UC encounters and hospitalizations, whereas those with immunity from infection and vaccination (including those who had received boosters) had the lowest risk. Protection from COVID-19 mRNA vaccination and/or prior SARS-CoV-2 infection against COVID-19–associated hospitalizations regardless of variant was high. This pattern was consistent for COVID-19–associated ED/UC encounters during Delta predominance. During Omicron predominance, protection was highest for those 3-dose mRNA vaccinated with or without a prior infection, highlighting the benefit of staying up-to-date regardless of prior infection history. Within each exposure group, protection was lower during Omicron predominance than Delta predominance, though the decline was smallest for those 3-dose mRNA vaccinated.

In this study, protection against COVID-19–associated hospitalizations was similar and high across combinations of mRNA vaccination and/or prior infection during Delta and Omicron predominance, except for 2-dose mRNA vaccination alone. Previous studies examining combinations of prior infection and vaccination both before and during Omicron predominance similarly report conferred high protection against hospitalization compared to each study's respective referent group (10-12, 19, 20), acknowledging that disease due to Omicron variant was less likely to result in hospitalization than Delta variant (21-23). However, in our study, protection conferred from 2-dose mRNA vaccination alone was lower than reported in other studies, especially during Omicron predominance, but likely reflects waning immunity from a

more distal receipt of a second dose (5, 24-26). We also observed that within each exposure group, protection was lower during Omicron predominance than during Delta predominance, though the decline was smallest for those 3-dose mRNA vaccinated. In another study, protection was similar for 2- or 3-dose vaccinated and previously infected adults during Delta and Omicron predominance, and all other combinations of prior infection and vaccination provided similar or lower protection during Omicron predominance relative to Delta predominance (11). Findings from both studies are consistent with evidence indicating that the number of immunizing events correlated with the quality and breadth of neutralizing antibody response, including against the Omicron variant, (27) and that neutralization of Omicron appeared to be best preserved in persons who were both previously infected with pre-Omicron variants and vaccinated (28). Our findings were consistent with similar studies showing that COVID-19 mRNA vaccination with or without infection and prior SARS-CoV-2 infection alone provides protection against subsequent COVID-19–associated encounters.

Our findings continue to highlight the benefit of staying up-to-date with recommended COVID-19 vaccination schedules, regardless of SARS-CoV-2 infection history. For persons without a documented prior infection, a third dose provided substantial protection compared to unvaccinated persons, and that protection was higher than that conferred from receipt of two mRNA doses alone (relative to unvaccinated persons), particularly during Omicron predominance, as consistent with other literature (5, 7, 24, 29). In addition, during Omicron predominance, a third dose provided additional protection against both COVID-19–associated ED/UC encounters and hospitalizations for previously infected persons compared to unvaccinated and previously uninfected persons. That protection was also similar/higher than the protection conferred from 2-dose mRNA vaccination and prior infection (relative to unvaccinated and previously uninfected persons), also consistent with literature (30).

Compared to COVID-19–associated ED/UC encounters, we observed that protection against COVID-19–associated hospitalization was generally higher and more consistent across exposure groups, especially during Omicron predominance. This finding suggests that protection against severe illness might be more robust and/or persist for a longer time, even as protection against comparatively more moderate illness wanes. This pattern has previously been demonstrated in studies comparing protection against SARS-CoV-2 infection vs. COVID-19–associated hospitalization (10-12), although other comparable data on moderate COVID-19 (including COVID-19–associated ED/UC encounters) are sparse.

Among adults with vaccine- and infection-induced immunity, we found that the order of immunizing events did not overall impact the magnitude of protection against COVID-19–associated encounters, though the occurrence of few events within some exposure groups limited a more thorough evaluation. The higher protection against COVID-19–associated ED/UC encounters during Omicron predominance in those 2-dose mRNA vaccinated who were subsequently infected may reflect a more recent infection (and thus conferring higher protection) relative to the second dose receipt in those infected who subsequently received two mRNA

doses. Other epidemiologic and in-vitro studies similarly observed that order did not impact protection against subsequent SARS-CoV-2 infection (9-11, 31). Although we sought to distinguish between more recent and more distal protection across combinations of immunizing events, more formal evaluations are needed to understand duration of protection from both types of immunity against moderate and severe COVID-19 as well as against emerging variants.

This analysis is subject to several limitations. First, although cohort selection was limited to adults engaged in care at partners' medical facilities to maximize data completeness, including about SARS-CoV-2 testing, we were unable to capture results primarily performed outside network facilities, including at-home SARS-CoV-2 testing. Thus, some positive SARS-CoV-2 test results might have been missed, especially if testing practices (including increased at-home testing) changed during Omicron predominance (32). Within our data, testing rates were consistently highest among 3-dose mRNA vaccinated persons and lowest among unvaccinated persons during the study period (Figure S5), resulting in detection of an infection differing by vaccination status; consequently, protection across all exposure groups could be underestimated if some unvaccinated and previously uninfected persons had infections that were not detected. However, we did not observe differences in testing rates associated with COVID-19–associated ED/UC encounters or hospitalizations by vaccination status, which may indicate non-differential misclassification. Second, residual confounding may exist because the study did not measure or adjust for behavioral differences that could modify the risk of the outcome (e.g., masking, socially distancing). Finally, results might not be generalizable to patients who have different access to medical care or different care-seeking or testing behaviors, particularly outside of the five states covered.

Within this U.S.-based study, COVID-19 mRNA vaccination with or without history of prior SARS-CoV-2 infection provided protection against COVID-19–associated hospitalizations and ED/UC encounters regardless of variant. Although infection-induced immunity provides protection, SARS-CoV-2 infection can cause severe disease, death, and long-term morbidity. COVID-19 vaccination is safe and effective at preventing severe COVID-19 disease, and staying up-to-date continues to provide protection, regardless of history of prior infection. COVID-19 vaccination also enhances protection in persons who have been previously infected.

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Table 1. Descriptive characteristics of persons aged ≥18 years included in the cohort during Delta predominance followed until COVID-19-associated emergency department/urgent care (ED/UC) encounter, overall and by exposure status— 5 states, August 2021 – June 2022

	No. (column %)							
	Entire cohort	Unvaccinated without documented prior infection	Unvaccinated with documented prior infection[1]	2-dose mRNA vaccinated[2] without documented prior infection	2-dose mRNA vaccinated[2] with documented prior infection[1]	3-dose mRNA vaccinated[2] without documented prior infection	3-dose mRNA vaccinated[2] with documented prior infection[1]	Standardized mean difference
Total number of person-time intervals[4]	1,569,173	501,671	140,706	565,034	108,954	222,589	30,219	
Sex								0.02
Male	611619 (39)	196348 (39)	57929 (41)	215035 (38)	42654 (39)	87579 (39)	12074 (40)	
Female	957367 (61)	305262 (61)	82759 (59)	349930	66290 (61)	134984	18142 (60)	

				(62)		(61)		
Other/Unknown	187 (0)	61 (0)	18 (0)	69 (0)	10 (0)	26 (0)	3 (0)	
Age group, years								0.35
18-49	779538 (50)	300765 (60)	90516 (64)	250488 (44)	55461 (51)	71643 (32)	10665 (35)	
50-64	398073 (25)	107020 (21)	30383 (22)	156342 (28)	31011 (28)	63787 (29)	9530 (31)	
65-74	234338 (15)	54628 (11)	11725 (8)	94903 (17)	13760 (13)	53160 (24)	6162 (20)	
75-84	117844 (7)	28015 (6)	5736 (4)	48051 (8)	6441 (6)	26710 (12)	2891 (10)	
≥85	39380 (2)	11243 (2)	2346 (2)	15250 (3)	2281 (2)	7289 (3)	971 (3)	
Race/Ethnicity								0.22
Hispanic	162982 (10)	55732 (11)	21641 (15)	51978 (9)	16953 (16)	13492 (6)	3186 (10)	
White, Non-Hispanic	1114156 (71)	337714 (67)	87704 (62)	417054 (74)	71500 (66)	177963 (80)	22221 (73)	
Black, Non-Hispanic	192931 (12)	82203 (16)	24462 (17)	54639 (10)	12819 (12)	15774 (7)	3034 (10)	

Other[5], Non-Hispanic	99104 (6)	26022 (5)	6899 (5)	41363 (7)	7682 (7)	15360 (7)	1778 (6)	
Presence of at least one underlying condition[6]								0.26
Yes	903476 (58)	246594 (49)	68101 (48)	350772 (62)	65132 (60)	152395 (68)	20482 (68)	
No	665697 (42)	255077 (51)	72605 (52)	214262 (38)	43822 (40)	70194 (31)	9737 (32)	
Presence of immunocompromised condition[7]								0.12
Yes	181249 (12)	46908 (9)	10421 (7)	72021 (13)	11239 (10)	36301 (16)	4359 (14)	
No	1387924 (88)	454763 (91)	130285 (93)	493013 (87)	97715 (90)	186288 (84)	25860 (86)	
COVID-19 Vaccinations								5.19
Unvaccinated	642377 (41)	501671 (100)	140706 (100)	0 (0)	0 (0)	0 (0)	0 (0)	

Moderna	324906 (21)	0 (0)	0 (0)	207425 (37)	36885 (34)	71821 (32)	8775 (29)	
Pfizer-BioNTech	578203 (37)	0 (0)	0 (0)	356626 (63)	71909 (66)	131301 (59)	18367 (61)	
Combination of mRNA products	23687 (1)	0 (0)	0 (0)	983 (0.2)	160 (0.1)	19467 (9)	3077 (10)	
ED/UC encounters with laboratory-confirmed COVID-19-like illness[8]	3866 (0.2)	2652 (0.5)	108 (0.1)	996 (0.2)	38 (0)	70 (0)	2 (0)	0.09
Month of index test date[9], among persons with COVID-19-associated ED/UC encounters								0.87
August 2021	252 (7)	194 (7)	4 (4)	52 (5)	1 (3)	1 (1)	0 (0)	
September 2021	1150 30)	852 (32)	19 (18)	271 (27)	5 (13)	3 (4)	0 (0)	

October 2021	703 (18)	483 (18)	10 (9)	198 (20)	3 (8)	8 (11)	1 (50)	
November 2021	822 (21)	538 (20)	22 (20)	234 (24)	8 (21)	20 (29)	0 (0)	
December 2021	939 (24)	585 (22)	53 (49)	241 (24)	21 (55)	38 (54)	1 (50)	
Time from most recent immunizing event to COVID-19-associated ED/UC encounter, median days (interquartile range (IQR))	-	-	384 (280-466)	259 (202-313)	235 (159-283)	105 (68-170)	85 (60-129)	

Abbreviations: Emergency Department (ED), Urgent Care (UC)

[1]Prior infection was defined as having a positive test result from rapid antigen or molecular assays performed ≥90 days before the index date of the COVID-19-associated encounter.

[2]Vaccination was defined as having received the listed number of doses of an mRNA-based COVID-19 vaccine ≥14 days before the medical event index date.

[3]Standardized mean difference calculation compared characteristics across all six exposure groups. For the six-level exposure variable, a single standardized mean difference (SMD) was calculated by averaging the absolute SMDs obtained from pairwise comparison of each exposure category versus unvaccinated without documented prior infection. Specifically, it was calculated as the average of the absolute value of the SMDs for 1) unvaccinated with documented prior infection versus unvaccinated without documented prior infection, 2) 2-dose mRNA vaccinated without documented prior infection versus unvaccinated without documented prior infection, 3) 2-dose mRNA vaccinated with documented prior infection versus unvaccinated without documented prior infection, 4) 3-dose mRNA vaccinated without documented prior infection versus unvaccinated without documented prior infection, and 5) 3-dose mRNA vaccinated with documented prior infection versus unvaccinated without documented prior infection.

[4]As people may be reflected in more than one exposure group, the number of person-time intervals was higher than the number of all members in the cohort.

[5]Other race included Asian, Hawaiian or Other Pacific Islander, American Indian or Alaskan Native, Other not-listed, multi-race, and those missing data on race/ethnicity.

[6]Underlying conditions included asthma, chronic obstructive pulmonary disease, other lung disease, heart failure, ischemic heart disease, hypertension, other heart disease, stroke, other cerebrovascular disease, diabetes (type 1, 2 and due to other specified conditions), other metabolic disease, clinical obesity, clinically underweight, renal disease, liver disease, blood disorder, other immunosuppressive conditions, organ transplant recipient, cancer, dementia, neurological/musculoskeletal disorder or Down's syndrome using diagnosis codes from the International Classification of Diseases, Ninth Revision and the International Classification of Diseases, Tenth Revision.

[7]Immunocompromising conditions were derived from lists used in previous studies of large hospital-based or administrative databases and included the following conditions: 1) solid malignancies, 2) hematologic malignancies, 3) rheumatologic or inflammatory disorders, 4) other intrinsic immune conditions or immunodeficiencies, and 5) organ or stem cell transplants.

[8]Medical events with a discharge code consistent with COVID-19–like illness were included. COVID-19–like illness included acute respiratory illness (e.g., COVID-19, respiratory failure, or pneumonia) or related signs or symptoms (cough, fever, dyspnea, vomiting, or diarrhea) using diagnosis codes from the International Classification of Diseases, Ninth Revision and International Classification of Diseases, Tenth Revision. Clinician-ordered molecular assays (e.g., real-time reverse transcription-polymerase chain reaction) for SARS-CoV-2 occurring ≤14 days before to <72 hours after the encounter date were included.

[9]Index date for each medical encounter was defined as the date of respiratory specimen collection associated with the most recent positive SARS-CoV-2 test result prior to the medical encounter or the date of the admission or medical encounter if testing only occurred after the admission or encounter date.

Table 2. Descriptive characteristics of persons aged ≥18 years included in the cohort during Delta predominance period followed until COVID-19-associated hospitalization, overall and by exposure status— 5 states, August 2021 – June 2022

	No. (column %)							
	Entire cohort	Unvaccinated without documented prior infection	Unvaccinated with documented prior infection[1]	2-dose mRNA vaccinated[2] without documented prior infection	2-dose mRNA vaccinated[2] with documented prior infection[1]	3-dose mRNA vaccinated[2] without documented prior infection	3-dose mRNA vaccinated[2] with documented prior infection[1]	Standardized mean difference

Total number of person-time intervals[4]	1,569,619	501,667	141,022	565,034	109,059	222,589	30,248	
Sex								0.02
Male	611710 (39)	196346 (39)	58009 (41)	215035 (38)	42662 (39)	87579 (39)	12079 (40)	
Female	957722 (61)	305260 (61)	82995 (59)	349930 (62)	66387 (61)	134984 (61)	18166 (60)	
Other/Unknown	187 (0)	61 (0)	18 (0)	69 (0)	10 (0)	26 (0)	3 (0)	
Age group, years								0.35
18-49	780047 (50)	300762 (60)	90906 (64)	250488 (44)	55571 (51)	71643 (32)	10677 (35)	
50-64	398117 (25)	107019 (21)	30394 (22)	156342 (28)	31035 (28)	63787 (29)	9540 (31)	
65-74	234285 (15)	54628 (11)	11680 (8)	94903 (17)	13752 (13)	53160 (24)	6162 (20)	
75-84	117808 (7)	28015 (6)	5706 (4)	48051 (8)	6428 (6)	26710 (12)	2898 (10)	
≥85	39362 (2)	11243 (2)	2336 (2)	15250 (3)	2273 (2)	7289 (3)	971 (3)	

Race/Ethnicity								0.22
Hispanic	163079 (10)	55732 (11)	21699 (15)	51978 (9)	16986 (16)	13492 (6)	3192 (11)	
White, Non-Hispanic	1114438 (71)	337711 (67)	87913 (62)	417054 (74)	71559 (66)	177963 (80)	22238 (73)	
Black, Non-Hispanic	192977 (12)	82202 (16)	24502 (17)	54639 (10)	12823 (12)	15774 (7)	3037 (10)	
Other[5], Non-Hispanic	99125 (6)	26022 (5)	6908 (5)	41363 (7)	7691 (7)	15360 (7)	1781 (6)	
Presence of at least one underlying condition[6]								0.26
Yes	903573 (58)	246592 (49)	68156 (48)	350772 (62)	65159 (60)	152395 (69)	20499 (68)	
No	666046 (42)	255075 (51)	72866 (52)	214262 (38)	43900 (40)	70194 (31)	9749 (32)	
Presence of immunocompromised								0.12

condition[7]								
Yes	181226 (11)	46908 (9)	10414 (7)	72021 (13)	11227 (10)	36301 (16)	4355 (14)	
No	1388393 (88)	454759 (91)	130608 (93)	493013 (87)	97832 (90)	186288 (84)	25893 (86)	
COVID-19 Vaccinations								5.19
Unvaccinated	642689 (41)	501667 (100)	141022 (100)	0 (0)	0 (0)	0 (0)	0 (0)	
Moderna	324945 (21)	0 (0)	0 (0)	207425 (37)	36913 (34)	71821 (32)	8786 (29)	
Pfizer-BioNTech	578298 (37)	0 (0)	0 (0)	356626 (63)	71986 (66)	131301 (59)	18385 (61)	
Combination of mRNA products	23687 (1)	0 (0)	0 (0)	983 (0.2)	160 (0.1)	19467 (9)	3077 (10)	
Hospitalized with laboratory-confirmed COVID-19-like illness[8]	2535 (0.2)	1820 (0.4)	40 (0)	619 (0.1)	17 (0)	36 (0)	3 (0)	0.07
Month of index test								0.81

date[9], among persons with COVID-19-associated hospitalizations								
August 2021	182 (7)	131 (7)	6 (15)	45 (7)	0 (0)	0 (0)	0 (0)	
September 2021	865 (34)	644 (35)	9 (22)	205 (33)	3 (18)	4 (11)	0 (0)	
October 2021	457 (18)	309 (17)	3 (7)	134 (22)	5 (29)	5 (14)	1 (33)	
November 2021	499 (20)	349 (19)	6 (15)	127 (20)	5 (29)	12 (33)	0 (0)	
December 2021	532 (21)	387 (21)	16 (40)	108 (17)	4 (23)	15 (42)	2 (67)	
Time from most recent immunizing event to COVID-19-associated hospitalization, median days (IQR)	-	-	372 (239-456)	258 (202-309)	251 (194-294)	118 (75-157)	90 (71-132)	

[1]Prior infection was defined as having a positive test result from rapid antigen or molecular assays performed ≥90 days before the index date of the COVID-19-associated encounter.

[2]Vaccination was defined as having received the listed number of doses of an mRNA-based COVID-19 vaccine ≥14 days before the medical event index date.

[3]Standardized mean difference calculation compared characteristics across all six exposure groups. For the six-level exposure variable, a single standardized mean difference (SMD) was calculated by averaging the absolute SMDs obtained from pairwise comparison of each exposure category versus unvaccinated without documented prior infection. Specifically, it was calculated as the average of the absolute value of the SMDs for 1) unvaccinated with documented prior

infection versus unvaccinated without documented prior infection, 2) 2-dose mRNA vaccinated without documented prior infection versus unvaccinated without documented prior infection, 3) 2-dose mRNA vaccinated with documented prior infection versus unvaccinated without documented prior infection, 4) 3-dose mRNA vaccinated without documented prior infection versus unvaccinated without documented prior infection, and 5) 3-dose mRNA vaccinated with documented prior infection versus unvaccinated without documented prior infection.[4]As people may be reflected in more than one exposure group, the number of person-time intervals was higher than the number of all members in the cohort. [5]Other race included Asian, Hawaiian or Other Pacific Islander, American Indian or Alaskan Native, Other not-listed, multi-race, and those missing data on race/ethnicity.

[6]Underlying conditions included asthma, chronic obstructive pulmonary disease, other lung disease, heart failure, ischemic heart disease, hypertension, other heart disease, stroke, other cerebrovascular disease, diabetes (type 1, 2 and due to other specified conditions), other metabolic disease, clinical obesity, clinically underweight, renal disease, liver disease, blood disorder, other immunosuppressive conditions, organ transplant recipient, cancer, dementia, neurological/musculoskeletal disorder or Down's syndrome using diagnosis codes from the International Classification of Diseases, Ninth Revision and the International Classification of Diseases, Tenth Revision.

[7]Immunocompromising conditions were derived from lists used in previous studies of large hospital-based or administrative databases and included the following conditions: 1) solid malignancies, 2) hematologic malignancies, 3) rheumatologic or inflammatory disorders, 4) other intrinsic immune conditions or immunodeficiencies, and 5) organ or stem cell transplants.

[8]Medical events with a discharge code consistent with COVID-19–like illness were included. COVID-19–like illness included acute respiratory illness (e.g., COVID-19, respiratory failure, or pneumonia) or related signs or symptoms (cough, fever, dyspnea, vomiting, or diarrhea) using diagnosis codes from the International Classification of Diseases, Ninth Revision and International Classification of Diseases, Tenth Revision. Clinician-ordered molecular assays (e.g., real-time reverse transcription-polymerase chain reaction) for SARS-CoV-2 occurring ≤14 days before to <72 hours after the encounter date were included.

[9]Index date for each medical encounter was defined as the date of respiratory specimen collection associated with the most recent positive SARS-CoV-2 test result prior to the medical encounter or the date of the admission or medical encounter if testing only occurred after the admission or encounter date.

Table 3. Descriptive characteristics of persons aged ≥18 years included in the cohort during Omicron predominance followed until COVID-19-associated emergency department/urgent care (ED/UC) encounter, overall and by exposure status— 5 states, August 2021 – June 2022

	No. (column %)							
	Entire cohort	Unvaccinated without documented	Unvaccinated with documented	2-dose mRNA vaccinated[2]	2-dose mRNA vaccinated[2]	3-dose mRNA vaccinated[2]	3-dose mRNA vaccinated[2]	Standardized mean difference

		prior infection	prior infection[1]	without documented prior infection	with documented prior infection[1]	without documented prior infection	with documented prior infection[1]	
Total number of person-time intervals[4]	1,583,564	502,816	185,573	370,855	111,858	342,929	69,533	
Sex								0.02
Male	613233 (39)	198180 (39)	74165 (40)	138567 (37)	41597 (37)	133799 (39)	26925 (39)	
Female	970141 (61)	304572 (61)	111388 (60)	232247 (63)	70251 (63)	209083 (61)	42600 (61)	
Other/Unknown	190 (0)	64 (0)	20 (0)	41 (0)	10 (0)	47 (0)	8 (0)	
Age group, years								0.25
18-49	831472 (52)	297728 (59)	119866 (65)	191777 (52)	64329 (57)	126890 (37)	30882 (44)	
50-64	396962 (25)	107432 (21)	40057 (22)	99476 (27)	29622 (26)	99336 (29)	21039 (30)	

65-74	213046 (13)	56924 (11)	15448 (8)	46909 (13)	10999 (10)	71736 (21)	11030 (16)	
75-84	106149 (7)	29188 (6)	7380 (4)	24100 (6)	5116 (5)	35339 (10)	5026 (7)	
≥85	35935 (2)	11544 (2)	2822 (1)	8593 (2)	1792 (2)	9628 (3)	1556 (2)	
Race/Ethnicity								0.20
Hispanic	172304 (11)	54709 (1)	24446 (13)	42781 (11)	18115 (16)	24014 (7)	8239 (12)	
White, Non-Hispanic	1103757 (70)	339115 (67)	120147 (65)	256823 (69)	72090 (64)	266163 (78)	49419 (71)	
Black, Non-Hispanic	204871 (13)	83058 (16)	32752 (18)	42338 (11)	13587 (12)	26361 (8)	6775 (10)	
Other[5], Non-Hispanic	102632 (6)	25934 (5)	8228 (4)	28913 (8)	8066 (7)	26391 (8)	5100 (7)	
Presence of at least one underlying condition[6]								0.20
Yes	892302 (56)	247995 (49)	94140 (51)	217457 (59)	64324 (57)	224441 (65)	43945 (63)	
No	691262 (44)	254821 (51)	91433 (49)	153398	47534 (42)	118488	25588 (37)	

				(41)		(35)		
Presence of immunocompromised condition[7]								0.08
Yes	170944 (11)	46324 (9)	14895 (8)	40086 (11)	10806 (10)	49973 (15)	8860 (13)	
No	1412620 (89)	456492 (91)	170678 (92)	330769 (89)	101052 (90)	292956 (85)	60673 (87)	
COVID-19 Vaccinations								4.08
Unvaccinated	688389 (43)	502816 100)	185573 (100)	0 (0)	0 (0)	0 (0)	0 (0)	
Moderna	307881 (19)	0 (0)	0 (0)	138424 (37)	37371 (33)	111790 (33)	20296 (29)	
Pfizer-BioNTech	544207 (34)	0 (0)	0 (0)	231379 (62)	74209 (66)	197227 (58)	41392 (60)	
Combination of mRNA products	43087 (3)	0 (0)	0 (0)	1052 (0.3)	278 (0.2)	33912 (10)	7845 (11)	
ED/UC encounters with	8472 (0.5)	3459 (0.7)	703 (0.4)	2799 (0.8)	323 (0.3)	1078 (0.3)	110 (0.2)	0.05

laboratory-confirmed COVID-19-like illness[8]								
Month of index test date[9], among persons with COVID-19-associated ED/UC encounters								0.38
December 2021	1535 (18)	714 (21)	133 (19)	507 (18)	68 (21)	103 (10)	10 (9)	
January 2022	5141 (61)	2193 (63)	437 (62)	1773 (63)	187 (58)	489 (45)	62 (56)	
February 2022	691 (8)	277 (8)	36 (5)	226 (8)	26 (8)	119 (11)	7 (6)	
March 2022	170 (2)	63 (2)	14 (2)	46 (2)	9 (3)	33 (3)	5 (5)	
April 2022	231 (3)	55 (2)	22 (3)	65 (2)	6 (2)	73 (7)	10 (9)	
May 2022	638 (8)	143 (4)	52 (7)	165 (6)	26 (8)	236 (22)	16 (15)	
June 2022	66 (1)	14 (0.4)	9 (1)	17 (1)	1 (0.3)	25 (2)	0 (0)	
Time from most recent immunizing event to	-	-	375 (230-459)	258 (199-308)	219 (145-272)	104 (63-159)	85 (52-128)	

COVID-19-associated ED/UC encounter, median days (IQR)								

Abbreviations: Emergency Department (ED), Urgent Care (UC)

[1]Prior infection was defined as having a positive test result from rapid antigen or molecular assays performed ≥90 days before the index date of the COVID-19-associated encounter.

[2]Vaccination was defined as having received the listed number of doses of an mRNA-based COVID-19 vaccine ≥14 days before the medical event index date.

[3]Standardized mean difference calculation compared characteristics across all six exposure groups. For the six-level exposure variable, a single standardized mean difference (SMD) was calculated by averaging the absolute SMDs obtained from pairwise comparison of each exposure category versus unvaccinated without documented prior infection. Specifically, it was calculated as the average of the absolute value of the SMDs for 1) unvaccinated with documented prior infection versus unvaccinated without documented prior infection, 2) 2-dose mRNA vaccinated without documented prior infection versus unvaccinated without documented prior infection, 3) 2-dose mRNA vaccinated with documented prior infection versus unvaccinated without documented prior infection, 4) 3-dose mRNA vaccinated without documented prior infection versus unvaccinated without documented prior infection, and 5) 3-dose mRNA vaccinated with documented prior infection versus unvaccinated without documented prior infection.[4]As people may be reflected in more than one exposure group, the number of person-time intervals was higher than the number of all members in the cohort.

[5]Other race included Asian, Hawaiian or Other Pacific Islander, American Indian or Alaskan Native, Other not-listed, multi-race, and those missing data on race/ethnicity.

[6]Underlying conditions included asthma, chronic obstructive pulmonary disease, other lung disease, heart failure, ischemic heart disease, hypertension, other heart disease, stroke, other cerebrovascular disease, diabetes (type 1, 2 and due to other specified conditions), other metabolic disease, clinical obesity, clinically underweight, renal disease, liver disease, blood disorder, other immunosuppressive conditions, organ transplant recipient, cancer, dementia, neurological/musculoskeletal disorder or Down's syndrome using diagnosis codes from the International Classification of Diseases, Ninth Revision and the International Classification of Diseases, Tenth Revision.

[7]Immunocompromising conditions were derived from lists used in previous studies of large hospital-based or administrative databases and included the following conditions: 1) solid malignancies, 2) hematologic malignancies, 3) rheumatologic or inflammatory disorders, 4) other intrinsic immune conditions or immunodeficiencies, and 5) organ or stem cell transplants.

[8]Medical events with a discharge code consistent with COVID-19–like illness were included. COVID-19–like illness included acute respiratory illness (e.g., COVID-19, respiratory failure, or pneumonia) or related signs or symptoms (cough, fever, dyspnea, vomiting, or diarrhea) using diagnosis codes from the International Classification of Diseases, Ninth Revision and International Classification of Diseases, Tenth Revision. Clinician-ordered molecular assays (e.g., real-time reverse transcription-polymerase chain reaction) for SARS-CoV-2 occurring ≤14 days before to <72 hours after the encounter date were included.

[9]Index date for each medical encounter was defined as the date of respiratory specimen collection associated with the most recent positive SARS-CoV-2 test result prior to the medical encounter or the date of the admission or medical encounter if testing only occurred after the admission or encounter date.

Table 4. Descriptive characteristics of persons aged ≥18 years included in the cohort during Omicron predominance followed until COVID-19-associated hospitalization, overall and by exposure status— 5 states, August 2021 – June 2022

	No. (column %)							
	Entire cohort	Unvaccinated without documented prior infection	Unvaccinated with documented prior infection[1]	2-dose mRNA vaccinated[2] without documented prior infection	2-dose mRNA vaccinated[2] with documented prior infection[1]	3-dose mRNA vaccinated[2] without documented prior infection	3-dose mRNA vaccinated[2] with documented prior infection[1]	Standardized mean difference
Total number of person-time intervals[4]	1,587,872	502,815	187,501	370,855	113,542	342,929	70,230	
Sex								0.02
Male	614391 (39)	198180 (39)	74677 (40)	138567 (37)	42036 (37)	133799 (39)	27132 (39)	
Female	973291 (61)	304571 (61)	112804 (60)	232247	71496 (63)	209083	43090 (61)	

				(63)		(61)		
Other/Unknown	190 (0)	64 (0)	20 (0)	41 (0)	10 (0)	47 (0)	8 (0)	
Age group, years								0.25
18-49	835049 (53)	297727 (59)	121735 (65)	191777 (52)	65624 (58)	126890 (37)	31296 (45)	
50-64	397776 (25)	107432 (21)	40302 (21)	99476 (27)	29997 (26)	99336 (29)	21233 (30)	
65-74	213128 (13)	56925 (11)	15389 (8)	46909 (13)	11054 (10)	71736 (21)	11115 (16)	
75-84	106068 (7)	29187 (6)	7294 (4)	24100 (6)	5113 (4)	35339 (10)	5035 (7)	
≥85	35851 (2)	11544 (2)	2781 (1)	8593 (2)	1754 (1)	9628 (3)	1551 (2)	
Race/Ethnicity								0.20
Hispanic	173292 (11)	54709 (11)	24888 (13)	42781 (11)	18523 (16)	24014 (7)	8377 (12)	
White, Non-Hispanic	1106093 (70)	339114 (67)	121141 (65)	256823 (69)	72998 (64)	266163 (78)	49854 (71)	
Black, Non-Hispanic	205575 (13)	83058 (16)	33161 (18)	42338 (11)	13825 (12)	26361 (8)	6832 (10)	
Other[5], Non-	102912 (6)	25934 (5)	8311 (4)	28913 (8)	8196 (7)	26391 (8)	5167 (7)	

Hispanic								
Presence of at least one underlying condition[6]								0.20
Yes	894214 (56)	247995 (49)	94776 (50)	217457 (59)	65157 (57)	224441 (65)	44388 (63)	
No	693658 (44)	254820 (51)	92725 (49)	153398 (41)	48385 (43)	118488 (35)	25842 (37)	
Presence of immunocompromised condition[7]								0.08
Yes	171104 (11)	46324 (9)	14922 (8)	40086 (11)	10881 (10)	49973 (15)	8918 (13)	
No	1416768 (89)	456491 (91)	172579 (92)	330769 (89)	102661 (90)	292956 (85)	61312 (87)	
COVID-19 Vaccinations								4.07
Unvaccinated	690316 (43)	502815 (100)	187501 (100)	0 (0)	0 (0)	0 (0)	0 (0)	
Moderna	308711 (19)	0 (0)	0 (0)	138424	37973	111790	20524 (29)	

				(37)	(33.4)	(32)		
Pfizer-BioNTech	545688 (34)	0 (0)	0 (0)	231379 (62)	75285 (66)	197227 (57)	41797 (59)	
Combination of mRNA products	43157 (3)	0 (0)	0 (0)	1052 (0.3)	284 (0.3)	33912 (10)	7909 (11)	
Hospitalized with laboratory-confirmed COVID-19-like illness[8]	2945 (0.2)	1496 (0.3)	108 (0.1)	913 (0.2)	57 (0.1)	347 (0.1)	24 (0)	0.05
Month of index test date[9], among persons with COVID-19-associated hospitalizations								0.44
December 2021	371 (13)	204 (14)	11 (10)	128 (14)	3 (5)	25 (7)	0 (0)	
January 2022	1845 (63)	971 (65)	66 (61)	575 (63)	38 (67)	183 (53)	12 (50)	
February 2022	474 (16)	234 (16)	22 (20)	138 (15)	7 (12)	68 (20)	5 (21)	

March 2022	89 (3)	28 (2)	3 (3)	27 (3)	3 (5)	25 (7)	3 (12)	
April 2022	59 (2)	18 (1)	1 (1)	17 (2)	5 (9)	15 (4)	3 (12)	
May 2022	104 (3)	39 (3)	5 (5)	27 (3)	1 (2)	31 (9)	1 (4)	
June 2022	3 (0.1)	2 (0.1)	0 (0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	
Time from most recent immunizing event to COVID-19-associated hospitalization, median days (IQR)	-	-	374 (183-479)	282 (236-318)	251 (152-292)	111 (69-152)	107 (58-133)	

[1]Prior infection was defined as having a positive test result from rapid antigen or molecular assays performed ≥90 days before the index date of the COVID-19-associated encounter.

[2]Vaccination was defined as having received the listed number of doses of an mRNA-based COVID-19 vaccine ≥14 days before the medical event index date.

[3]Standardized mean difference calculation compared characteristics across all six exposure groups. For the six-level exposure variable, a single standardized mean difference (SMD) was calculated by averaging the absolute SMDs obtained from pairwise comparison of each exposure category versus unvaccinated without documented prior infection. Specifically, it was calculated as the average of the absolute value of the SMDs for 1) unvaccinated with documented prior infection versus unvaccinated without documented prior infection, 2) 2-dose mRNA vaccinated without documented prior infection versus unvaccinated without documented prior infection, 3) 2-dose mRNA vaccinated with documented prior infection versus unvaccinated without documented prior infection, 4) 3-dose mRNA vaccinated without documented prior infection versus unvaccinated without documented prior infection, and 5) 3-dose mRNA vaccinated with documented prior infection versus unvaccinated without documented prior infection.[4]As people may be reflected in more than one exposure group, the number of person-time intervals was higher than the number of all members in the cohort.

[5]Other race included Asian, Hawaiian or Other Pacific Islander, American Indian or Alaskan Native, Other not-listed, multi-race, and those missing data on race/ethnicity.

[6]Underlying conditions included asthma, chronic obstructive pulmonary disease, other lung disease, heart failure, ischemic heart disease, hypertension, other heart disease, stroke, other cerebrovascular disease, diabetes (type 1, 2 and due to other specified conditions), other metabolic disease, clinical obesity, clinically underweight, renal disease, liver disease, blood disorder, other immunosuppressive conditions, organ transplant recipient, cancer, dementia,

neurological/musculoskeletal disorder or Down's syndrome using diagnosis codes from the International Classification of Diseases, Ninth Revision and the International Classification of Diseases, Tenth Revision.

[7]Immunocompromising conditions were derived from lists used in previous studies of large hospital-based or administrative databases and included the following conditions: 1) solid malignancies, 2) hematologic malignancies, 3) rheumatologic or inflammatory disorders, 4) other intrinsic immune conditions or immunodeficiencies, and 5) organ or stem cell transplants.

[8]Medical events with a discharge code consistent with COVID-19–like illness were included. COVID-19–like illness included acute respiratory illness (e.g., COVID-19, respiratory failure, or pneumonia) or related signs or symptoms (cough, fever, dyspnea, vomiting, or diarrhea) using diagnosis codes from the International Classification of Diseases, Ninth Revision and International Classification of Diseases, Tenth Revision. Clinician-ordered molecular assays (e.g., real-time reverse transcription-polymerase chain reaction) for SARS-CoV-2 occurring ≤14 days before to <72 hours after the encounter date were included.

[9]Index date for each medical encounter was defined as the date of respiratory specimen collection associated with the most recent positive SARS-CoV-2 test result prior to the medical encounter or the date of the admission or medical encounter if testing only occurred after the admission or encounter date.

Figure 1. Estimated protection conferred from prior SARS-CoV-2 infection and/or COVID-19 mRNA vaccination against laboratory-confirmed COVID-19–associated Emergency Department or Urgent Care encounters, separately during Delta predominance and Omicron predominance

Protection is calculated as ((1-adjusted hazard ratio) x 100), analogous to how vaccine effectiveness is calculated.

Prior infections during Delta predominance includes infections during pre-Delta and Delta variant periods, and prior infections during Omicron predominance includes infections that occurred before and during Omicron predominance.

Exposure Group	Total person days	COVID-19-associated ED/UC encounters	Protection (95% CI)
Delta Predominance Period			
Unvaccinated without documented prior infection	55,887,313	2,652	Ref
Unvaccinated with documented prior infection	13,915,758	108	85 (81 - 87)
2-dose mRNA vaccinated without documented prior infection	53,846,891	996	72 (70 - 74)
2-dose mRNA vaccinated with documented prior infection	10,451,611	38	94 (92 - 96)
3-dose mRNA vaccinated without documented prior infection	9,609,910	70	91 (89 - 93)
3-dose mRNA vaccinated with documented prior infection	1,062,517	2	98 (91 - 99)
Omicron Predominance Period			
Unvaccinated without documented prior infection	80,404,869	3,459	Ref
Unvaccinated with documented prior infection	27,534,302	703	37 (31 - 41)
2-dose mRNA vaccinated without documented prior infection	48,601,528	2,799	18 (14 - 22)
2-dose mRNA vaccinated with documented prior infection	13,620,814	323	62 (58 - 66)
3-dose mRNA vaccinated without documented prior infection	51,486,337	1,078	66 (64 - 69)
3-dose mRNA vaccinated with documented prior infection	9,137,786	110	76 (71 - 80)

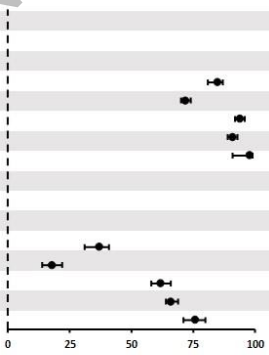
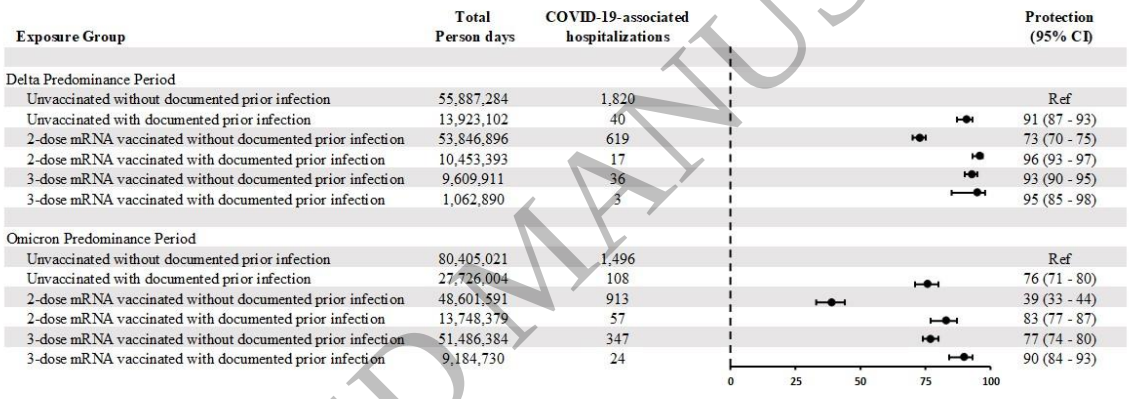


Figure 2. Estimated protection conferred from prior SARS-CoV-2 infection and/or COVID-19 mRNA vaccination against laboratory-confirmed COVID-19–associated hospitalizations, separately during Delta predominance and Omicron predominance

Protection is calculated as ((1-adjusted hazard ratio) x 100), analogous to how vaccine effectiveness is calculated.

Prior infections during Delta predominance includes infections during pre-Delta and Delta variant periods, and prior infections during Omicron predominance includes infections that occurred before and during Omicron predominance.



Exposure Group	Total Person days	COVID-19-associated hospitalizations	Protection (95% CI)
Delta Predominance Period			
Unvaccinated without documented prior infection	55,887,284	1,820	Ref
Unvaccinated with documented prior infection	13,923,102	40	91 (87 - 93)
2-dose mRNA vaccinated without documented prior infection	53,846,896	619	73 (70 - 75)
2-dose mRNA vaccinated with documented prior infection	10,453,393	17	96 (93 - 97)
3-dose mRNA vaccinated without documented prior infection	9,609,911	36	93 (90 - 95)
3-dose mRNA vaccinated with documented prior infection	1,062,890	3	95 (85 - 98)
Omicron Predominance Period			
Unvaccinated without documented prior infection	80,405,021	1,496	Ref
Unvaccinated with documented prior infection	27,726,004	108	76 (71 - 80)
2-dose mRNA vaccinated without documented prior infection	48,601,591	913	39 (33 - 44)
2-dose mRNA vaccinated with documented prior infection	13,748,379	57	83 (77 - 87)
3-dose mRNA vaccinated without documented prior infection	51,486,384	347	77 (74 - 80)
3-dose mRNA vaccinated with documented prior infection	9,184,730	24	90 (84 - 93)