Supplement to:

‘Effectiveness of an mRNA vaccine booster dose against COVID-19 among U.S. healthcare personnel, October 2021–July 2022

Supplementary Methods:

Participants with multiple test results

Participants were only eligible for inclusion if there was no known previous positive SARS-CoV-2 infection. For participants with multiple test results, the test date was derived from the earliest recent test result. For control-participants, re-enrollment was possible provided any symptoms had resolved at least 4 weeks previously. Additional details of the component of the study performed at PREVENT sites, including the study protocol and forms, is available at: https://medicine.uiowa.edu/content/preventing-emerging-infections-through-vaccine-effectiveness-testing-prevent-project (accessed February 11 2023).

Additional analyses of vaccine effectiveness

To account for different recommendations for timing of a third vaccine dose among immunocompromised persons, we repeated the main analysis of VE among immunocompromised persons comparing receipt of a 3rd dose at least 28 days after dose 2 with a referent group who were also at least 28 days after dose 2.

To assess the effect of stratum size on conditional model performance we repeated overall estimates using different size clusters by calendar time and site. Since subgroup analyses can generate unbalanced strata, and unconditional analyses can be used with matched data, particularly if strata are sparse[1], we also generated estimates using unconditional logistic regression models that included calendar time and site or region, in addition to other covariates.

To consider the robustness of our findings to potential bias related to presence of symptoms, illness severity, interview timing, type of SARS-CoV-2 test, access to vaccination or testing, and demographic group we conducted further subgroup analyses of VE by these categories.

As context for the assessment of booster VE after two doses, we also assessed VE of a booster dose compared with unvaccinated participants as the referent, using the same definition of a booster dose and same time period as in the primary analysis. To assess whether estimated protection remained by 2 doses during the

[1] Pearce N. Analysis of matched case-control studies. *BMJ*. 2016;352:i969. doi:10.1136/bmj.i969

analysis period we also estimated VE after 2 doses for all participants with a test date from January 1, 2021, or later, using unvaccinated participants as the referent, by product and time since dose 2, within each variant period.

Box S1: Occupational groups included in the definition of healthcare personnel in the study, by anticipated level of direct patient contact

Anticipated substantial patient contact

- Home health aide/caregiver
- Licensed practical nurse
- Medical assistant
- Nurse practitioner
- Nursing assistant
- Occupational therapist
- Phlebotomist
- Physical therapist
- Physician (attending)
- Physician (fellow)
- Physician (intern/resident)
- Physician assistant
- Registered nurse
- Respiratory therapist
- Speech therapist

Anticipated moderate patient contact

- Chaplain
- Environmental services worker
- Food services worker
- Nutritionist
- Social worker
- Student

Anticipated minimal patient contact

- Administrative staff
- Cytotechnologist
- Facilities/maintenance worker
- Histotechnologist
- Laboratory personnel
- Medical laboratory technician
- Medical/clinical lab scientist
- Other laboratory personnel
- Pharmacist or pharmacy personnel
- PhD laboratory scientist
- Ward clerk

Box S2: COVID-19–like symptoms defined for analysis purposes

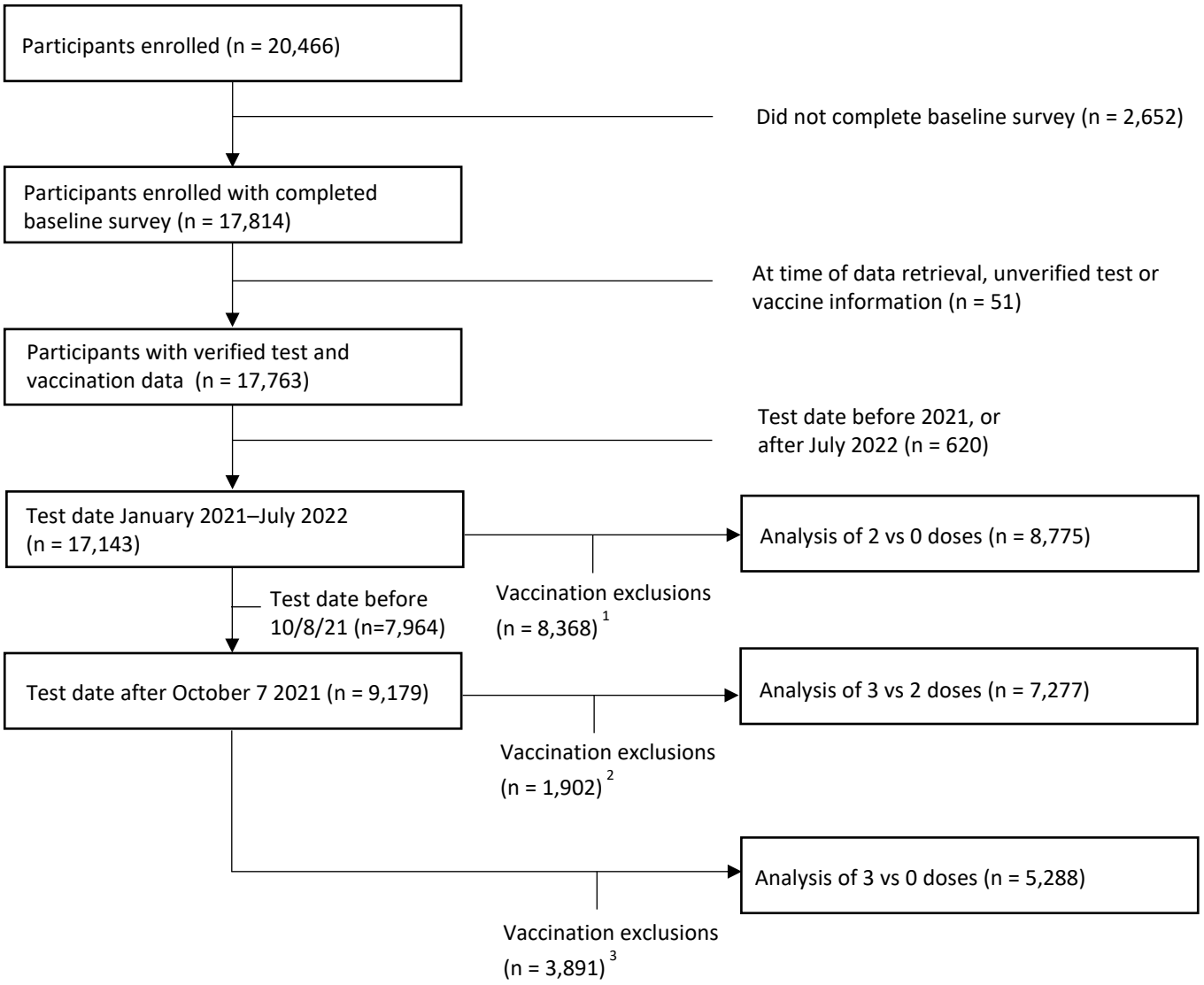
- Abdominal pain
- Altered sense of smell or taste
- Chest pain/tightness
- Chills
- Congestion
- Diarrhea
- Documented fever ≥100.0°F
- Dry cough
- Fatigue or malaise
- Felt feverish
- Headache
- Loss of appetite
- Muscle aches
- Nausea or vomiting
- Productive cough
- Red or bruised toes or feet
- Runny nose
- Shortness of breath
- Sore throat

Supplementary Table 1: Categorization of underlying health conditions and pregnancy among U.S. healthcare personnel

Category	Notes	Source from survey	Source from medical chart
Pulmonary disease	Includes asthma, chronic pulmonary disease	Questions on asthma, COPD, other pulmonary disease; free text	Questions on asthma, COPD, other pulmonary disease; free text
Cardiac disease	Cardiac disease, excluding hypertension, peripheral vascular disease, or findings that might not be pathologic	Question on cardiovascular disease; free text	Question on cardiovascular disease; free text
Liver disease	Chronic liver disease	Question on chronic liver disease; free text	Question on chronic liver disease; free text
Renal disease	Chronic renal disease, including renal dialysis patients	Questions on chronic renal disease, renal dialysis; free text	Questions on chronic renal disease, renal dialysis; free text
Diabetes mellitus type 1 or 2	Excludes pre-diabetes	Question on diabetes; free text	Question on diabetes, free text
Obesity	Based on clinical diagnosis or BMI	Reported BMI ≥30	Question on obesity, BMI ≥30
Overweight without obesity	Excludes diagnosis of obesity	Reported BMI ≥25 and BMI<30	BMI ≥25 and BMI<30
Cancer	Current or previous solid organ or hematologic cancer	Question on history of cancer; free text	Question on history of cancer; free text
Immunocompromised	Includes list of any specific condition or medication associated with immunocompromised state, including HIV, hematopoietic stem cell or solid organ transplant	Question on survey regarding medication or conditions, or free text, *if* specific medications or conditions listed that are associated with immunocompromise	Questions on any specific condition or medication associated with immunocompromised state, including HIV, hematopoietic stem cell or solid organ transplant
Mood disorder	Limited to depressive and mood disorders, including schizophrenia	Free text	Free text
Smoking or substance abuse	Current or previous cigarette smoking	Question on history of smoking; free text	Question on history of smoking; free text
Other diagnosis	Other conditions contributing to the definition of 'underlying health condition': congenital disorders, neurodegenerative disorders, sickle cell disease or thalassemia major, TB disease.	Free text	Free text
Pregnancy	Current pregnancy on date of specimen collection	Question on pregnancy and gestation	Question on pregnancy and gestation

Abbreviation: BMI – body mass index in kg/m^2

Supplementary Figure 1: Inclusion of U.S. healthcare personnel in analyses comparing different vaccine schedules



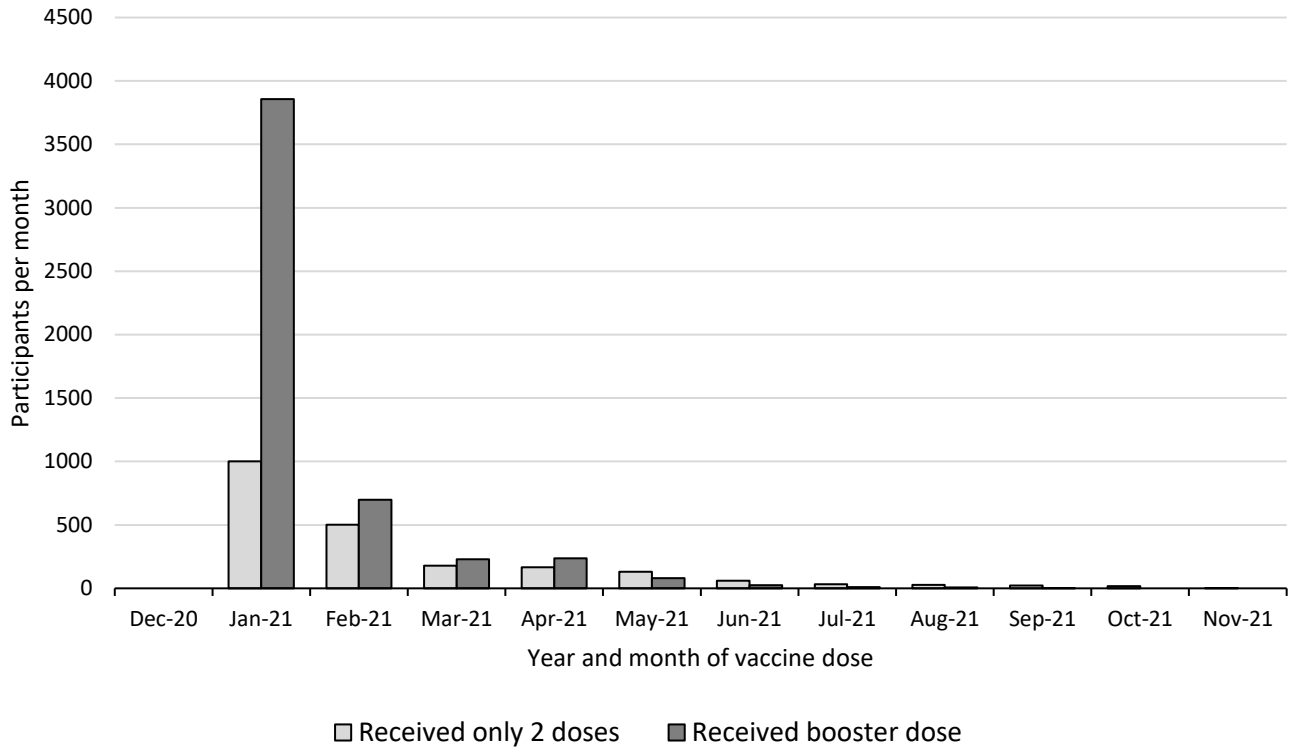
1) not confirmed as mRNA (n=361); 1 dose (n=1,212); ≥3 doses (n=6,268); 2 doses, <14 days (n=523); Dose 1 before December 2020 (n=4)
2) not confirmed as mRNA (n=272); Unvaccinated (n=139); 1 dose (n=78); >3 doses (n=143); <14d after dose 2 or 3 (n=265); Dose 1 before 12/1/2020 or dose 3 before 9/24/21 (n=616); test or dose 3 <5mo after dose 2 (n=389)
3) not confirmed as mRNA (n=272); 1 dose (n=78); 2 doses (n=2,508); >3 doses (n=143); <14d after dose 3 (n=252); Dose 1 before 12/1/2020 or dose 3 before 9/24/21 (n=609); test or dose 3 <5mo after dose 2 (n=29)

Supplementary Table 2: States of participating health facilities for case- and control-participants included in the primary and supportive analyses of mRNA COVID-19 vaccine effectiveness among U.S. healthcare personnel

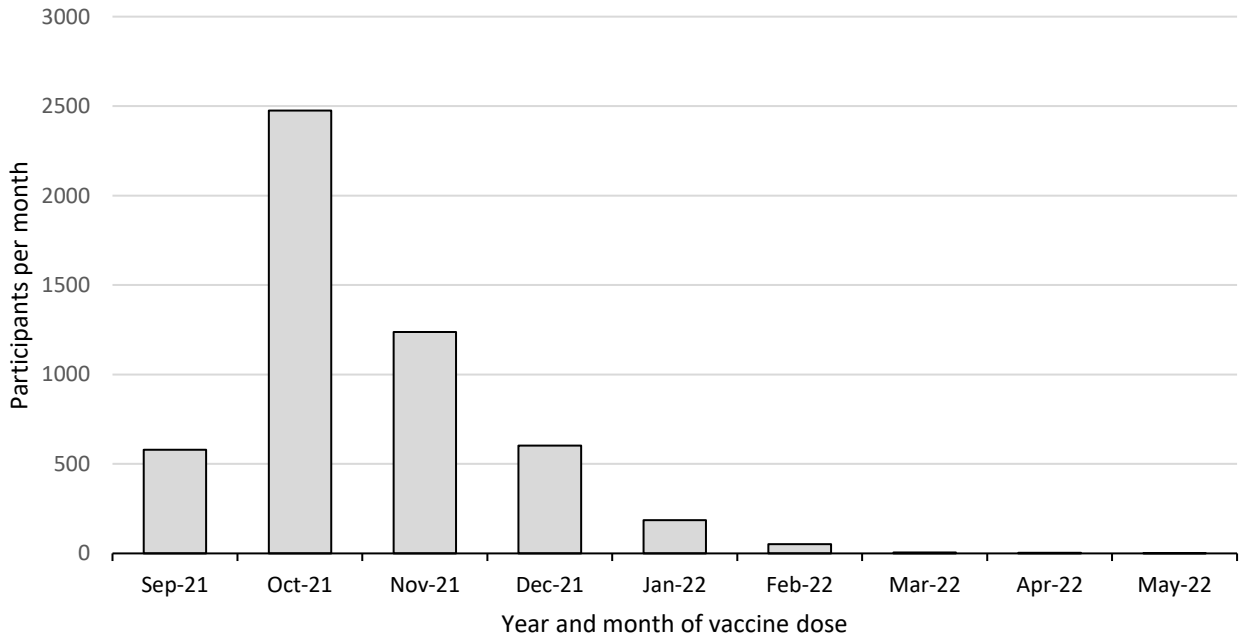
	Primary VE analysis (3 doses compared with 2 doses)		Supportive analysis of booster VE (3 doses compared with unvaccinated)		Supportive analysis of 2-dose VE (2 doses compared with unvaccinated)	
State	**No. Case-participants**	**No. Control-participants**	**No. Case-participants**	**No. Control-participants**	**No. Case-participants**	**No. Control-participants**
Alabama	239	58	94	39	370	96
Arizona	18	16	14	13	26	13
California[1]	53	45	33	37	75	110
Colorado	94	161	60	135	161	325
Connecticut	124	148	77	101	133	184
Florida	16	11	11	7	50	51
Georgia	145	41	81	30	137	97
Iowa	234	481	182	411	160	366
Illinois	81	85	60	71	48	95
Louisiana	0	5	0	2	18	28
Massachusetts[a]	472	403	272	278	454	530
Maryland	48	73	33	57	146	301
Minnesota	6	9	1	4	26	51
Missouri	110	108	58	88	127	145
Mississippi	65	31	28	28	198	185
New Mexico	85	21	29	14	204	158
New York	568	1216	336	1042	644	981
Oregon	351	425	275	386	257	277
Pennsylvania	248	162	93	89	416	452
Tennessee	219	438	177	409	189	363
Washington	103	61	79	54	71	57
Total	**3279**	**3998**	**1993**	**3295**	**3910**	**4865**

Footnote: a. Includes more than one participating site

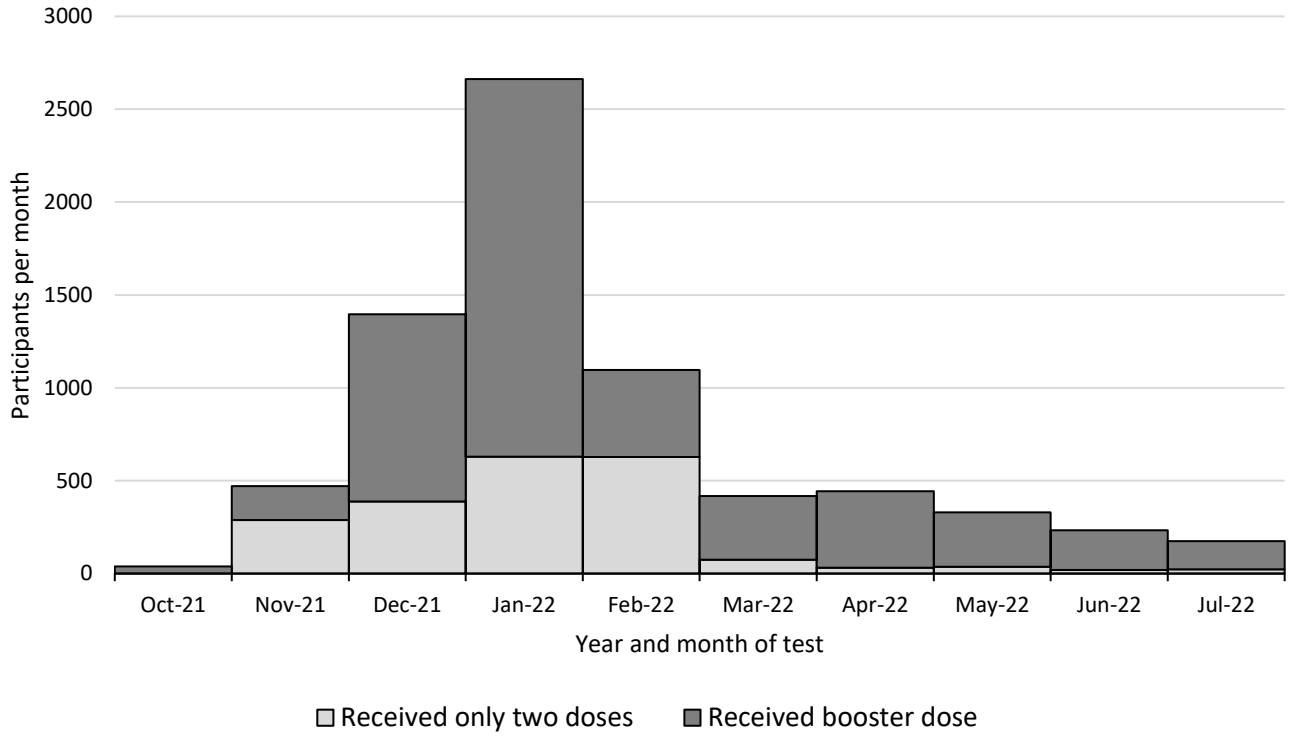
Supplementary Figure 2: Year and month of 2nd mRNA COVID-19 vaccine dose among U.S. healthcare personnel, by whether received a booster dose or only two doses



Supplementary Figure 3: Year and month of an mRNA COVID-19 vaccine booster dose among U.S. healthcare personnel



Supplementary Figure 4: Year and month of SARS-CoV-2 test among U.S. healthcare personnel, by whether received an mRNA COVID-19 booster dose or only the primary series of two doses



Supplementary Table 3: Additional Characteristics of Healthcare Personnel with COVID-19 (Case-participants) or who tested negative for SARS-CoV-2 (Control-participants) at 24 U.S. Sites, October 2021–July 2022

Characteristic	Case-participants No. with characteristic / Total (%)	Control-participants No. with characteristic / Total (%)	SMD
HHS region			
1	596/3279 (18.2%)	551/3998 (13.8%)	0.120
2	568/3279 (17.3%)	1216/3998 (30.4%)	-0.311
3	296/3279 (9%)	235/3998 (5.9%)	0.120
4	684/3279 (20.9%)	579/3998 (14.5%)	0.168
5	87/3279 (2.7%)	94/3998 (2.4%)	0.019
6	85/3279 (2.6%)	26/3998 (0.7%)	0.154
7	344/3279 (10.5%)	589/3998 (14.7%)	-0.128
8	94/3279 (2.9%)	161/3998 (4%)	-0.064
9	71/3279 (2.2%)	61/3998 (1.5%)	0.048
10	454/3279 (13.8%)	486/3998 (12.2%)	0.050
Health insurance			
Private	3007/3273 (91.9%)	3686/3996 (92.2%)	-0.014
Government	112/3273 (3.4%)	136/3996 (3.4%)	0.001
Other	9/3273 (0.3%)	13/3996 (0.3%)	-0.009
No insurance	145/3273 (4.4%)	161/3996 (4%)	0.020
Household income			
<50k	413/3271 (12.6%)	479/3997 (12%)	0.020
50–100k	1059/3271 (32.4%)	1254/3997 (31.4%)	0.021
≥100k	1524/3271 (46.6%)	1941/3997 (48.6%)	-0.039
Declined	275/3271 (8.4%)	323/3997 (8.1%)	0.012
Complete precautions if close contact with a patient			
Always or mostly	184/471 (39.1%)	257/762 (33.7%)	0.111
Sometimes	108/471 (22.9%)	166/762 (21.8%)	0.027
Rarely or never	146/471 (31%)	284/762 (37.3%)	-0.132
Not sure	33/471 (7%)	55/762 (7.2%)	-0.008
Number of symptoms, if reported			
1–3	756/3161 (23.9%)	1801/3296 (54.6%)	-0.663
>3	2405/3161 (76.1%)	1495/3296 (45.4%)	0.663
Hospitalized with illness			
No	195/203 (96.1%)	168/192 (87.5%)	0.315
Yes	8/203 (3.9%)	24/192 (12.5%)	-0.315
Work in an ED or hospital			
No	868/3279 (26.5%)	1250/3998 (31.3%)	-0.106
Yes	2411/3279 (73.5%)	2748/3998 (68.7%)	0.106
Days from test date to interview			
14–60	3232/3278 (98.6%)	3720/3996 (93.1%)	0.278
>60	46/3278 (1.4%)	276/3996 (6.9%)	-0.278

Abbreviations: SMD, standardized mean difference. ED, emergency department

Supplementary Table 4: Characteristics of healthcare personnel who received a second COVID-19 mRNA vaccine dose by whether an mRNA booster dose was also received at 24 U.S. Sites, October 2021–July 2022

Characteristic	Did not receive booster dose (n=2129)	Received booster dose (n=5070)	SMD
Age group, years			
18–29	529/2120 (25.0%)	968/5103 (19.0%)	0.145
30–39	693/2120 (32.7%)	1749/5103 (34.3%)	-0.034
40–49	455/2120 (21.5%)	1113/5103 (21.8%)	-0.008
≥50	443/2120 (20.9%)	1273/5103 (24.9%)	-0.096
Sex			
Male	361/2129 (17.0%)	978/5139 (19.0%)	-0.054
Female	1767/2129 (83%)	4153/5139 (80.8%)	0.057
Unknown	1/2129 (0%)	8/5139 (0.2%)	-0.034
Race and ethnicity			
White, non-Hispanic	1593/2094 (76.1%)	4099/5055 (81.1%)	-0.122
Black, non-Hispanic	200/2094 (9.6%)	258/5055 (5.1%)	0.171
Hispanic	199/2094 (9.5%)	310/5055 (6.1%)	0.126
Other, non-Hispanic	102/2094 (4.9%)	388/5055 (7.7%)	-0.116
Educational level			
No college degree	375/2127 (17.6%)	434/5141 (8.4%)	0.275
College degree	1536/2127 (72.2%)	3471/5141 (67.5%)	0.103
Doctoral or professional degree	211/2127 (9.9%)	1224/5141 (23.8%)	-0.377
Unknown	5/2127 (0.2%)	12/5141 (0.2%)	0.000
Categories of underlying health conditions			
0	542/2134 (25.4%)	1597/5143 (31.1%)	-0.126
1	924/2134 (43.3%)	2115/5143 (41.1%)	0.044
≥2	668/2134 (31.3%)	1431/5143 (27.8%)	0.076
Variant period of test			
Delta	926/2134 (43.4%)	528/5143 (10.3%)	0.806
Omicron	1208/2134 (56.6%)	4615/5143 (89.7%)	-0.806
Vaccination status (overall)			
After dose 2	2134/2134 (100%)	0/5143 (0%)	-
After booster	0/2134 (0%)	5143/5143 (100%)	-
Known COVID-19 contact in 14 days before symptom onset or positive test	1388/2131 (65.1%)	3284/5143 (63.9%)	0.027
At work, patient	686/1697 (40.4%)	1593/4138 (38.5%)	0.026
At work, not a patient	481/1544 (31.2%)	1189/3781 (31.4%)	-0.013
Outside work	786/2005 (39.2%)	1951/4558 (42.8%)	-0.022
Fever present, if any symptoms			
No	1011/2134 (47.4%)	3588/5143 (69.8%)	-0.467
Yes	1123/2134 (52.6%)	1555/5143 (30.2%)	0.467

Abbreviations: SMD, standardized mean difference.

Supplementary Table 5: Characteristics of healthcare personnel tested during the Delta-predominant period or during the Omicron-predominant period at 24 U.S. Sites, October 2021–July 2022

Characteristic	Delta-predominant period[a]	Omicron-predominant period[a]	SMD
Age group, years			
18–29	323/1448 (22.3%)	1174/5775 (20.3%)	0.048
30–39	485/1448 (33.5%)	1957/5775 (33.9%)	-0.008
40–49	300/1448 (20.7%)	1268/5775 (22%)	-0.030
≥50	340/1448 (23.5%)	1376/5775 (23.8%)	-0.008
Sex			
Male	284/1453 (19.5%)	1055/5815 (18.1%)	0.036
Female	1168/1453 (80.4%)	4752/5815 (81.7%)	-0.034
Unknown	1/1453 (0.1%)	8/5815 (0.1%)	-0.021
Race and ethnicity			
White, non-Hispanic	1186/1436 (82.6%)	4506/5713 (78.9%)	0.094
Black, non-Hispanic	60/1436 (4.2%)	398/5713 (7.0%)	-0.122
Hispanic	125/1436 (8.7%)	384/5713 (6.7%)	0.074
Other, non-Hispanic	65/1436 (4.5%)	425/5713 (7.4%)	-0.123
Educational level			
No college degree	176/1453 (12.1%)	633/5815 (10.9%)	0.038
College degree	1029/1453 (70.8%)	3978/5815 (68.4%)	0.052
Doctoral or professional degree	246/1453 (16.9%)	1189/5815 (20.4%)	-0.090
Unknown	2/1453 (0.1%)	15/5815 (0.3%)	-0.027
Underlying health conditions			
0	433/1454 (29.8%)	1706/5823 (29.3%)	0.011
1	594/1454 (40.9%)	2445/5823 (42.0%)	-0.023
≥2	427/1454 (29.4%)	1672/5823 (28.7%)	0.014
Variant period of test[a]			
Delta	1454/1454 (100%)	0/5823 (0%)	-
Omicron	0/1454 (0%)	5823/5823 (100%)	-
Vaccination status (overall)			
After dose 2	926/1454 (63.7%)	1208/5823 (20.7%)	0.965
After booster	528/1454 (36.3%)	4615/5823 (79.3%)	-0.965
Known COVID-19 contact in 14 days before symptom onset or positive test	830/1453 (57.1%)	3842/5821 (66.0%)	-0.183
At work, patient	448/1216 (36.8%)	1831/4619 (39.6%)	-0.014
At work, not a patient	220/1146 (19.2%)	1450/4179 (34.7%)	-0.246
Outside work	436/1362 (32.0%)	2301/5201 (44.2%)	-0.201

Abbreviations: SMD, standardized mean difference.

a. During this analysis period, the Delta-predominant period was defined as before December 19, 2021; the Omicron-predominant period was defined as December 19, 2021 or later.

Supplementary Table 6: Characteristics of Healthcare Personnel with COVID-19 (Case-participants) or who tested negative for SARS-CoV-2 (Control-participants) at 24 U.S. Sites, October 2021–July 2022 (subset of participants who received a booster dose or were unvaccinated)

Characteristic	Case-participants No. with characteristic / Total (%)	Control-participants No. with characteristic / Total (%)	SMD
Age group, years			
18–29	399/1977 (20.2%)	603/3265 (18.5%)	0.043
30–39	683/1977 (34.5%)	1118/3265 (34.2%)	0.006
40–49	420/1977 (21.2%)	725/3265 (22.2%)	-0.023
≥50	475/1977 (24.0%)	819/3265 (25.1%)	-0.025
Sex			
Male	400/1993 (20.1%)	599/3291 (18.2%)	0.048
Female	1591/1993 (79.8%)	2686/3291 (81.6%)	-0.045
Unknown	2/1993 (0.1%)	6/3291 (0.2%)	-0.022
Race and ethnicity			
White, non-Hispanic	1535/1957 (78.4%)	2667/3236 (82.4%)	-0.100
Black, non-Hispanic	126/1957 (6.4%)	149/3236 (4.6%)	0.080
Hispanic	138/1957 (7.1%)	187/3236 (5.8%)	0.052
Other, non-Hispanic	158/1957 (8.1%)	233/3236 (7.2%)	0.033
Educational level			
No college degree	178/1991 (8.9%)	279/3295 (8.5%)	0.017
College degree	1375/1991 (69.1%)	2212/3295 (67.1%)	0.041
Doctoral or professional degree	432/1991 (21.7%)	797/3295 (24.2%)	-0.059
Unknown	6/1991 (0.3%)	7/3295 (0.2%)	0.018
Underlying health conditions			
0	647/1993 (32.5%)	994/3295 (30.2%)	0.050
1	820/1993 (41.1%)	1354/3295 (41.1%)	0.001
≥2	526/1993 (26.4%)	947/3295 (28.7%)	-0.053
Variant period of test			
Delta	144/1993 (7.2%)	460/3295 (14%)	-0.220
Omicron	1849/1993 (92.8%)	2835/3295 (86.0%)	0.220
Vaccination status (overall)			
Unvaccinated	85/1993 (4.3%)	54/3295 (1.6%)	0.156
After booster	1908/1993 (95.7%)	3241/3295 (98.4%)	-0.156
Known COVID-19 contact in 14 days before symptom onset or positive test	1392/1993 (69.8%)	1972/3295 (59.8%)	0.210
At work, patient	597/1568 (38.1%)	1043/2690 (38.8%)	-0.037
At work, not a patient	416/1372 (30.3%)	801/2521 (31.8%)	-0.082
Outside work	949/1733 (54.8%)	1045/2963 (35.3%)	0.329

Abbreviations: SMD, standardized mean difference.

Supplementary Table 7: Characteristics of Healthcare Personnel with COVID-19 (Case Participants) or who tested negative for SARS-CoV-2 (Control Participants) at 24 U.S. Sites, January 2021–July 2022 (subset of participants who received two doses or were unvaccinated)

Characteristic	Case-participants No. with characteristic / Total (%)	Case-participants No. with characteristic / Total (%)	SMD
Age group, years			
18–29	959/3884 (24.7%)	1010/4822 (20.9%)	0.089
30–39	1288/3884 (33.2%)	1825/4822 (37.8%)	-0.098
40–49	866/3884 (22.3%)	944/4822 (19.6%)	0.067
≥50	771/3884 (19.9%)	1043/4822 (21.6%)	-0.044
Sex			
Male	662/3897 (17%)	853/4856 (17.6%)	-0.015
Female	3230/3897 (82.9%)	3997/4856 (82.3%)	0.015
Unknown	5/3897 (0.1%)	6/4856 (0.1%)	0.001
Race and ethnicity			
White, non-Hispanic	2693/3829 (70.3%)	3656/4761 (76.8%)	-0.147
Black, non-Hispanic	517/3829 (13.5%)	418/4761 (8.8%)	0.151
Hispanic	411/3829 (10.7%)	403/4761 (8.5%)	0.077
Other, non-Hispanic	208/3829 (5.4%)	284/4761 (6%)	-0.023
Educational level			
No college degree	709/3898 (18.2%)	752/4856 (15.5%)	0.072
College degree	2784/3898 (71.4%)	3203/4856 (66%)	0.118
Doctoral or professional degree	398/3898 (10.2%)	889/4856 (18.3%)	-0.233
Unknown	7/3898 (0.2%)	12/4856 (0.2%)	-0.015
Underlying health conditions			
0	999/3910 (25.5%)	1246/4865 (25.6%)	-0.001
1	1768/3910 (45.2%)	2069/4865 (42.5%)	0.054
≥2	1143/3910 (29.2%)	1550/4865 (31.9%)	-0.057
Variant period of test[a]			
Pre-Delta period	885/3910 (22.6%)	1695/4865 (34.8%)	-0.272
Delta-predominant period	1950/3910 (49.9%)	2710/4865 (55.7%)	-0.117
Omicron-predominant period	1075/3910 (27.5%)	460/4865 (9.5%)	0.478
Vaccination status (overall)			
Unvaccinated	956/3910 (24.5%)	750/4865 (15.4%)	0.228
After dose 2	2954/3910 (75.5%)	4115/4865 (84.6%)	-0.228
Known COVID-19 contact in 14 days before symptom onset or positive test	2601/3902 (66.7%)	2426/4859 (49.9%)	0.344
At work, patient	1187/3192 (37.2%)	1498/4092 (36.6%)	-0.009
At work, not a patient	699/2885 (24.2%)	818/3913 (20.9%)	0.029
Outside work	1630/3677 (44.3%)	935/4626 (20.2%)	0.504

Abbreviations: SMD, standardized mean difference.

a. The Delta-predominant period was defined as June 20, 2021–December 18, 2021; the Omicron-predominant period was defined as December 19, 2021 or later.

Supplementary Table 8: Estimated Vaccine Effectiveness of an mRNA booster dose against COVID-19 among U.S. healthcare personnel who received two mRNA doses, by variant-predominant period, October 2021–July 2022 (including unadjusted and adjusted estimates)

Characteristic	Case-participants after a booster dose / No. received 2 doses ≥5 months earlier (%)[a]	Control-participants after a booster dose / No. received 2 doses ≥5 months earlier (%)[a]	Unadjusted VE (95% CI)[b]	Case-participants after a booster dose / No. received 2 doses ≥5 months earlier (%)[c]	Control-participants after a booster dose / No. received 2 doses ≥5 months earlier (%)[c]	Adjusted VE (95% CI)[b]
Any period						
Booster product						
Any mRNA	1904/3279 (58.1%)	3239/3998 (81.0%)	**71.5 (67.3-75.2)**	1854/3190 (58.1%)	3153/3892 (81.0%)	**71.1 (66.7-75.0)**
Pfizer BioNTech	1412/2372 (59.5%)	2394/2887 (82.9%)	**72.1 (67.1-76.3)**	1373/2301 (59.7%)	2327/2808 (82.9%)	**71.2 (65.8-75.7)**
Moderna	395/801 (49.3%)	708/971 (72.9%)	**70.9 (61.0-78.2)**	391/790 (49.5%)	693/948 (73.1%)	**71.6 (61.3-79.2)**
Days since booster dose						
<60	362/1737 (20.8%)	845/1604 (52.7%)	**78.4 (74.1-82.0)**	356/1692 (21.0%)	817/1556 (52.5%)	**78.2 (73.6-82.0)**
60-119	1007/2382 (42.3%)	1536/2295 (66.9%)	**68.0 (62.3-72.9)**	982/2318 (42.4%)	1505/2244 (67.1%)	**67.1 (60.9-72.3)**
≥120	535/1910 (28.0%)	858/1617 (53.1%)	**34.8 (9.6-52.9)**	516/1852 (27.9%)	831/1570 (52.9%)	**33.6 (6.6-52.8)**
Delta-predominant period[d]						
Booster product						
Any mRNA	96/620 (15.5%)	432/834 (51.8%)	**85.8 (80.6-89.6)**	96/613 (15.7%)	422/815 (51.8%)	**86.3 (81.1-90.1)**
Pfizer BioNTech	76/421 (18.1%)	342/593 (57.7%)	**86.8 (80.9-90.9)**	76/416 (18.3%)	335/580 (57.8%)	**88.0 (82.3-91.9)**
Moderna	17/195 (8.7%)	76/226 (33.6%)	**84.5 (69.4-92.2)**	17/193 (8.8%)	73/220 (33.2%)	**85.4 (69.4-93.0)**
Days since booster dose						
<60	68/592 (11.5%)	340/742 (45.8%)	**85.1 (79.3-89.3)**	68/585 (11.6%)	331/724 (45.7%)	**86.2 (80.4-90.3)**
60-119	28/552 (5.1%)	92/494 (18.6%)	**86.8 (75.6-92.8)**	28/545 (5.1%)	91/484 (18.8%)	**86.6 (74.8-92.9)**
≥120	0/524 (0%)	0/402 (0%)	-	0/517 (0%)	0/393 (0%)	-
Omicron-predominant period[d]						
Booster product						
Any mRNA	1808/2659 (68.0%)	2807/3164 (88.7%)	**65.4 (59.6-70.3)**	1758/2577 (68.2%)	2731/3077 (88.8%)	**64.6 (58.4-69.9)**
Pfizer BioNTech	1336/1951 (68.5%)	2052/2294 (89.5%)	**65.4 (58.4-71.3)**	1297/1885 (68.8%)	1992/2228 (89.4%)	**63.6 (55.8-69.9)**
Moderna	378/606 (62.4%)	632/745 (84.8%)	**65.8 (52.6-75.4)**	374/597 (62.6%)	620/728 (85.2%)	**66.8 (53.0-76.6)**
Days since booster dose						
<60	294/1145 (25.7%)	505/862 (58.6%)	**74.3 (67.9-79.4)**	288/1107 (26.0%)	486/832 (58.4%)	**73.4 (66.6-78.9)**
60-119	979/1830 (53.5%)	1444/1801 (80.2%)	**65.2 (58.7-70.8)**	954/1773 (53.8%)	1414/1760 (80.3%)	**63.8 (56.6-69.8)**
≥120	535/1386 (38.6%)	858/1215 (70.6%)	**34.8 (9.6-52.9)**	516/1335 (38.7%)	831/1177 (70.6%)	**32.1 (4.5-51.7)**

a. Case-participants had symptomatic SARS-CoV-2 infection confirmed by antigen or nucleic acid amplification test; control-participants had a negative SARS-CoV-2 nucleic acid amplification test, 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 that was administered ≥5 months after dose 2. The referent group was receipt of dose 2 ≥5 months before the test date without a booster dose.
b. Vaccine effectiveness was estimated as 100% multiplied by the reciprocal of the odds ratio for vaccination status by case/control status. A conditional model was used with a cluster of two-week matching period and enrolling site to account for matching. Adjusted vaccine effectiveness included age group in years (18–29, 30–39, 40–49, ≥50), sex, race and ethnicity (White non-Hispanic, other), educational level (doctoral or professional degree, other), underlying health conditions (yes, no), known contact with a person with COVID-19 outside the workplace (yes, no).
c. Observations restricted to participants included in the multivariable model (with no missing covariate information).
d. The Delta-predominant period was defined as June 20, 2021–December 18, 2021; the Omicron-predominant period was defined as December 19, 2021, or later.

Supplementary Table 9: Estimated Effectiveness of mRNA vaccines against COVID-19 among U.S. healthcare personnel who received two mRNA doses by variant-predominant period, October 2021–July 2022, using *conditional* logistic regression

Characteristic	Case-participants after a booster dose / All case-participants (%)[a]	Control-participants after a booster dose / All control-participants (%)[a]	Unadjusted VE (95% CI)[b]	Case-participants after a booster dose / All case-participants (%)[c]	Control-participants after a booster dose / All control-participants (%)[c]	Adjusted VE (95% CI)[b]
Overall period[d]						
Age, years						
<50	1433/2519 (56.9%)	2397/2988 (80.2%)	**70.9 (66.2-75.0)**	1407/2472 (56.9%)	2356/2938 (80.2%)	**70.4 (65.4-74.6)**
≥50	458/739 (62.0%)	815/977 (83.4%)	**73.5 (65.4-79.7)**	447/718 (62.3%)	797/954 (83.5%)	**73.8 (65.6-80.1)**
Underlying health conditions						
No	619/962 (64.3%)	978/1177 (83.1%)	**68.4 (60.1-75.0)**	599/929 (64.5%)	941/1132 (83.1%)	**67.6 (58.7-74.6)**
Yes	1285/2317 (55.5%)	2261/2821 (80.1%)	**72.8 (68.2-76.7)**	1255/2261 (55.5%)	2212/2760 (80.1%)	**72.3 (67.5-76.3)**
Pregnancy[e]						
No	1114/1977 (56.3%)	1890/2362 (80.0%)	**74.4 (69.9-78.2)**	1096/1947 (56.3%)	1864/2328 (80.1%)	**74.7 (70.2-78.6)**
Yes	37/69 (53.6%)	70/89 (78.7%)	**76.0 (50.7-88.3)**	37/69 (53.6%)	70/89 (78.7%)	**74.2 (46.5-87.6)**
Immunocompromised[f]						
No	1869/3217 (58.1%)	3162/3910 (80.9%)	**75.3 (71.9-78.3)**	1820/3132 (58.1%)	3076/3804 (80.9%)	**75.1 (71.5-78.2)**
Yes	35/62 (56.5%)	77/88 (87.5%)	**86.6 (69.0-94.2)**	34/58 (58.6%)	77/88 (87.5%)	**85.0 (64.8-93.6)**
Delta-predominant period[d]						
Age, years						
<50	76/490 (15.5%)	313/618 (50.6%)	**84.3 (77.8-88.8)**	76/485 (15.7%)	309/608 (50.8%)	**85.3 (78.8-89.7)**
≥50	20/129 (15.5%)	115/211 (54.5%)	**89.2 (80.2-94.1)**	20/128 (15.6%)	113/207 (54.6%)	**89.2 (80.0-94.2)**
Underlying health conditions						
No	39/193 (20.2%)	131/240 (54.6%)	**83.1 (72.5-89.6)**	39/189 (20.6%)	125/230 (54.3%)	**82.8 (71.2-89.7)**
Yes	57/427 (13.3%)	301/594 (50.7%)	**87.1 (81.3-91.1)**	57/424 (13.4%)	297/585 (50.8%)	**87.8 (82.1-91.7)**
Pregnancy[e]						
No	58/375 (15.5%)	234/472 (49.6%)	**84.1 (76.8-89.1)**	58/374 (15.5%)	232/465 (49.9%)	**85.9 (79.0-90.6)**
Yes	2/14 (14.3%)	14/26 (53.8%)	**90.6 (48.1-98.3)**	2/14 (14.3%)	14/26 (53.8%)	**86.7 (23.3-97.7)**
Immunocompromised[f]						
No	95/605 (15.7%)	426/822 (51.8%)	**85.3 (80.4-88.9)**	95/599 (15.9%)	416/803 (51.8%)	**85.4 (80.3-89.2)**
Yes	1/15 (6.7%)	6/12 (50.0%)	**94.6 (43.4-99.5)**	1/14 (7.1%)	6/12 (50.0%)	**93.3 (25.0-99.4)**
Omicron-predominant period[d]						
Age, years						
<50	1357/2029 (66.9%)	2084/2370 (87.9%)	**65.2 (58.7-70.7)**	1331/1987 (67.0%)	2047/2330 (87.9%)	**64.0 (57.1-69.9)**
≥50	438/610 (71.8%)	700/766 (91.4%)	**65.9 (52.1-75.7)**	427/590 (72.4%)	684/747 (91.6%)	**66.9 (53.1-76.7)**
Underlying health conditions						
No	580/769 (75.4%)	847/937 (90.4%)	**56.3 (41.2-67.6)**	560/740 (75.7%)	816/902 (90.5%)	**55.5 (39.4-67.3)**
Yes	1228/1890 (65.0%)	1960/2227 (88%)	**68.2 (62.0-73.3)**	1198/1837 (65.2%)	1915/2175 (88.0%)	**67.2 (60.6-72.7)**
Pregnancy[e]						
No	1056/1602 (65.9%)	1656/1890 (87.6%)	**71.2 (65.5-75.9)**	1038/1573 (66.0%)	1632/1863 (87.6%)	**70.9 (65.0-75.8)**
Yes	35/55 (63.6%)	56/63 (88.9%)	**75.3 (34.5-90.7)**	35/55 (63.6%)	56/63 (88.9%)	**74.3 (31.6-90.3)**
Immunocompromised[f]						
No	1774/2612 (67.9%)	2736/3088 (88.6%)	**72.1 (67.7-75.8)**	1725/2533 (68.1%)	2660/3001 (88.6%)	**71.6 (67.0-75.6)**
Yes	34/47 (72.3%)	71/76 (93.4%)	**77.6 (31.4-92.7)**	33/44 (75.0%)	71/76 (93.4%)	**74.7 (20.1-92.0)**

a. Case-participants had symptomatic SARS-CoV-2 infection confirmed by antigen or nucleic acid amplification test; control-participants had a negative SARS-CoV-2 nucleic acid amplification test, 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 that was administered ≥5 months after dose 2; the referent group for analysis was receipt of dose 2 ≥5 months before the test date without a booster dose.
b. Vaccine effectiveness was estimated as 100% multiplied by the reciprocal of 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 two-week matching period and enrolling site; to account for sparse data in estimates by pregnancy status and immunocompromised status, broader clusters were used comprising four-week period and U.S. census region of enrolling site. Adjusted vaccine effectiveness included age group in years (18–29, 30–39, 40–49, ≥50), sex, race and ethnicity (White non-Hispanic, other), educational level (doctoral or professional degree, other), underlying health conditions (yes, no), known contact with a person with COVID-19 outside the workplace (yes, no).
c. Observations restricted to participants included in the multivariable model (with no missing covariate information).
d. The Delta-predominant period was defined as June 20, 2021–December 18, 2021; the Omicron-predominant period was defined as December 19, 2021, or later.
e. Pregnancy was defined as pregnant on the test date. Analyses by pregnancy status were restricted to female participants age <50 years.
f. Immunocompromised status was determined based on self-reported diagnoses or medical chart review. During the Omicron-predominant period, VE by a 3rd dose administered >28 days after dose 2 (instead of after >150 days) was 80.2% (39.4%–93.5%) among immunocompromised participants, compared with 71.5% (67.2%–75.2%) among other participants.

Supplementary Table 10: Estimated Effectiveness of mRNA vaccines against COVID-19 among U.S. healthcare personnel who received two mRNA doses by variant-predominant period, October 2021–July 2022, using *unconditional* logistic regression

Characteristic	Case-participants after a booster dose / All case-participants (%)[a]	Control-participants after a booster dose / All control-participants (%)[a]	Unadjusted VE (95% CI)[b]	Case-participants after a booster dose / All case-participants (%)[c]	Control-participants after a booster dose / All control-participants (%)[c]	Adjusted VE (95% CI)[b]
Overall period[d]						
Age, years						
<50	1433/2519 (56.9%)	2397/2988 (80.2%)	**72.4 (68.0-76.1)**	1407/2472 (56.9%)	2356/2938 (80.2%)	**71.8 (67.2-75.7)**
≥50	458/739 (62.0%)	815/977 (83.4%)	**70.9 (62.6-77.4)**	447/718 (62.3%)	797/954 (83.5%)	**71.3 (62.9-77.8)**
Underlying health conditions						
No	619/962 (64.3%)	978/1177 (83.1%)	**71.5 (64.1-77.3)**	599/929 (64.5%)	941/1132 (83.1%)	**70.6 (62.7-76.8)**
Yes	1285/2317 (55.5%)	2261/2821 (80.1%)	**72.6 (68.2-76.4)**	1255/2261 (55.5%)	2212/2760 (80.1%)	**72.0 (67.4-76.0)**
Pregnancy[e]						
No	1114/1977 (56.3%)	1890/2362 (80.0%)	**70.8 (65.6-75.3)**	1096/1947 (56.3%)	1864/2328 (80.1%)	**70.8 (65.3-75.4)**
Yes	37/69 (53.6%)	70/89 (78.7%)	**75.7 (49.1-88.4)**	37/69 (53.6%)	70/89 (78.7%)	**73.9 (44.8-87.7)**
Immunocompromised[f]						
No	1869/3217 (58.1%)	3162/3910 (80.9%)	**71.9 (67.9-75.4)**	1820/3132 (58.1%)	3076/3804 (80.9%)	**71.5 (67.3-75.2)**
Yes	35/62 (56.5%)	77/88 (87.5%)	**82.9 (59.3-92.8)**	34/58 (58.6%)	77/88 (87.5%)	**80.6 (53.0-92.0)**
Delta-predominant period[d]						
Age, years						
<50	76/490 (15.5%)	313/618 (50.6%)	**84.5 (78.5-88.9)**	76/485 (15.7%)	309/608 (50.8%)	**85.2 (79.0-89.5)**
≥50	20/129 (15.5%)	115/211 (54.5%)	**88.9 (80.0-93.8)**	20/128 (15.6%)	113/207 (54.6%)	**89.1 (80.0-94.0)**
Underlying health conditions						
No	39/193 (20.2%)	131/240 (54.6%)	**83.9 (74.2-90.0)**	39/189 (20.6%)	125/230 (54.3%)	**83.5 (72.8-90.0)**
Yes	57/427 (13.3%)	301/594 (50.7%)	**87.0 (81.4-91.0)**	57/424 (13.4%)	297/585 (50.8%)	**87.4 (81.7-91.3)**
Pregnancy[e]						
No	58/375 (15.5%)	234/472 (49.6%)	**84.9 (77.7-89.8)**	58/374 (15.5%)	232/465 (49.9%)	**87.0 (80.2-91.5)**
Yes	2/14 (14.3%)	14/26 (53.8%)	**89.6 (39.0-98.2)**	2/14 (14.3%)	14/26 (53.8%)	**83.9 (1.9-97.4)**
Immunocompromised[f]						
No	95/605 (15.7%)	426/822 (51.8%)	**85.7 (80.7-89.4)**	95/599 (15.9%)	416/803 (51.8%)	**86.1 (80.9-89.8)**
Yes	1/15 (6.7%)	6/12 (50.0%)	**94.8 (39.9-99.5)**	1/14 (7.1%)	6/12 (50.0%)	**93.8 (25.6-99.5)**
Omicron-predominant period[d]						
Age, years						
<50	1357/2029 (66.9%)	2084/2370 (87.9%)	**65.6 (59.2-70.9)**	1331/1987 (67%)	2047/2330 (87.9%)	**64.3 (57.6-70.0)**
≥50	438/610 (71.8%)	700/766 (91.4%)	**66.0 (52.6-75.6)**	427/590 (72.4%)	684/747 (91.6%)	**67.1 (53.8-76.6)**
Underlying health conditions						
No	580/769 (75.4%)	847/937 (90.4%)	**59.2 (45.3-69.5)**	560/740 (75.7%)	816/902 (90.5%)	**58.3 (43.6-69.2)**
Yes	1228/1890 (65.0%)	1960/2227 (88.0%)	**67.7 (61.5-72.8)**	1198/1837 (65.2%)	1915/2175 (88.0%)	**66.8 (60.3-72.3)**
Pregnancy[e]						
No	1056/1602 (65.9%)	1656/1890 (87.6%)	**64.4 (57.0-70.6)**	1038/1573 (66%)	1632/1863 (87.6%)	**63.8 (56.0-70.2)**
Yes	35/55 (63.6%)	56/63 (88.9%)	**70.5 (19.6-89.1)**	35/55 (63.6%)	56/63 (88.9%)	**69.7 (16.2-89.0)**
Immunocompromised[f]						
No	1774/2612 (67.9%)	2736/3088 (88.6%)	**65.4 (59.7-70.3)**	1725/2533 (68.1%)	2660/3001 (88.6%)	**64.9 (58.8-70.0)**
Yes	34/47 (72.3%)	71/76 (93.4%)	**70.6 (3.5-91.0)**	33/44 (75.0%)	71/76 (93.4%)	**65.6 (-17.1-89.9)**

a. Case-participants had symptomatic SARS-CoV-2 infection confirmed by antigen or nucleic acid amplification test; control-participants had a negative SARS-CoV-2 nucleic acid amplification test, 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 that was administered ≥5 months after dose 2; the referent group for analysis was receipt of dose 2 ≥5 months before the test date without a booster dose.
b. Vaccine effectiveness was estimated as 100% multiplied by the reciprocal of the odds ratio for vaccination status by case/control status. Unconditional adjusted vaccine effectiveness estimates included enrolling site, two-week period, age group in years (18–29, 30–39, 40–49, ≥50), sex, race and ethnicity (White non-Hispanic, other), educational level (doctoral or professional degree, other), underlying health conditions (yes, no), known contact with a person with COVID-19 outside the workplace (yes, no).
c. Observations restricted to participants included in the multivariable model (with no missing covariate information).
d. The Delta-predominant period was defined as June 20, 2021–December 18, 2021; the Omicron-predominant period was defined as December 19, 2021, or later.
e. Pregnancy was defined as pregnant on the test date. Analyses by pregnancy status were restricted to female participants age <50 years.
f. Immunocompromised status was determined based on self-reported diagnoses or medical chart review. During the Omicron-predominant period, VE by a 3rd dose administered >28 days after dose 2 (instead of after >150 days) was 72.6% (10.7%–91.6%) among immunocompromised participants, compared with 65.0% (59.4%–69.8%) among other participants.

Supplementary Table 11: Supportive analyses: Estimated Effectiveness of an mRNA Booster Dose against COVID-19 among U.S. healthcare personnel who received two mRNA doses using different models and by subgroup, October 2021–July 2022

Characteristic	Case-participants after a booster dose / All case-participants (%)[a]	Control-participants after a booster dose / All control-participants (%)[a]	Adjusted VE (95% CI)[b]
Model type			
Unconditional, 2-week period by site	1854/3190 (58.1%)	3153/3892 (81.0%)	**71.7 (67.5-75.3)**
Conditional, 1-week strata by site	1854/3190 (58.1%)	3153/3892 (81.0%)	**71.0 (66.5-75.0)**
Conditional, 2-week strata by site	1854/3190 (58.1%)	3153/3892 (81.0%)	**71.1 (66.7-75.0)**
Conditional, 4-week strata by site	1854/3190 (58.1%)	3153/3892 (81.0%)	**70.8 (66.4-74.7)**
Conditional, 4-week strata by HHS region	1854/3190 (58.1%)	3153/3892 (81.0%)	**74.6 (70.9-77.8)**
Conditional, 4-week strata by USC region	1854/3190 (58.1%)	3153/3892 (81.0%)	**75.3 (71.8-78.3)**
Sensitivity analyses			
Nucleic acid amplification test results only	1778/3034 (58.6%)	3153/3892 (81.0%)	**70.7 (66.2-74.7)**
Symptomatic illness	1854/3190 (58.1%)	2580/3234 (79.8%)	**70.5 (65.7-74.6)**
Interview during 14–60 days after test date	1831/3144 (58.2%)	2968/3624 (81.9%)	**70.0 (65.3-74.1)**
Subgroup analyses			
Sex			
Male	377/603 (62.5%)	571/692 (82.5%)	**69.6 (58.9-77.5)**
Female	1477/2587 (57.1%)	2582/3200 (80.7%)	**71.4 (66.7-75.4)**
Race and ethnicity			
White, non-Hispanic	1463/2466 (59.3%)	2605/3184 (81.8%)	**71.5 (66.6-75.6)**
Other race or ethnicity	391/724 (54.0%)	548/708 (77.4%)	**70.0 (60.8-77.0)**
Educational level			
No professional or doctoral degree	1436/2654 (54.1%)	2381/3033 (78.5%)	**71.5 (67.0-75.5)**
Professional or doctoral degree	418/536 (78.0%)	772/859 (89.9%)	**67.6 (53.6-77.4)**
Anticipated level of patient contact			
Substantial	673/1162 (57.9%)	1238/1512 (81.9%)	**74.1 (68.1-79.1)**
Minimal, moderate, or unknown	1181/2028 (58.2%)	1915/2380 (80.5%)	**69.0 (63.3-73.9)**
Works at hospital or ED?			
No	491/836 (58.7%)	988/1212 (81.5%)	**72.2 (64.8-78.1)**
Yes	1363/2354 (57.9%)	2165/2680 (80.8%)	**70.8 (65.6-75.1)**
Reason for testing			
Symptoms	1578/2739 (57.6%)	2201/2761 (79.7%)	**70.5 (65.4-74.9)**
Exposure without symptoms	213/349 (61.0%)	278/340 (81.8%)	**71.0 (57.1-80.4)**
Other	63/102 (61.8%)	101/133 (75.9%)	**60.4 (24.5-79.3)**
No. symptoms if symptomatic			
1-3	526/736 (71.5%)	1434/1756 (81.7%)	**53.5 (40.9-63.4)**
>3	1274/2339 (54.5%)	1135/1464 (77.5%)	**69.9 (63.7-75.1)**
Fever, if symptomatic			
No	1000/1461 (68.4%)	2502/3020 (82.8%)	**60.4 (52.5-67.0)**
Yes	854/1729 (49.4%)	651/872 (74.7%)	**67.4 (59.6-73.7)**

a. Case-participants had symptomatic SARS-CoV-2 infection confirmed by antigen or nucleic acid amplification test; control-participants had a negative SARS-CoV-2 nucleic acid amplification test, 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 that was administered ≥5 months after dose 2; the referent group for analysis was receipt of dose 2 ≥5 months before the test date without a booster dose.
b. Vaccine effectiveness was estimated as 100% multiplied by the reciprocal of the odds ratio for vaccination status by case/control status. Unless otherwise specified, a conditional model was used with a cluster of two-week matching period and enrolling site to account for matching. Adjusted vaccine effectiveness included age group in years (18–29, 30–39, 40–49, ≥50), sex, race and ethnicity (White non-Hispanic, other), educational level (doctoral or professional degree, other), underlying health conditions (yes, no), known contact with a person with COVID-19 outside the workplace (yes, no).

Supplementary Table 12: Estimated vaccine effectiveness of an mRNA booster dose against COVID-19 among U.S. healthcare personnel compared with unvaccinated status, by variant-predominant period, October 2021–July 2022

Characteristic	Case-participants after a booster dose / Case-participants after a booster or unvaccinated (%)[a]	Control-participants after a booster dose / Control-participants after a booster or unvaccinated (%)[a]	Unadjusted VE (95% CI)[b]	Case-participants after a booster dose / Case-participants after a booster or unvaccinated (%)[c]	Control-participants after a booster dose / Control-participants after a booster or unvaccinated (%)[c]	Adjusted VE (95% CI)[b]
Any period [d]						
Booster product						
Any mRNA	1908/1993 (95.7%)	3241/3295 (98.4%)	**73.9 (61.2-82.5)**	1858/1937 (95.9%)	3155/3204 (98.5%)	**76.0 (63.7-84.2)**
Pfizer BioNTech	1415/1500 (94.3%)	2396/2450 (97.8%)	**73.0 (59.8-81.9)**	1376/1455 (94.6%)	2329/2378 (97.9%)	**75.1 (62.3-83.6)**
Moderna	396/481 (82.3%)	708/762 (92.9%)	**70.7 (52.4-81.9)**	392/471 (83.2%)	693/742 (93.4%)	**74.4 (56.8-84.8)**
Days since booster dose						
<60	363/448 (81.0%)	846/900 (94.0%)	**78.8 (67.8-86.1)**	357/436 (81.9%)	818/867 (94.3%)	**80.3 (69.4-87.3)**
60-119	1009/1094 (92.2%)	1537/1591 (96.6%)	**65.1 (44.8-77.9)**	984/1063 (92.6%)	1506/1555 (96.8%)	**68.7 (49.4-80.6)**
≥120	536/621 (86.3%)	858/912 (94.1%)	[e]	517/596 (86.7%)	831/880 (94.4%)	[e]
Delta period [d]						
Booster product						
Any mRNA	96/144 (66.7%)	432/460 (93.9%)	**89.3 (80.3-94.2)**	96/140 (68.6%)	422/448 (94.2%)	**89.0 (79.0-94.3)**
Pfizer BioNTech	76/124 (61.3%)	342/370 (92.4%)	**89.0 (79.5-94.0)**	76/120 (63.3%)	335/361 (92.8%)	**88.4 (77.6-94.0)**
Moderna	17/65 (26.2%)	76/104 (73.1%)	**91.3 (76.2-96.8)**	17/61 (27.9%)	73/99 (73.7%)	**94.7 (80.5-98.5)**
Days since booster dose						
<60	68/116 (58.6%)	340/368 (92.4%)	**89.6 (80.8-94.4)**	68/112 (60.7%)	331/357 (92.7%)	**89.8 (80.1-94.8)**
60-119	28/76 (36.8%)	92/120 (76.7%)	**88.1 (67.5-95.7)**	28/72 (38.9%)	91/117 (77.8%)	**88.3 (65.4-96.0)**
≥120	0/48 (0%)	0/28 (0%)	[e]	0/44 (0%)	0/26 (0%)	[e]
Omicron period [d]						
Booster product						
Any mRNA	1812/1849 (98.0%)	2809/2835 (99.1%)	**49.3 (15.5-69.5)**	1762/1797 (98.1%)	2733/2756 (99.2%)	**56.7 (25.6-74.8)**
Pfizer BioNTech	1339/1376 (97.3%)	2054/2080 (98.8%)	**48.1 (13.5-68.8)**	1300/1335 (97.4%)	1994/2017 (98.9%)	**54.7 (22.1-73.7)**
Moderna	379/416 (91.1%)	632/658 (96.0%)	**52.6 (16.4-73.1)**	375/410 (91.5%)	620/643 (96.4%)	**60.9 (27.2-79.0)**
Days since booster dose						
<60	295/332 (88.9%)	506/532 (95.1%)	**59.1 (27.9-76.8)**	289/324 (89.2%)	487/510 (95.5%)	**64.9 (36.0-80.8)**
60-119	981/1018 (96.4%)	1445/1471 (98.2%)	**52.7 (19.8-72.1)**	956/991 (96.5%)	1415/1438 (98.4%)	**58.0 (26.7-75.9)**
≥120	536/573 (93.5%)	858/884 (97.1%)	[e]	517/552 (93.7%)	831/854 (97.3%)	[e]

a. Case-participants had symptomatic SARS-CoV-2 infection confirmed by antigen or nucleic acid amplification test; control-participants had a negative SARS-CoV-2 nucleic acid amplification test, 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 that was administered ≥5 months after dose 2. The referent group was unvaccinated.

b. Vaccine effectiveness was estimated as 100% multiplied by the reciprocal of the odds ratio for vaccination status by case/control status. A conditional model was used with a cluster of two-week matching period and enrolling site to account for matching. Adjusted vaccine effectiveness included age group in years (18–29, 30–39, 40–49, ≥50), sex, race and ethnicity (White non-Hispanic, other), educational level (doctoral or professional degree, other), underlying health conditions (yes, no), known contact with a person with COVID-19 outside the workplace (yes, no).

c. Observations restricted to participants included in the multivariable model (with no missing covariate information).

d. The Delta-predominant period was defined as June 20, 2021–December 18, 2021; the Omicron-predominant period was defined as December 19, 2021, or later.

e. Estimates not shown if not calculable (for example, if zero observations) or if confidence intervals were >100%.

Supplementary Table 13: Estimated effectiveness of a second mRNA dose against COVID-19 among U.S. healthcare personnel compared with unvaccinated status, by variant-predominant period, January–December, 2021

Characteristic	Case-participants after dose 2 / Total (%)[a]	Control-participants after dose 2 / Total (%)[a]	Unadjusted VE (95% CI)[b]	Case-participants after dose 2 / Total (%)[c]	Control-participants after dose 2 / Total (%)[c]	Adjusted VE (95% CI)[b]
Pre-Delta period[d]						
Vaccine product						
Any mRNA	195/885 (22.0%)	1116/1695 (65.8%)	**89.0 (86.1-91.3)**	188/853 (22%)	1084/1652 (65.6%)	**88.7 (85.2-91.4)**
Pfizer BioNTech	166/856 (19.4%)	845/1424 (59.3%)	**87.2 (83.5-90.0)**	161/826 (19.5%)	823/1391 (59.2%)	**86.3 (81.8-89.6)**
Moderna	29/719 (4%)	271/850 (31.9%)	**93.6 (89.9-96.0)**	27/692 (3.9%)	261/829 (31.5%)	**93.8 (89.8-96.3)**
Days since dose 2						
<90	112/802 (14%)	763/1342 (56.9%)	**89.5 (86.3-91.9)**	107/772 (13.9%)	743/1311 (56.7%)	**89.5 (85.8-92.2)**
90-179	83/773 (10.7%)	353/932 (37.9%)	**84.8 (77.5-89.8)**	81/746 (10.9%)	341/909 (37.5%)	**81.7 (71.7-88.1)**
180-269	0/690 (0%)	0/579 (0%)	[e]	0/665 (0%)	0/568 (0%)	[e]
270-359	0/690 (0%)	0/579 (0%)	[e]	0/665 (0%)	0/568 (0%)	[e]
Delta period[d]						
Vaccine product						
Any mRNA	1721/1950 (88.3%)	2565/2710 (94.6%)	**59.4 (49.2-67.6)**	1692/1909 (88.6%)	2486/2622 (94.8%)	**57.6 (46.1-66.7)**
Pfizer BioNTech	1338/1567 (85.4%)	1925/2070 (93.0%)	**57.9 (47.2-66.5)**	1317/1534 (85.9%)	1867/2003 (93.2%)	**55.3 (42.9-65.0)**
Moderna	382/611 (62.5%)	636/781 (81.4%)	**65.9 (55.3-74.0)**	374/591 (63.3%)	615/751 (81.9%)	**65.5 (53.5-74.4)**
Days since dose 2						
<90	44/273 (16.1%)	90/235 (38.3%)	**71.6 (55.0-82.1)**	43/260 (16.5%)	89/225 (39.6%)	**73.9 (57.7-83.9)**
90-179	231/460 (50.2%)	473/618 (76.5%)	**67.8 (57.5-75.5)**	220/437 (50.3%)	459/595 (77.1%)	**69.2 (58.5-77.1)**
180-269	1073/1302 (82.4%)	1776/1921 (92.5%)	**59.3 (48.5-67.8)**	1060/1277 (83.0%)	1716/1852 (92.7%)	**54.6 (41.4-64.9)**
270-359	373/602 (62%)	226/371 (60.9%)	**6.0 (-51.2-41.6)**	369/586 (63.0%)	222/358 (62.0%)	[e]

a. Case-participants had symptomatic SARS-CoV-2 infection confirmed by antigen or nucleic acid amplification test; control-participants had a negative SARS-CoV-2 nucleic acid amplification test, with or without symptoms. Vaccination status was assigned on the test date as after dose 2 if ≥14 days after a second mRNA booster dose, with unvaccinated participants as the referent group.

b. Vaccine effectiveness was estimated as 100% multiplied by the reciprocal of the odds ratio for vaccination status by case/control status. A conditional model was used with a cluster of two-week matching period and enrolling site to account for matching. Adjusted vaccine effectiveness included age group in years (18–29, 30–39, 40–49, ≥50), sex, race and ethnicity (White non-Hispanic, other), educational level (doctoral or professional degree, other), underlying health conditions (yes, no), known contact with a person with COVID-19 outside the workplace (yes, no).

c. Observations restricted to participants included in the multivariable model (with no missing covariate information).

d. The pre-Delta period was defined as January 2021–June 19, 2021; the Delta-predominant period was defined as June 20, 2021–December 18, 2021.

e. Estimates not shown if not calculable (for example, if zero observations) or if confidence intervals were >100%.

Supplementary Table 14: Estimated effectiveness of a second mRNA dose against COVID-19 among U.S. healthcare personnel compared with unvaccinated status, by variant-predominant period, October 2021–July 2022

Characteristic	Case-participants after dose 2 / Total (%)[a]	Control-participants after dose 2 / Total (%)[a]	Unadjusted VE (95% CI)[b]	Case-participants after dose 2 / Total (%)[c]	Control-participants after dose 2 / Total (%)[c]	Adjusted VE (95% CI)[b]
Delta period included in primary analysis[d]						
Vaccine product						
Any mRNA	566/614 (92.2%)	455/483 (94.2%)	**28.7 (-17.2-56.7)**	557/601 (92.7%)	445/471 (94.5%)	**26.1 (-25.7-56.5)**
Pfizer BioNTech	381/429 (88.8%)	288/316 (91.1%)	**25.7 (-23.5-55.3)**	374/418 (89.5%)	282/308 (91.6%)	**20.5 (-37.0-53.9)**
Moderna	184/232 (79.3%)	165/193 (85.5%)	**38.7 (-7.6-65.1)**	182/226 (80.5%)	161/187 (86.1%)	**47.0 (1.7-71.4)**
Days since dose 2[e]						
≤150	42/90 (46.7%)	53/81 (65.4%)	**59.1 (19.2-79.3)**	40/84 (47.6%)	52/78 (66.7%)	**56.8 (5.5-80.2)**
>150	524/572 (91.6%)	402/430 (93.5%)	**23.4 (-26.4-53.6)**	517/561 (92.2%)	393/419 (93.8%)	**19.2 (-37.8-52.7)**
Omicron period[d]						
Vaccine product						
Any mRNA	1038/1075 (96.6%)	434/460 (94.3%)	[f]	997/1032 (96.6%)	417/440 (94.8%)	[f]
Pfizer BioNTech	764/801 (95.4%)	301/327 (92%)	[f]	729/764 (95.4%)	289/312 (92.6%)	[f]
Moderna	264/301 (87.7%)	131/157 (83.4%)	[f]	258/293 (88.1%)	126/149 (84.6%)	[f]
Days since dose 2 [e]			[f]			[f]
≤150	187/224 (83.5%)	77/103 (74.8%)	[f]	178/213 (83.6%)	71/94 (75.5%)	[f]
>150	851/888 (95.8%)	357/383 (93.2%)	[f]	819/854 (95.9%)	346/369 (93.8%)	[f]

a. Case-participants had symptomatic SARS-CoV-2 infection confirmed by antigen or nucleic acid amplification test; control-participants had a negative SARS-CoV-2 nucleic acid amplification test, with or without symptoms. Vaccination status was assigned on the test date as after dose 2 if ≥14 days after a second mRNA booster dose, with unvaccinated participants as the referent group.

b. Vaccine effectiveness was estimated as 100% multiplied by the reciprocal of the odds ratio for vaccination status by case/control status. A conditional model was used with a cluster of two-week matching period and enrolling site to account for matching. Adjusted vaccine effectiveness included age group in years (18–29, 30–39, 40–49, ≥50), sex, race and ethnicity (White non-Hispanic, other), educational level (doctoral or professional degree, other), underlying health conditions (yes, no), known contact with a person with COVID-19 outside the workplace (yes, no).

c. Observations restricted to participants included in the multivariable model (with no missing covariate information).

d. The Delta-predominant period included in the primary analysis was defined as October 9–December 18, 2021; the Omicron-predominant period was defined as December 19, 2021, or later.

e. During the Delta-predominant period, the median days (range) since dose 2 was 84 (16–149) for participants classified as ≤150 days, and 281 (151–345) for participants classified as >150 days; during the Omicron-predominant period, the median days (range) since dose 2 was 109 (17–150) for participants classified as ≤150 days, and 332 (152–557) for participants classified as >150 days.

f. Estimates not shown if not calculable (for example, if zero observations) or if confidence intervals were >100%.

Supplementary Table 15: Collaborators and other team members acknowledged by site

Site or other affiliation	Study team members acknowledged
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