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Background. Protection against symptomatic severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (coronavirus disease 2019 [COVID-19]) can limit transmission and the risk of post-COVID conditions, and is particularly important among healthcare personnel. However, lower vaccine effectiveness (VE) has been reported since predominance of the Omicron SARS-CoV-2 variant.

Methods. We evaluated the VE of a monovalent messenger RNA (mRNA) booster dose against COVID-19 from October 2021 to June 2022 among US healthcare personnel. After matching case-participants with COVID-19 to control-participants by 2-week period and site, we used conditional logistic regression to estimate the VE of a booster dose compared with completing only 2 mRNA doses >150 days previously, adjusted for multiple covariates.

Results. Among 3279 case-participants and 3998 control-participants who had completed 2 mRNA doses, we estimated that the VE of a booster dose against COVID-19 declined from 86% (95% confidence interval, 81%–90%) during Delta predominance to 65% (58%–70%) during Omicron predominance. During Omicron predominance, VE declined from 73% (95% confidence interval, 67%–79%) 14–60 days after the booster dose, to 32% (4%–52%) ≥120 days after a booster dose. We found that VE was similar by age group, presence of underlying health conditions, and pregnancy status on the test date, as well as among immunocompromised participants.

Conclusions. A booster dose conferred substantial protection against COVID-19 among healthcare personnel. However, VE was lower during Omicron predominance, and waning effectiveness was observed 4 months after booster dose receipt during this period. Our findings support recommendations to stay up to date on recommended doses of COVID-19 vaccines for all those eligible.

Keywords. COVID-19; SARS-CoV-2; vaccine effectiveness; Omicron; healthcare personnel.

Coronavirus disease 2019 (COVID-19) messenger RNA (mRNA) vaccines have provided direct protection against symptomatic infection, severe disease, and death from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1, 2]. COVID-19 vaccines can also protect others indirectly via reduced transmission—an estimated 20% of global deaths prevented in 2021 were averted by indirect protection [3–5].

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For healthcare personnel, COVID-19 vaccination offers the potential to protect individuals, decrease transmission in healthcare settings, and avoid disruption of critical services [6]. However, vaccine effectiveness (VE) against symptomatic SARS-CoV-2 infection has waned over time and has been reported to be lower against the Omicron variant [7–10].

During 2021, analysis of a multisite case-control study among US healthcare personnel showed high VE of 2 mRNA vaccine doses against COVID-19, including by pregnancy or immunocompromised status [11, 12]. Using the same multisite network, we estimated the VE of a monovalent mRNA vaccine booster dose against COVID-19 among US healthcare personnel who had received 2 mRNA doses. We estimated VE during periods of Delta and Omicron predominance, evaluated waning of VE over time, and compared VE among subgroups.

METHODS

Setting

We conducted a case-control study to estimate effectiveness of a monovalent mRNA COVID-19 booster vaccine dose among US healthcare personnel from October 2021 to July 2022, and we performed supportive analyses using data collected from January 2021 to July 2022. Using a previously described network [11], we enrolled healthcare personnel from participating healthcare facilities in 21 US states. Healthcare personnel were eligible to enroll if they were aged ≥18 years, had a positive or new negative SARS-CoV-2 test result (see Supplementary Methods), reported no previous SARS-CoV-2 infection, and had an occupation with potential contact with patients or infectious clinical materials (see Supplementary Box 1). Participants were excluded from the analysis if they reported enrollment in a COVID-19 vaccine trial.

This project was reviewed in accordance with CDC human research protection procedures and was determined to be nonresearch public health surveillance. At each site, it was deemed either a public health assessment or human subjects research, for which approval was granted by local institutional review boards. At one of the sites the project was considered to be human subjects research, and written consent was obtained for all participants; all other sites considered the study to be nonresearch.

Case-Control Status

We defined case-participants as those with a positive SARS-CoV-2 antigen test or nucleic acid amplification test (NAAT) result and ≥1 COVID-19–like symptom on the test date or during the ensuing 14 days (see Supplementary Box 2) [11]. We defined control-participants as those with a negative NAAT result and no known positive SARS-CoV-2 results before the participant's test date. In addition to inclusion of symptomatic case- and control-participants that could be considered as a "test-negative" design [13], control-participants were also eligible for inclusion if asymptomatic in a subset of sites. Using a sensitivity analysis, we assessed the potential impact of excluding asymptomatic control-participants on VE estimates.

Vaccination Status

We defined vaccination status on the day of the positive or negative SARS-CoV-2 test as "unvaccinated" if no COVID-19 vaccine was received, and "2 doses" if a second mRNA vaccine dose was administered ≥14 days before the test date. We defined participants as having received a booster dose if 3 doses of any mRNA vaccine were received ≥14 days before the test date, dose 3 was >150 days (approximately 5 months) after dose 2, and no additional doses were received. Booster doses were considered if received on or after 24 September 2021 [14]. Participants were excluded from the analysis if their vaccination status on the test date did not meet these definitions of "unvaccinated," receiving 2 mRNA doses, or receiving a booster mRNA dose.

Data Collection

After consent and enrollment, participants completed an in-person, phone, or online standardized survey that included questions regarding demographic characteristics, socioeconomic indicators, underlying health conditions, test results, symptoms, behaviors associated with possible SARS-CoV-2 exposure, and vaccination. Participants were also asked about behaviors associated with possible SARS-CoV-2 exposure during the 14 days before symptom onset (or test date if asymptomatic), and whether they had known COVID-19 exposure to a patient, another person in the workplace, or a person outside the workplace during the same period.

For participants seeking care for COVID-19–like illness at a participating healthcare institution or other healthcare facility, we summarized clinical course and underlying health conditions from medical records. We verified all SARS-CoV-2 test and COVID-19 vaccine information using independent information, including medical records and vaccine registries. SARS-CoV-2 antigen tests could be included for case-participants provided there was independent evidence of the test product. We categorized underlying health conditions using survey responses and record reviews (Supplementary Table 1).

Estimation of VE

To estimate the VE of a booster dose among recipients of 2 mRNA doses, we included participants who were tested for SARS-CoV-2 between 8 October 2021 (ie, 14 days after a recommendation for booster doses on 24 September 2021) and 31 July 2022. We matched case- and control-participants by enrollment site and test date (2-week intervals) and used conditional logistic regression to estimate VE as 100% multiplied by 1 minus the odds ratio for vaccination status for case-

participants versus control-participants. Because of sparse data among subgroups, we used broader matched sets as strata (4-week intervals within each US census region) to estimate VE against COVID-19 during pregnancy, and among those who were immunocompromised. We adjusted models for several covariates based on postulated causal relationships between vaccination and COVID-19: age group in years (18–29, 30–39, 40–49, or ≥ 50 years), sex, race and ethnicity (white, non-Hispanic, or other racial and ethnic groups), number of underlying health conditions (0, 1, or ≥ 2), educational level (professional/doctoral degree or not), and reported COVID-19 exposure outside the workplace during the 14 days before the test date.

For the primary analysis of VE by a booster dose, participants in the referent group had received only 2 doses ≥150 days before the test date and thus were eligible for a booster dose. We evaluated VE by product and by time since receiving dose 3. We stratified analyses by time periods when variants were estimated to represent >50% of SARS-CoV-2 infections in the United States; for the primary analysis we defined the Delta-predominant period as before 19 December 2021 and the Omicron-predominant period as 19 December 2021 or later [15]. To assess waning by time since a booster dose we performed conditional logistic regression, replacing vaccination status with a categorical variable representing 30-day periods after receipt of a booster dose. We estimated VE by age group, pregnancy status, and comorbid conditions using interaction terms between vaccination status and the subgroup characteristic. When estimating VE against COVID-19 by pregnancy status, we restricted analyses to female participants aged <50 years, using a similar approach to a previous study of VE against medically attended COVID-19 during pregnancy [16]. Since a third vaccine dose is recommended for immunocompromised persons as part of a primary series [17], we also estimated VE of a third dose administered >28 days after the second dose, by immunocompromised status.

We conducted additional supportive analyses to assess the impact of different assumptions on analyses (see Supplementary Methods). As context for our primary analysis of VE by a booster dose compared with receipt of 2 mRNA doses, we also assessed VE of a booster dose compared with no vaccine doses and VE of 2 mRNA doses compared with no vaccine doses (see Supplementary Methods). We performed all analyses using Stata 15.1 software (StataCorp), and we used standardized mean differences (using the stddiff software package) to describe differences in participant characteristics. In adjusted analyses we excluded observations with missing covariate values.

RESULTS

Study Participants

Overall, 7277 participants were included in the primary analyses of VE (Supplementary Figure 1), of whom 1454 (20%) were tested during the Delta-predominant and 5823 (80%) during the Omicron-predominant period. Numbers of case-participants and control-participants included are summarized by the state of the participating health facility in Supplementary Table 2. Among 3279 case-participants, 163 (5.0%) had an antigen test result rather than a NAAT result. The median age of participants was 38 years (range, 18–91 years), and 5920 (81% of 7259) were female. Overall, 5138 participants (71%) reported ≥1 underlying health condition, including 150 immunocompromised persons (2.0%). Among 5914 female participants, 159 (2.7%) had been pregnant on the test date, with a median gestation of 20 weeks (range, 1–40 weeks). Of 108 pregnant persons who had received a booster dose, 40 (37%) were reported to be pregnant when the dose was administered.

Distributions of age, sex, and presence of comorbid condition were generally similar between case-participants and control-participants (Tables 1 and 2 and Supplementary Table 3). However, case-participants were less likely than control-participants to be white non-Hispanic or have a professional or doctoral degree, more likely to report a fever, and more likely to report close contact with a person with COVID-19 outside the work setting during the 14 days before illness onset or test date.

Overall, 1904 case-participants (58.1%) and 3239 control-participants (81.0%) received a booster dose in addition to their second mRNA dose. Differences in participant characteristics by receipt of a booster dose are summarized in Supplementary Table 4. Recipients of a booster dose were more likely to be white non-Hispanic, and less likely to report any underlying health conditions. Recipients of a booster dose were less likely to report a fever, among both case-participants and control-participants. Illness was generally mild—only 32 participants (0.4%) were reported to be hospitalized with COVID-19–like symptoms. Overall, characteristics of participants were similar between the Delta- and Omicron-predominant periods (Supplementary Table 5). Differences in characteristics among participants included in secondary analyses are summarized in Supplementary Tables 6 and 7.

Among the 7277 participants included in the primary analysis of VE, 4857 (66.7%) received their second dose during January 2021 (Supplementary Figure 2). Among 5143 participants (70.7%) who later received a booster dose, 2475 (48.1%) received the booster dose during October 2021 (Supplementary Figure 3); booster recipients represented an increasing proportion of participants over time (Supplementary Figure 4). In total, 4909 (95.5%) booster dose recipients received the same product for each dose; 3806 (74.0%) received a booster dose of the Pfizer-BioNTech vaccine, at a median of 266 days after dose 2 (range, 151–441 days), and 1103 (21.4%) received a booster dose of the Moderna vaccine, at a median of 285 days after dose 2 (153–461 days).

Table 1. Demographic and Clinical Characteristics of Healthcare Personnel With Symptomatic SARS-CoV-2 Infection (Case-Participants) or Without SARS-CoV-2 Infection (Control-Participants) at 24 US Sites, October 2021–June 2022

Characteristic	Participants With Characteristic/Total No. (%)[a]		SMD
	Case-Participants	Control-Participants	
Age group, y			
18–29	721/3258 (22.1)	776/3965 (19.6)	0.063
30–39	1072/3258 (32.9)	1370/3965 (34.6)	−0.035
40–49	726/3258 (22.3)	842/3965 (21.2)	0.025
≥ 50	739/3258 (22.7)	977/3965 (24.6)	−0.046
Sex			
Male	626/3275 (19.1)	713/3993 (17.9)	0.032
Female	2646/3275 (80.8)	3274/3993 (82.0)	−0.031
Unknown	3/3275 (0.1)	6/3993 (0.2)	−0.017
Race and ethnicity			
White, non-Hispanic	2478/3218 (77.0)	3214/3931 (81.8)	−0.118
Black, non-Hispanic	254/3218 (7.9)	204/3931 (5.2)	0.109
Hispanic	273/3218 (8.5)	236/3931 (6.0)	0.096
Other, non-Hispanic	213/3218 (6.6)	277/3931 (7.0)	−0.017
Educational level			
No college degree	408/3271 (12.5)	401/3997 (10.0)	0.077
College degree	2302/3271 (70.4)	2705/3997 (67.7)	0.058
Doctoral or professional degree	553/3271 (16.9)	882/3997 (22.1)	−0.131
Unknown	8/3271 (0.2)	9/3997 (0.2)	0.004
No. of underlying health conditions[b]			
0	962/3279 (29.3)	1177/3998 (29.4)	−0.002
1	1419/3279 (43.3)	1620/3998 (40.5)	0.056
≥2	898/3279 (27.4)	1201/3998 (30.0)	−0.059
Underlying health conditions[b]			
Pulmonary disease	464/3279 (14.2)	723/3998 (18.1)	−0.107
Cardiac disease	67/3279 (2.0)	96/3998 (2.4)	−0.024
Liver disease	13/3279 (0.4)	17/3998 (0.4)	−0.004
Renal disease	24/3279 (0.7)	27/3998 (0.7)	0.007
DM type 1 or 2	123/3279 (3.8)	160/3998 (4.0)	−0.013
Obesity	976/3279 (29.8)	1226/3998 (30.7)	−0.020
Overweight without obesity	987/3279 (30.1)	1101/3998 (27.5)	0.057
Cancer	18/3279 (0.5)	36/3998 (0.9)	−0.041
Immunocompromised[c]	62/3279 (1.9)	88/3998 (2.2)	−0.022
Mood disorder	138/3279 (4.2)	152/3998 (3.8)	0.021
Smoking or substance abuse	626/3279 (19.1)	799/3998 (20.0)	−0.023
Other	3/3279 (0.1)	0/3998 (0)	0.043
Pregnancy	69/3277 (2.1)	90/3994 (2.3)	−0.010
Vaccination status on test date[d]			
2 Doses	1375/3279 (41.9)	759/3998 (19.0)	0.515
2 Doses + booster dose	1904/3279 (58.1)	3239/3998 (81.0)	−0.515

Abbreviations: COVID-19, coronavirus disease 2019; DM, diabetes mellitus; SMD, standardized mean difference.

[a]Case-participants had symptomatic severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection confirmed by antigen test or nucleic acid amplification test (NAAT); control-participants had a negative SARS-CoV-2 NAAT result, with or without symptoms.

[b]Underlying health conditions as defined in Supplementary Table 1.

[c]Reported condition associated with immunocompromise or an immunosuppressant medication. Cancer was considered to be associated with immunocompromise if an active solid organ cancer was reported. Human immunodeficiency virus infection was reported in <5% of participants categorized as immunocompromised.

[d]Note: "2 doses" was defined as receipt of a second dose of messenger RNA (mRNA) vaccine ≥5 months before severe acute respiratory syndrome coronavirus 2 test date; "booster dose," as any mRNA vaccine dose administered ≥5 months after dose 2.

VE of a Booster Dose After 2 mRNA Doses

The estimated adjusted VE of a booster mRNA dose (compared with 2 mRNA doses) against COVID-19 during October 2021–July 2022 was 71.1% (95% confidence interval [CI], 66.7%–75.0%) and was similar for the Pfizer-BioNTech (71.2% [65.8%–75.7%]) and Moderna (71.6% [61.3%–79.2%]) vaccines. The VE of any mRNA vaccine was lower during Omicron predominance (64.6% [95% CI, 58.4%–69.9%]) than during Delta predominance (86.3% [1.1%–90.1%]); the VE within 60 days of a booster dose was 73.4%

Table 2. Test Characteristics and Reported Exposures of Healthcare Personnel With Symptomatic SARS-CoV-2 Infection (Case-Participants) or Without SARS-CoV-2 Infection (Control-Participants) at 24 US Sites, October 2021–June 2022

Characteristic	Participants With Characteristic/Total No. (%)[a]		SMD
	Case-Participants	Control-Participants	
Variant period of SARS-CoV-2 test[b]			
Delta	620/3279 (18.9)	834/3998 (20.9)	−0.049
Omicron	2659/3279 (81.1)	3164/3998 (79.1)	0.049
Type of test			
NAAT	3116/3279 (95.0)	3998/3998 (100.0)	−0.323
Antigen test	163/3279 (5.0)	0/3998 (0)	0.323
Symptoms reported[c]			
No	0/3279 (0)	686/3998 (17.2)	−0.644
Yes	3279/3279 (100)	3312/3998 (82.8)	0.644
Reason for SARS-CoV-2[d]			
Symptoms	2802/3279 (85.5)	2827/3312 (85.4)	0.003
Exposure, no symptoms	371/3279 (11.3)	351/3312 (10.6)	0.023
Screening, no symptoms or known exposure	35/3279 (1.1)	59/3312 (1.8)	−0.060
Other	62/3279 (1.9)	71/3312 (2.1)	−0.018
Unknown or missing	9/3279 (0.3)	4/3312 (0.1)	0.035
If symptoms reported, fever[e]			
No	1496/3279 (45.6)	3103/3998 (77.6)	−0.696
Yes	1783/3279 (54.4)	895/3998 (22.4)	0.696
Any COVID-19 close contact ≤14 d before symptom onset or positive test result[f]	2286/3277 (69.8)	2386/3997 (59.7)	0.212
At work, patient	1013/2582 (39.2)	1266/3253 (38.9)	−0.016
At work, not a patient	720/2270 (31.7)	950/3055 (31.1)	−0.043
Outside work	1493/2934 (50.9)	1244/3629 (34.3)	0.300
Level of anticipated direct patient contact[g]			
Substantial	931/3279 (28.4)	1258/3998 (31.5)	−0.067
Moderate	241/3279 (7.3)	272/3998 (6.8)	0.021
Minimal	2079/3279 (63.4)	2439/3998 (61.0)	0.049
Undefined	28/3279 (0.9)	29/3998 (0.7)	0.015
Exposures representing possible risk in the community			
Close contact with an ill person[f]	1369/3022 (45.3)	1560/3678 (42.4)	0.056
Attended gathering with nonhousehold members	1674/3258 (51.4)	1835/3931 (46.7)	0.103
Public transport	641/3268 (19.6)	798/3978 (20.1)	−0.010
Shared transport	522/3271 (16.0)	667/3976 (16.8)	−0.021
Attended daycare or school	1216/3098 (39.3)	1635/3769 (43.4)	−0.082
Household member in daycare	203/3273 (6.2)	340/3989 (8.5)	−0.089

Abbreviations: COVID-19, coronavirus disease 2019; NAAT, nucleic acid amplification test; SARS- CoV-2, severe acute respiratory syndrome coronavirus 2; SMD, standardized mean difference.

[a]Case-participants had symptomatic SARS-CoV-2 infection confirmed by antigen test or NAAT; control-participants had a negative SARS-CoV-2 NAAT result, with or without symptoms.

[b]The Delta-predominant period was defined as before 19 December 2021; the Omicron-predominant period, as 19 December 2021 or later.

[c]Among 90 pregnant control-participants, 15 (16.7%) had no symptoms reported.

[d]Among persons with symptoms reported during the 14 days after the test date; some participants had initially tested for other reasons listed.

[e]Among symptomatic case-participants, 884 of 1904 booster dose recipients (46%) reported a fever, compared with 899 of 1375 (65%) of those who did not receive a booster; among symptomatic control-participants, these numbers were 671 of 3239 (21%) and 224 of 759 (30%), respectively.

[f]Close contact was defined as being within 6 ft of another person for ≥15 minutes or having unprotected contact with body secretions or excretions.

[g]The anticipated level of patient contact was categorized according to reported occupation using the same methods as a previous analysis [11]. Among 4487 participants anticipated to have substantial direct patient contact, 2263 (50.0%) were nurses and 947 (21.0%) were physicians.

(95% CI, 66.6%–78.9%) during the Omicron-predominant period and 86.2% (80.4%–90.3%) during the Delta-predominant period. Within the Omicron period, VE declined by time since receipt of a booster dose and was 32.1% (95% CI, 4.5%–51.7%) ≥120 days after a booster (Table 3 and Supplementary Table 8). Increased time since receipt of a booster dose was associated with increased odds of COVID-19 during the Omicron-predominant period ($P < .001$); limited data during the Delta-predominant period precluded assessment of waning beyond 120 days.

VE of a Booster Dose Among Subgroups

Within each period, VE was similar by age group, presence of underlying health conditions, pregnancy, and immunocompromised status (Table 4). During the Omicron-predominant period, the VE of a booster dose was 66.9% (95% CI, 53.1%–

Table 3. Estimated Vaccine Effectiveness of a Messenger RNA (mRNA) Booster Dose Against Coronavirus Disease 2019 Among US Healthcare Personnel who Received 2 mRNA Doses, October 2021–June 2022

Characteristic by Variant Period	Booster Dose Recipients/Recipients of 2 Doses ≥5 mo Earlier (%)[a]		Adjusted VE (95% CI)[b]
	Case-Participants	Control-Participants	
Overall period			
Booster product			
Any mRNA	1854/3190 (58.1)	3153/3892 (81.0)	71.1 (66.7–75.0)
Pfizer BioNTech	1373/2301 (59.7)	2327/2808 (82.9)	71.2 (65.8–75.7)
Moderna	391/790 (49.5)	693/948 (73.1)	71.6 (61.3–79.2)
Time since booster, d			
<60	356/1692 (21.0)	817/1556 (52.5)	78.2 (73.6–82.0)
60–119	982/2318 (42.4)	1505/2244 (67.1)	67.1 (60.9–72.3)
≥120	516/1852 (27.9)	831/1570 (52.9)	33.6 (6.6–52.8)
Delta period[c]			
Booster product			
Any mRNA	96/613 (15.7)	422/815 (51.8)	86.3 (81.1–90.1)
Pfizer BioNTech	76/416 (18.3)	335/580 (57.8)	88.0 (82.3–91.9)
Moderna	17/193 (8.8)	73/220 (33.2)	85.4 (69.4–93.0)
Time since booster, d			
<60	68/585 (11.6)	331/724 (45.7)	86.2 (80.4–90.3)
60–119	28/545 (5.1)	91/484 (18.8)	86.6 (74.8–92.9)
≥120	0/517 (0)	0/393 (0)	…
Omicron period[c]			
Booster product			
Any mRNA	1758/2577 (68.2)	2731/3077 (88.8)	64.6 (58.4–69.9)
Pfizer BioNTech	1297/1885 (68.8)	1992/2228 (89.4)	63.6 (55.8–69.9)
Moderna	374/597 (62.6)	620/728 (85.2)	66.8 (53.0–76.6)
Time since booster, d			
<60	288/1107 (26.0)	486/832 (58.4)	73.4 (66.6–78.9)
60–119	954/1773 (53.8)	1414/1760 (80.3)	63.8 (56.6–69.8)
≥120	516/1335 (38.7)	831/1177 (70.6)	32.1 (4.5–51.7)

Abbreviations: CI, confidence interval; mRNA, messenger RNA; VE, vaccine effectiveness.

[a]Case-participants had symptomatic severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection confirmed by antigen test or nucleic acid amplification test (NAAT); control-participants had a negative SARS-CoV-2 NAAT result, with or without symptoms. Vaccination status was assigned on the test date as after a booster dose if ≥14 days after an mRNA booster dose administered ≥5 months after dose 2; the referent group was participants with dose 2 receipt ≥5 months before the test date without a booster dose.

[b]VE was estimated as 100% multiplied by (1 minus the odds ratio for vaccination status) by case/control status. A conditional model was used with a cluster of 2-week matching period and enrolling site to account for matching. Adjusted VE included age group in years (18–29, 30–39, 40–49, or ≥50 years), race and ethnicity (white non-Hispanic or other), educational level (doctoral/professional degree or other), underlying health conditions (yes or no), known contact with a person with coronavirus disease 2019 outside the workplace (yes or no).

[c]The Delta-predominant period was defined as before 19 December 2021; the Omicron-predominant period, as 19 December 2021 or later.

76.7%) for participants aged ≥50 years versus 64.0% (57.1%–69.9%) for younger participants, and 67.2% (60.6%–72.7%) for those with underlying health conditions versus 55.5% (39.4%–67.3%) for those with none. The VE was 74.3% (95% CI, 31.6%–90.3%) against COVID-19 during pregnancy compared with 70.9% (65.0%–75.8%) among non-pregnant female participants aged <50 years. Among immunocompromised participants, the VE was 74.7% (95% CI, 20.1%–92.0%) versus 71.6% (67.0%–75.6%) among other participants; we obtained similar estimates for the VE of dose 3 received >28 days after dose 2 (Table 4 footnotes). Adjusted estimates by subgroup were similar to unadjusted estimates (Supplementary Table 9) and to estimates obtained using unconditional logistic regression (Supplementary Table 10).

Supportive Analyses

Overall estimates of VE by a booster dose were similar when we applied different sizes of matched sets in conditional models (for example, matched on test date using 1-week or 4-week periods) or when we used unconditional regression, adjusted by variables used for matching and other covariates (Supplementary Table 11). Estimates were similar in various sensitivity analyses, including those limited to NAAT results, symptomatic control-participants, and participants with interviews conducted up to 60 days after the test date (to limit potential recall bias). Estimates were also similar among demographic subgroups, and by factors that might be associated with study enrollment, such as level of patient contact, reason for testing, and number of symptoms (Supplementary Table 11).

Table 4. Estimated Vaccine Effectiveness of a Messenger RNA (mRNA) Booster Dose Against Coronavirus Disease 2019 Among US Healthcare Personnel Who Received 2 mRNA Doses, by Subgroup, October 2021–June 2022

Characteristic by Variant Period	Booster Dose Recipients/All Participants in Group (%)[a]		Adjusted VE (95% CI)[b]
	Case-Participants	Control-Participants	
Overall period			
Age, y			
<50	1407/2472 (56.9)	2356/2938 (80.2)	70.4 (65.4–74.6)
≥50	447/718 (62.3)	797/954 (83.5)	73.8 (65.6–80.1)
Underlying health conditions			
No	599/929 (64.5)	941/1132 (83.1)	67.6 (58.7–74.6)
Yes	1255/2261 (55.5)	2212/2760 (80.1)	72.3 (67.5–76.3)
Pregnancy[c]			
No	1096/1947 (56.3)	1864/2328 (80.1)	74.7 (70.2–78.6)
Yes	37/69 (53.6)	70/89 (78.7)	74.2 (46.5–87.6)
Immunocompromised[d]			
No	1820/3132 (58.1)	3076/3804 (80.9)	75.1 (71.5–78.2)
Yes	34/58 (58.6)	77/88 (87.5)	85.0 (64.8–93.6)
Delta period[e]			
Age, y			
<50	76/485 (15.7)	309/608 (50.8)	85.3 (78.8–89.7)
≥50	20/128 (15.6)	113/207 (54.6)	89.2 (80.0–94.2)
Underlying health conditions			
No	39/189 (20.6)	125/230 (54.3)	82.8 (71.2–89.7)
Yes	57/424 (13.4)	297/585 (50.8)	87.8 (82.1–91.7)
Pregnancy[c]			
No	58/374 (15.5)	232/465 (49.9)	85.9 (79.0–90.6)
Yes	2/14 (14.3)	14/26 (53.8)	86.7 (23.3–97.7)
Immunocompromised[d]			
No	95/599 (15.9)	416/803 (51.8)	85.4 (80.3–89.2)
Yes	1/14 (7.1)	6/12 (50.0)	93.3 (25.0–99.4)
Omicron period[e]			
Age, y			
<50	1331/1987 (67.0)	2047/2330 (87.9)	64.0 (57.1–69.9)
≥50	427/590 (72.4)	684/747 (91.6)	66.9 (53.1–76.7)
Underlying health conditions			
No	560/740 (75.7)	816/902 (90.5)	55.5 (39.4–67.3)
Yes	1198/1837 (65.2)	1915/2175 (88.0)	67.2 (60.6–72.7)
Pregnancy[c]			
No	1038/1573 (66.0)	1632/1863 (87.6)	70.9 (65.0–75.8)
Yes	35/55 (63.6)	56/63 (88.9)	74.3 (31.6–90.3)
Immunocompromised[d]			
No	1725/2533 (68.1)	2660/3001 (88.6)	71.6 (67.0–75.6)
Yes	33/44 (75.0)	71/76 (93.4)	74.7 (20.1–92.0)

Abbreviations: CI, confidence interval; VE, vaccine effectiveness.

[a]Case-participants had symptomatic severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection confirmed by antigen or nucleic acid amplification test (NAAT); control-participants had a negative SARS-CoV-2 NAAT result, with or without symptoms. Vaccination status was assigned on the test date as after a booster dose if ≥14 days after a messenger RNA (mRNA) booster dose administered ≥5 months after dose 2; the referent group for analysis was participants with dose 2 receipt ≥5 months before the test date without a booster dose.

[b]VE was estimated as 100% multiplied by 1 minus the odds ratio for vaccination status by case/control status. To account for matching, for estimates by age group and underlying health conditions we used a conditional model with clustering by 2-week matching period and enrolling site; to account for sparse data in estimates by pregnancy status and immunocompromised status, broader clusters were used comprising 4-week periods and the US census region of the enrolling site. Adjusted VE included age group in years (18–29, 30–39, 40–49, or ≥50 years), race and ethnicity (white non-Hispanic or other), educational level (doctoral/professional degree or other), underlying health conditions (yes or no), and known contact with a person with coronavirus disease 2019 outside the workplace (yes or no).

[c]Pregnancy was defined as pregnant on the test date. Analyses by pregnancy status were restricted to female participants aged <50 years.

[d]Immunocompromised status was determined based on self-reported diagnoses or medical record review. During the Omicron-predominant period, the VE of a third dose administered >28 days (instead of >150 days) after dose 2 was 80.2% (39.4%–93.5%) among immunocompromised participants, compared with 71.5% (67.2%–75.2%) among other participants. *P* values for interactions between subgroups were all >.05.

[e]The Delta-predominant period was defined as before 19 December 2021; the Omicron-predominant period, as 19 December 2021 or later.

Estimates of VE up to 120 days after a booster dose were similar overall, irrespective of whether the referent group was receipt of two mRNA doses, or no COVID-19 (Supplementary Table 12). Compared with receiving no COVID-19 vaccine doses, the VE of 2 mRNA doses from January to December 2021 was 88.7% (95% CI, 85.2%–91.4%) during the pre-Delta and 57.6% (46.1%–66.7%) during the Delta period (Supplementary Table 13). However, the VE of 2 doses waned over time. During the Delta-predominant period included in the primary analysis (from 9 October 2021), the VE for 2 doses >150 days since the second dose was 19.2% (95% CI, −37.8% to 52.7%). During the Omicron-predominant period, the VE for 2 doses could not be estimated because of sparse data (Supplementary Table 14).

DISCUSSION

In this multisite case-control study we demonstrated that a booster dose of mRNA vaccines provided additional protection against COVID-19 among US healthcare personnel during Omicron variant predominance. However, protection during this period was lower than during Delta predominance, declining from approximately 75% within 60 days of a booster dose to 30% at ≥120 days (approximately 4 months) after a booster dose. Our findings among US healthcare personnel are consistent with those from other studies among adults in the general population that indicate lower protection by booster doses since predominance of the Omicron variant and its subvariants [9, 10, 18–23].

Declining protection against symptomatic infection by COVID-19 vaccines is driven by waning immunity within individuals, combined with partial immune evasion by new SARS-CoV-2 variants [7, 21, 24, 25]. However, VE wanes less against severe COVID-19 than against milder SARS-CoV-2 infection, likely because underlying cellular immunity is preserved [19, 26–28]. Nevertheless, protection by a booster dose also declines against severe COVID-19 [9, 10] and can be improved by receiving a fourth vaccine dose [29, 30]. Together with higher immunogenicity of bivalent vaccines against the SARS-CoV-2 Omicron variant, this led to recommendations for bivalent vaccines [31, 32]. In September 2023, COVID-19 vaccines with updated monovalent formulations were recommended in the United States for all persons aged 6 months and older [33, 34].

We found that protection by a booster dose was similar among subgroups. COVID-19 during pregnancy is associated with elevated maternal mortality rate, obstetric complications, and neonatal morbidity [34, 35]. Our findings of protection by a booster mRNA dose against relatively symptomatic SARS-CoV-2 infection during pregnancy complement a previous findings indicating protection against medically attended COVID-19 [16]. Other studies have indicated that COVID-19 vaccination during pregnancy is both safe and effective [36–40] and can also protect infants [41, 42]. However, vaccination coverage during pregnancy has lagged behind that of the overall US population [15]. Collectively, these findings support recommendations for COVID-19 vaccination before or during pregnancy.

Among individuals categorized as immunocompromised, we found evidence of comparable effectiveness of an mRNA booster dose ≥5 months after dose 2, and of effectiveness of a third dose received ≥28 days after dose 2. In general, immunocompromised persons are at increased risk of COVID-19–associated death [43] and frequently have impaired humoral responses to COVID-19 vaccines [44–46]. However, additional vaccine doses can improve seroconversion rates [44, 46]. Our findings fit with other evidence of the effectiveness of a booster dose against infection and severe disease among immunocompromised persons [18, 47, 48].

In contrast to estimated protection by a booster dose, we did not find evidence of comparable protection by 2 mRNA doses during the same period (October 2021 to July 2022). During the Omicron-predominant period, the VE of a 2-dose series could not be estimated, and case-participants and control-participants had similar odds of having received 2 doses. This represented a substantial decline from initial estimates of 90% VE that were consistent with estimated VE in the previous analysis [11]. Lack of evidence of ongoing protection from 2 doses among the referent group is consistent with our finding that estimates of booster VE were similar regardless of whether the comparison group had received 2 mRNA doses or no COVID-19 vaccine doses, as has been noted elsewhere [18, 49].

It is important to consider several potential limitations of our findings. First, although the test-negative component of our design mitigates selection bias [50], recipients of a booster dose reported milder COVID-19–like symptoms at presentation than dose 2 recipients, even without COVID-19. This suggests potential overrepresentation of booster recipients among control-participants, which could inflate VE estimates [51, 52]. However, VE estimates were broadly consistent, irrespective of symptom severity, SARS-CoV-2 test type, type of healthcare facility, and level of contact, suggesting that the overall impact of selection bias was limited. Although asymptomatic control-participants might have been selected differently from those reporting symptoms, inclusion of asymptomatic control-participants can yield valid estimates if they represent the source population for case-participants [13]. Consistent with a previous analysis [11], >80% of control-participants reported symptoms, and estimates varied by <1% when restricting analysis to symptomatic participants. Second, although we required a negative NAAT result for control-participants because of the limited sensitivity of antigen tests [53], imperfect performance of SARS-CoV-2 tests could lead to some misclassification. Third, unmeasured factors, such as differential mask use by

vaccination status [54] or increased use of monoclonal antibody among immunocompromised persons [55], could bias VE estimates. Although we excluded participants with known prior infection, higher accrual of immunity from unknown SARS-CoV-2 infection among referent groups might have attenuated VE estimates over time, particularly during periods of high transmission or when initial VE is lower [56].

Fourth, by the end of the analysis period only a small minority of participants remained unvaccinated or without a booster dose, limiting the sample size and the representativeness of the referent groups. Several VE estimates had wide CIs, and for subgroup analyses we were not able to estimate the VE compared with receiving no COVID-19 vaccine doses. Fifth, during the Omicron-predominant period several new subvariants have predominated [15] for which COVID-19 vaccines are less effective [10, 19], which might have contributed to decreased protection during this time. Sixth, categorization of underlying conditions depended on both self-report and available electronic health record information. Finally, the generalizability of our findings might be limited. Participants were more likely to be female, younger, and white non-Hispanic than the general US population. Although the proportion of immunocompromised participants was similar to national estimates [57], the extent of reported immunocompromise was sometimes unknown, and immunocompromised healthcare personnel might have milder illness than immunocompromised persons in the general population. Nevertheless, participants represented a range of demographic groups in 21 states, and VE estimates were similar among demographic subgroups.

In summary, we found that a booster dose was effective in protecting US healthcare personnel against symptomatic SARS-CoV-2 infection during the Delta-predominant and Omicron-predominant periods, including for subgroups such as pregnant and immunocompromised persons. During the analysis period, healthcare personnel who had received 2 vaccine doses >150 days previously had similar susceptibility to COVID-19 as those who were unvaccinated, reflecting waning protection by 2 doses over time and against SARS-CoV-2 variants. Despite the benefit of a booster dose, protection was lower during the Omicron-predominant than during the Delta-predominant period, and protection waned over time. Our findings of a substantial but waning benefit of booster doses reinforce the importance of staying up to date with COVID-19 vaccines to maximize protection against COVID-19 [58], and they support recommendations to receive an updated COVID-19 vaccine dose when eligible [31, 33].

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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Author contributions. All authors certify that they meet authorship criteria. I. D. P. wrote the first draft and incorporated feedback from coauthors, who had also contributed to conduct of the study. The analysis was planned by I. D. P., M. H., R. W., and T. P., with input from other coauthors. Data were prepared by J. J. G. and G. A. and analyzed by I. D. P., who had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Data availability. Data for the study are classified as restricted and are not publicly available.

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