Effectiveness of a bivalent mRNA vaccine dose against symptomatic SARS-CoV-2 infection among U.S. healthcare personnel, September 2022–May 2023

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Abstract

Background—Bivalent mRNA vaccines were recommended since September 2022. However, coverage with a recent vaccine dose has been limited, and there are few robust estimates of bivalent VE against symptomatic SARS-CoV-2 infection (COVID-19). We estimated VE of a bivalent mRNA vaccine dose against COVID-19 among eligible U.S. healthcare personnel who had previously received monovalent mRNA vaccine doses.

Methods—We conducted a case-control study in 22 U.S. states, and enrolled healthcare personnel with COVID-19 (case-participants) or without COVID-19 (control-participants) during September 2022–May 2023. Participants were considered eligible for a bivalent mRNA dose if they had received 2–4 monovalent (ancestral-strain) mRNA vaccine doses, and were 67 days after the most recent vaccine dose. We estimated VE of a bivalent mRNA dose using conditional logistic regression, accounting for matching by region and four-week calendar period. We adjusted estimates for age group, sex, race and ethnicity, educational level, underlying health conditions, community COVID-19 exposure, prior SARS-CoV-2 infection, and days since the last monovalent mRNA dose.

Results—Among 3,647 healthcare personnel, 1,528 were included as case-participants and 2,119 as control-participants. Participants received their last monovalent mRNA dose a median of 404 days previously; 1,234 (33.8%) also received a bivalent mRNA dose a median of 93 days previously. Overall, VE of a bivalent dose was 34.1% (95% CI, 22.6%–43.9%) against COVID-19 and was similar by product, days since last monovalent dose, number of prior doses, age group, and presence of underlying health conditions. However, VE declined from 54.8% (95% CI, 40.7%–65.6%) after 7–59 days to 21.6% (95% CI 5.6%–34.9%) after 60 days.

Conclusions—Bivalent mRNA COVID-19 vaccines initially conferred approximately 55% protection against COVID-19 among U.S. healthcare personnel. However, protection waned after two months. These findings indicate moderate initial protection against symptomatic SARS-CoV-2 infection by remaining up-to-date with COVID-19 vaccines.

Keywords

BACKGROUND

COVID-19 monovalent mRNA vaccines were initially highly effective in preventing illness and death from SARS-CoV-2 infection.[1, 2] However, vaccine effectiveness (VE) waned over time, and was lower against the Omicron SARS-CoV-2 variant and its subvariants.[2–4] To address these challenges, in September 2022 bivalent vaccines, that induce immunity against the spike protein from both ancestral SARS-CoV-2 (Wuhanhu-1) and Omicron

subvariants (BA.4/BA.5), were recommended in the United States.[5] Subsequent studies have demonstrated that these vaccines conferred substantial protection against severe illness, including against other subvariants of Omicron.[6–8]

Although bivalent vaccines might have also protected against overall symptomatic SARS-CoV-2 infection, relatively few studies have addressed this outcome.[9–13] Previous studies of ancestral monovalent vaccines suggested that VE against milder outcomes is generally lower and wanes more rapidly than protection against severe illness,[2, 14] Protection against symptomatic SARS-CoV-2 infection remains important to avert the risks of post-COVID conditions,[15, 16] and to prevent transmission to others.[17] Indirect protection of others has been estimated to prevent substantial mortality at the global scale,[1] and may be vital in protecting individuals who are at elevated risk of severe outcomes. For healthcare personnel, preventing SARS-CoV-2 infection is important to limit transmission between staff and patients, who might be at increased risk of severe illness, and to protect the healthcare workforce.[18, 19] Since coverage with a recent COVID-19 vaccine dose has been limited, understanding vaccine effectiveness against symptomatic infection can inform prevention efforts.

Using data from an ongoing case-control VE study, we evaluated the effectiveness of a bivalent mRNA COVID-19 vaccine dose against symptomatic SARS-CoV-2 infection (COVID-19 illness). We estimated VE of a bivalent dose among eligible U.S. healthcare personnel who had previously received ancestral monovalent mRNA doses. We summarized VE by product and by time since receiving a bivalent dose. To assess the robustness of our findings, we compared VE estimates among different subgroups of the study population, and conducted a range of supportive analyses.

METHODS

Setting and participants

Using previously described methods, we conducted a multisite case-control study to estimate COVID-19 vaccine effectiveness by comparing vaccination status among U.S. healthcare personnel with or without COVID-19.[4, 20] We limited the current analysis to participants with SARS-CoV-2 test results during September 2022–May 2023. During this period, the BA.5 Omicron subvariant was predominant in the United States, followed by other Omicron subvariants.[21] The current analysis included healthcare facilities in 22 U.S. states, such as hospitals, emergency departments, urgent care providers, outpatient clinics, and long-term care facilities (Supplementary Table 1).

At each facility, healthcare personnel aged 18 years were considered eligible for enrollment if they had potential direct or indirect exposure to patients or contaminated clinical materials (Supplementary Box 1), and had new SARS-CoV-2 nucleic acid amplification test (NAAT) or antigen test results. Participants with a reported SARS-CoV-2 infection >90 days before the recent test result were initially not eligible for enrollment in the study. Participants reporting prior infection became eligible for inclusion in some sites from October 2022, and in all sites from December 2022.

Following enrollment, we used standardized surveys conducted 14–60 days after the participant's test date to collect information on demographic, health and behavioral characteristics, prior infection, test results and vaccination status. We verified all SARS-CoV-2 tests, COVID-19 vaccine doses received, and any hospitalization with COVID-19–like illness using independent objective information, such as vaccine registries, medical charts, and state public health databases.

Analysis definitions and eligibility

We defined case-participants as those with a positive SARS-CoV-2 nucleic acid amplification test (NAAT) or antigen test result within 14 days of COVID-19–like symptoms (see Supplementary Box 2), and no prior positive SARS-CoV-2 test result during the previous 90 days. We defined control-participants as those with a negative SARS-CoV-2 NAAT result, and no positive NAAT or antigen test result during the previous 90 days to subsequent 30 days; we did not rely on negative antigen test results because of limited sensitivity.[22]

Healthcare personnel were eligible to re-enroll in the study if more than 60 days had elapsed since a previous SARS-CoV-2 test resulting in classification as a control-participant. However, we limited the current analysis to one enrollment per individual by excluding any re-enrollments during the analysis period. For analysis purposes, we defined prior SARS-CoV-2 infection as a self-reported positive NAAT or antigen test result more than 90 days before the test date. Based on previous studies of infection-induced immunity,[23, 24] we defined a recent previous SARS-CoV-2 infection as a self-reported prior infection between 90 days and 12 months before the index test date and since predominance of the Omicron variant. We categorized vaccination status based on the recent SARS-CoV-2 test date, and categorized underlying health conditions using a combination of survey responses and medical chart reviews (Supplementary Table 2).

Case- and control-participants were eligible to be included in the analysis if: 1) the test date was on or after September 8 (7 days after U.S. recommendations for a bivalent dose [5]), 2) they had received 2–4 monovalent mRNA vaccine doses before the test date, and 3) receipt of the most recent monovalent dose was   67 days before the test date. Participants were excluded from the analysis if they had enrolled in a COVID-19 clinical trial; participants were also excluded if they received a non-mRNA COVID-19 dose, an mRNA dose with unknown valency, >4 monovalent doses, >1 bivalent dose, doses after dose 2 <60 days apart, or a bivalent mRNA dose <7 days before the test date.

Estimation of vaccine effectiveness

To describe participants included in the analysis, we used standardized mean differences to compare characteristics by case-control and vaccination status. To estimate protection conferred by a bivalent dose against COVID-19, we estimated VE of a bivalent dose compared with only receiving monovalent doses, with the last dose at least 67 days before the index test date (allowing for 60 days since the last dose and 7 days since a bivalent dose). We estimated VE as 100% multiplied by one minus the odds ratio of vaccination status by case-control status. We used conditional logistic regression to estimate this odds

ratio,[25] after matching by four-week calendar period and U.S. Census region to account for varying risks of exposure to SARS-CoV-2. Based on postulated causal relationships, we adjusted estimates for age group, sex, race and ethnicity, educational level, underlying health conditions, reported community exposure to SARS-CoV-2 before the test date, reported recent prior SARS-CoV-2 infection, and days since the referent dose.[4, 24]

We estimated VE of a bivalent dose against symptomatic infection by product (Pfizer-BioNTech or Moderna), time since the bivalent dose, number of monovalent doses received, time since a referent dose, age group, and presence of underlying health conditions. We excluded participants from the analysis if they had missing values in covariates used for multivariable models, and limited subgroup analyses to those with at least 50 case-participants to account for sparse data.

Supportive analyses

To assess any residual protection from monovalent doses among the referent groups, we estimated relative VE from receiving 4 rather than 3 monovalent doses, or from receiving 3 rather than 2 monovalent doses. We performed sensitivity analyses to assess how estimates varied using unconditional logistic regression, conditional logistic regression with narrower strata (by site and two-week period), excluding asymptomatic control-participants, excluding case-participants with antigen test results, or excluding participants with reported immunocompromising conditions or medications. We also generated stratified estimates by reason for testing, estimated level of patient exposure, reported recent prior infection, reported fever, and by demographic factors. To address potential limitations arising at individual sites, we performed a 'leave-one-out' analysis, by repeating VE estimates excluding data from each site in turn.

We used Stata Statistical Software release 15.1 (StataCorp LLC, College Station, TX, 2017) to perform all analyses. This activity was reviewed by the Centers for Disease Control and Prevention (CDC) and was conducted consistent with applicable federal law and CDC policy.[1]

RESULTS

Overall characteristics

Our analysis included 3,647 participants enrolled from health systems in 22 U.S. states (Figure 1, Supplementary Table 3). Median age of participants was 38 years (range 18–77), and 3,023 (83.0%) were female. Participants had SARS-CoV-2 test dates between September 8, 2022 and May 31, 2023. Based on SARS-CoV-2 test results, 1,528 (41.9%) were included as case-participants, and 2,119 (58.1%) as control-participants. Illness was generally mild—among those with available information, 16 of 1,076 (1.5%) case-participants and 45 of 1,526 (3.0%) of control-participants reported being hospitalized within 14 days of their test date. During the period of analysis, participants had received a monovalent dose a median of 404 days (IQR, 333, 476) before the test date. Additionally,

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[1]This investigation was defined as having met the requirements for public health surveillance as defined in 45 C.F.R. part 46.102(l)(2) 21 C.F.R. part 56; 42 U.S.C. Sect. 241(d); 5 U.S.C. Sect. 552a; 44 U.S.C. Sect. 3501 et seq.

1,234 (33.8%) participants had received a bivalent mRNA COVID-19 vaccine dose a median of 93 days previously (interquartile range [IQR] 56, 138). Numbers of participants included by the most recent dose are summarized in Supplementary Figure 1.

Differences by case-control status

Differences in characteristics of participants by case-control status are summarized in Tables 1 and 2, and in Supplementary Table 4. Although case-participants were more frequently older than control-participants, other characteristics were generally similar by case-control status (Tables 1 and 2, Supplementary Table 4). Some differences between case- and control-participants reflected definitions used—656 (42.9%) of case-participants had an antigen-test–based SARS-CoV-2 result, whereas a negative NAAT result was required for control-participants, and all 1,528 case-participants reported symptoms, compared with 2,015 (95.1%) of control-participants. Among those reporting symptoms, 1,345 (88.0%) of case-participants and 1,560 (77.4%) of control-participants reported that symptoms were the reason for the SARS-CoV-2 test. Case-participants were more likely than control-participants to report community exposure to SARS-CoV-2, but were not more likely to report SARS-CoV-2 exposure at work. Control-participants were more likely than case-participants to report prior infection, although only if the reported prior infection occurred during Omicron predominance and within 12 months before the test date. Before the SARS-CoV-2 test date, 443 (29.0%) of case-participants and 791 (37.3%) of control-participants had received a bivalent mRNA dose (Table 2).

Differences by vaccination status

Compared with participants who only received monovalent doses, those who received a bivalent dose were generally older, more likely to be male, less likely to be Black non-Hispanic or Hispanic, more likely to have a doctoral or professional degree, and less likely to have a fever if symptomatic (Table 3). Differences in characteristics by the most recent dose received are summarized in Supplementary Table 5. Median days since the most recent monovalent dose was similar by vaccination status: 427 days (IQR, 353, 482) among bivalent dose recipients and 393 days (IQR, 327, 470) among those who did not receive bivalent dose.

Estimated effectiveness of a bivalent vaccine dose

During the analysis period, overall estimated effectiveness of a bivalent mRNA COVID-19 dose was 34.1% (95% confidence interval [95% CI] 22.6%–43.9%, Table 4). We estimated that VE was 34.0% (95% CI 21.1%–44.7%) for the Pfizer BioNTech bivalent vaccine, and 34.6% (95% CI 13.9%–50.3%) for the Moderna bivalent vaccine. Overall VE declined from 54.8% (95% CI 40.7%–65.6%) during the 7–59 days after the bivalent dose, to 21.6% (95% CI 5.6%–34.9%) 60 days after a bivalent dose. Among subgroups, VE estimates were similar by time since the last monovalent dose (<360 days or 360 days), number of prior monovalent doses, participant age (<50 years or 50 years), and by whether or not there were underlying health conditions (Table 4).

Supportive analyses

VE estimates that accounted for clustering by four-week period and U.S. Census region but without adjusting for other covariates were generally 5%–10% lower than adjusted estimates, and had overlapping confidence intervals (Supplementary Table 6). We found that estimates were similar to those in the primary analysis if using unconditional models, narrower strata, or if restricting analyses to NAAT results, symptomatic illness, or no known immunocompromise (Supplementary Table 7). Estimates appeared to be lower among those with symptomatic illness if the symptoms led to testing (rather than other reasons such as exposure). However, confidence intervals for these estimates overlapped. VE estimates also had overlapping confidence intervals when compared by demographic group, anticipated patient contact, work location, febrile status, or prior infection status (Supplementary Table 7). Overall estimates were largely unaffected by excluding data from each individual study site (Supplementary Table 8). Among participants who only received monovalent doses, estimated relative VE of three doses compared with two doses was 23.3% (2.4%–39.7%), and of four compared with three doses was 10.3% (−32.3%–39.2%; Supplementary Table 9).

DISCUSSION

Our analysis indicates that receiving a bivalent mRNA COVID-19 vaccine dose provided protection against COVID-19 among U.S. healthcare personnel who had received a monovalent dose at least two months earlier. Overall effectiveness was approximately 35% and was similar by mRNA vaccine product, number of monovalent doses received, and by time since the last monovalent dose. However, effectiveness of a bivalent vaccine dose declined over time, from approximately 55% within 60 days of vaccination to approximately 20% more than 60 days after vaccination.

Overall, our estimates of initial VE against symptomatic infection by a bivalent mRNA dose are consistent with other studies that have estimated VE of between 20% and 50%. Our findings that VE was similar by age group are similar to those from previous studies,[26] and we found that VE was similar by presence of underlying health conditions. However, protection against COVID-19 was modest when compared with high VE estimates of a primary series before predominance of the Omicron variant, including previous estimates from this study.[2, 4, 20] Additionally, we found that protection waned in the months after vaccination. Other studies have also noted evidence of declining vaccine effectiveness against SARS-CoV-2 infection of a bivalent dose, estimating VE of approximately 10% after four months.[10, 12, 27]

Decreased protection against COVID-19 over time may reflect both waning immunity within an individual and lower protection against newly circulating SARS-CoV-2 variants or subvariants.[2] Protection against symptomatic SARS-CoV-2 infection is mediated to a large extent by neutralizing antibodies that wane in concentration, and that may be less effective against new subvariants.[28, 29] Although bivalent COVID-19 vaccine formulations elicit antibody against the BA.4/BA.5 subvariant, more recent subvariants such as XBB.1.5 may be less susceptible to neutralizing antibodies from the bivalent vaccine.[30] An additional potential challenge is that immune imprinting may limit redirection of the immune response against new variants.[31, 32] Whereas progression to severe illness may be attenuated

by recall of cellular immunity, protection against initial infection is more difficult to achieve.[33–36] Other studies have indicated that vaccine effectiveness is generally lower against milder illness compared with protection against severe COVID-19,[7, 37] although protection against severe illness also wanes over time.[38]

VE against symptomatic infection might depend on the level of pre-existing immunity, either from vaccination or from prior infection.[26, 39] Since we estimated benefit of a single mRNA bivalent dose among those eligible, all participants included in our analysis had received previous monovalent mRNA doses. We estimated some residual protection among recipients of three monovalent vaccine doses compared with those who only received two monovalent doses, although confidence intervals overlapped the null value when comparing four doses with three doses. Consistent with these findings, some studies have indicated partial vaccine-induced protection for longer than six months.[2, 14, 40] VE of a single dose using a previously vaccinated referent group ('relative VE') might be lower than that of VE of a vaccine series using an unvaccinated referent group ('absolute VE'). However, estimates of relative and absolute VE by a bivalent dose are generally similar, and estimating absolute VE may be challenging if the unvaccinated referent group has different risks of exposure or infection compared with vaccine recipients.[2, 4, 26, 37, 41] Although prior immunity might be expected to attenuate VE, similar to others we estimated that VE was similar regardless of known prior infection.[42, 43] Our finding that control-participants were more likely than case-participants to report recent prior infection is consistent with other evidence of infection-induced immunity.[23, 24] For individuals with recent prior infection, previous studies indicate that combined 'hybrid' immunity from both vaccination and infection confers stronger protection than vaccination alone.[23]

Our analysis has several notable strengths. We adjusted for a range of potential confounders, including known exposure to SARS-CoV-2 infection, presence of underlying health conditions, time since last monovalent dose, and known prior infection. We verified the vaccination status and test information for each participant, and our estimates were robust to a range of assumptions in sensitivity analyses. For example, we obtained similar estimates when excluding antigen test results or immunocompromised participants. Our case-control study was based on a test-negative approach that was extended by inclusion of asymptomatic controls. Such an approach can yield valid estimates if controls represent the same source population as cases,[44, 45], and our findings were similar when limited to symptomatic participants.

Test-negative and other observational studies are also subject to a range of potential limitations.[46–48] Although conditioning on SARS-CoV-2 results can limit overall selection bias, VE estimates might be distorted by a collider bias, if the probability of testing or enrolling in the study varied by receipt of a bivalent dose.[47] To estimate VE, we assumed that the contribution of vaccination status to differential risk of infection could be estimated apart from any differences in exposure, infection-induced immunity, or ascertainment of the outcome. Differences in such factors by bivalent vaccine uptake might have resulted in unmeasured or residual confounding. Although we adjusted for known prior infection, and obtained similar estimates with or without known prior infection, prior infection status relied on self-report and was likely under-ascertained, given high national

seroprevalence.[49] Interpretations of differences in VE estimates between strata deserve caution because of the potential impact of non-collapsibility on estimates based on odds ratios.[50]

We enrolled U.S. healthcare personnel representing a range of demographic and socioeconomic characteristics in 22 U.S. states, and did not find evidence that VE varied by age group, sex, race/ethnicity, educational level, or place of work, similar to previous analyses.[4, 20] Our findings are likely to be generalizable to other healthcare personnel, and included a variety of occupations and levels of patient contact. Although participants were more likely to be female and younger compared with the general U.S. population, our estimates were similar by age and sex, and are also more broadly applicable.

Our estimates of protection against symptomatic infection that wanes over time highlight benefits of remaining up-to-date with COVID-19 vaccines.[51] In September 2023, updated monovalent vaccines were recommended in the United States for all persons aged 6 months and older. However, only one in three healthcare personnel had received a bivalent dose before the test date in our analysis, and COVID-19 vaccine uptake with a recent dose has been limited in the United States and internationally.[49, 52] Reported reasons for lack of COVID-19 vaccine uptake included perceived immunity to infection;[53] evidence for vaccine effectiveness against infection might support efforts to improve vaccine coverage. For healthcare settings, our analysis can inform occupational health practitioners who are seeking to mitigate the risks of transmission between staff and patients, and to retain the workforce during future surges in infections[53], in addition to other recommended measures such as wearing a face mask.[54] Finally, shifts in the epidemiology of SARS-CoV-2 and in vaccine effectiveness during the pandemic underscore the need for ongoing robust studies to monitor VE over time.[55]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data analysis and availability:

The analysis was planned by Ian D. Plumb, Ryan Wiegand, and Melissa Hagen, with input from other coauthors. Data preparation was conducted by Glen Abedi and Jade James Gist, and data were analyzed by Ian D. Plumb. Dr. Plumb 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. Data for the study are classified as restricted and are not shared publicly.

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Highlights:

- Protection from COVID-19 remains important, particularly for healthcare personnel.

- Healthcare personnel in 22 U.S. states were enrolled in a case-control study.

- Overall, a bivalent mRNA dose conferred 34% protection against COVID-19.

- Effectiveness was similar by subgroup, but waned from 55% to 22% after two months.

- Up-to-date vaccination is recommended to optimize protection against COVID-19.

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┌─────────────────────────┐
│ Participants enrolled with │
│ reported test date on or after │
│   September 8, 2022     │
│     (N = 5,034)          │
└─────────────────────────┘
              │
              │      Insufficient or unverified information
              │      Positive SARS-CoV-2 test <90 days before test date (N = 14)
              │      Unvalidated test information (N = 676)
              │      Unvalidated vaccine information (N = 112)
              ▼
┌─────────────────────────┐
│ Participants with verified │
│  information (N = 4,232) │
└─────────────────────────┘
              │
              │      Test date outside analysis period
              │      Verified test date before 9/8/22 (N = 37)
              │      Verified test date after 5/31/23 (N = 47)
              ▼
┌─────────────────────────┐
│ Verified test date September 8, │
│ 2022 to May 31, 2023 (N = 4,148) │
└─────────────────────────┘
              │
              │      Vaccine exclusions
              │       0 to 1 doses (N = 105)
              │       Any non-mRNA dose (N = 91)
              │       Dose 1 or 2 marked as bivalent (N = 2)
              │       <67 days after dose 2 (N = 1)
              ▼
┌─────────────────────────┐
│ ≥67 (60+7) days after monovalent │
│    dose 2 (N = 3,949)   │
└─────────────────────────┘
              │
              │      Vaccine exclusions
              │      >5 doses (N = 11)
              │      <60 days between doses after dose 2 (N = 27)
              │      Unknown valency of doses 3, 4 or 5 (N = 45)
              │      Monovalent dose <67 days before test (N = 8)
              │      Monovalent dose 5 (N = 1)
              │      Bivalent dose <7 days before test (N = 47)
              ▼
┌─────────────────────────┐
│   Preliminary dataset    │
│     (N =  3,810)         │
└─────────────────────────┘
              │
              │      Additional exclusions
              │      Information unavailable on age group, sex, race and ethnicity,
              │      educational level, underlying conditions, reported community
              │      COVID-19 contact, prior infection information, or time since referent
              │      dose (N = 116)
              ▼      Participants previously enrolled during the analysis period (N = 47)
┌─────────────────────────┐
│    Analysis dataset      │
│     (N = 3,647)          │
└─────────────────────────┘
```
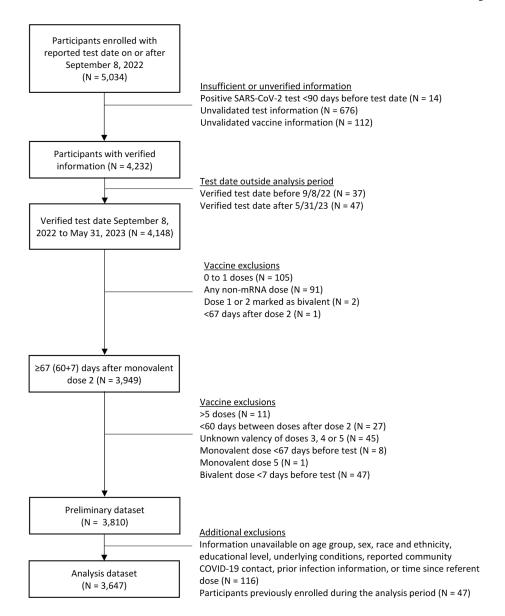
Figure 1:
U.S. healthcare personnel included in analysis of bivalent mRNA COVID-19 vaccine effectiveness[a]

a. Numbers refer to enrollments as a case or control-participant. Re-enrollments during the analysis period were excluded from the analysis dataset.

Table 1:

Demographic and Clinical Characteristics of U.S. Healthcare Personnel with COVID-19 (Case-participants) or who tested negative for SARS-CoV-2 (Control-participants), September 2022–May 2023

Characteristic	Case-participants No. with characteristic / Total (%)	Control-participants No. with characteristic / Total (%)	Standardized mean difference
Age group, years			
18–29	295/1528 (19.3%)	513/2119 (24.2%)	0.119
30–39	483/1528 (31.6%)	737/2119 (34.8%)	0.067
40–49	329/1528 (21.5%)	375/2119 (17.7%)	0.097
50	421/1528 (27.6%)	494/2119 (23.3%)	0.097
Sex			
Male	284/1528 (18.6%)	340/2119 (16.0%)	0.067
Female	1244/1528 (81.4%)	1779/2119 (84.0%)	0.067
Race and ethnicity[a]			
White, non-Hispanic	1111/1528 (72.7%)	1547/2119 (73.0%)	0.007
Black, non-Hispanic	151/1528 (9.9%)	191/2119 (9.0%)	0.030
Hispanic	137/1528 (9.0%)	239/2119 (11.3%)	0.077
Other, non-Hispanic	129/1528 (8.4%)	142/2119 (6.7%)	0.066
Highest educational level			
No college degree	219/1528 (14.3%)	292/2119 (13.8%)	0.016
College degree	1051/1528 (68.8%)	1444/2119 (68.1%)	0.014
Doctoral or professional degree	258/1528 (16.9%)	383/2119 (18.1%)	0.031
Number of underlying health conditions[b]			
0	353/1528 (23.1%)	505/2119 (23.8%)	0.017
1	680/1528 (44.5%)	901/2119 (42.5%)	0.040
2	495/1528 (32.4%)	713/2119 (33.6%)	0.027
Underlying health conditions[b]			
Pulmonary disease	303/1528 (19.8%)	439/2119 (20.7%)	0.022
Cardiac disease	64/1528 (4.2%)	82/2119 (3.9%)	0.016
Liver disease	12/1528 (0.8%)	14/2119 (0.7%)	0.015
Renal disease	9/1528 (0.6%)	24/2119 (1.1%)	0.059
Diabetes mellitus type 1 or 2	83/1528 (5.4%)	112/2119 (5.3%)	0.007
Obesity	547/1528 (35.8%)	760/2119 (35.9%)	0.001
Overweight without obesity	432/1528 (28.3%)	597/2119 (28.2%)	0.002
Cancer	19/1528 (1.2%)	30/2119 (1.4%)	0.015
Immunocompromised	36/1528 (2.4%)	67/2119 (3.2%)	0.049
Mood disorder	22/1528 (1.4%)	20/2119 (0.9%)	0.046
Smoking or substance abuse	342/1528 (22.4%)	450/2119 (21.2%)	0.028
Other	0/1528 (0%)	4/2119 (0.2%)	0.061
Pregnant on test date	38/1527 (2.5%)	45/2117 (2.1%)	0.024
Known prior infection[c]			

Characteristic	Case-participants No. with characteristic / Total (%)	Control-participants No. with characteristic / Total (%)	Standardized mean difference
No	1028/1528 (67.3%)	1055/2119 (49.8%)	0.361
Yes, >12 months ago, or before Omicron predominance	270/1528 (17.7%)	362/2119 (17.1%)	0.015
Yes, 12 months *and* after Omicron predominance	230/1528 (15.1%)	702/2119 (33.1%)	0.432

[a.]For Hispanic ethnicity, participants were asked whether Hispanic or Latino.

[b.]Number of underlying conditions, using categories defined in Supplementary Table 1.

[c.]Prior infection defined as self-reported positive SARS-COV-2 nucleic acid amplification test or antigen test result >90 days before test date; Omicron predominance defined based on national estimates as on or after 12/19/2021.

Table 2:

Test Characteristics, Reported Exposures, and Vaccination Status of U.S. Healthcare Personnel with COVID-19 (Case-participants) or who tested negative for SARS-CoV-2 (Control-participants), September 2022–May 2023

Characteristic	Case-participants No. with characteristic / Total (%)	Control-participants No. with characteristic / Total (%)	Standardized mean difference
Type of SARS-CoV-2 test			
Nucleic acid amplification test	872/1528 (57.1%)	2119/2119 (100%)	1.226
Antigen test	656/1528 (42.9%)	0/2119 (0%)	1.226
Symptoms reported			
No	0/1528 (0%)	103/2118 (4.9%)	0.320
Yes	1528/1528 (100%)	2015/2118 (95.1%)	0.320
Reason for SARS-CoV-2 test[a]			
Symptoms	1345/1528 (88%)	1560/2015 (77.4%)	0.283
Exposure, no symptoms	80/1528 (5.2%)	205/2015 (10.2%)	0.186
Screening, no symptoms or exposure	14/1528 (0.9%)	60/2015 (3.0%)	0.150
Other	85/1528 (5.6%)	188/2015 (9.3%)	0.144
Unknown or missing	4/1528 (0.3%)	2/2015 (0.1%)	0.038
If symptoms reported, fever present			
No	689/1528 (45.1%)	1315/2015 (65.3%)	0.414
Yes	839/1528 (54.9%)	700/2015 (34.7%)	0.414
Any COVID-19 close contact in 14 days before symptom onset or positive test[b]	823/1528 (53.9%)	929/2119 (43.8%)	0.201
At work, patient	355/1104 (32.2%)	552/1601 (34.5%)	0.065
At work, not a patient	272/1004 (27.1%)	345/1493 (23.1%)	0.040
Outside work	478/1405 (34.0%)	372/1897 (19.6%)	0.324
Vaccination status on test date			
Received monovalent doses only	1085/1528 (71.0%)	1328/2119 (62.7%)	0.178
Received bivalent dose	443/1528 (29.0%)	791/2119 (37.3%)	0.178
Number of monovalent mRNA doses			
2	258/1528 (16.9%)	303/2119 (14.3%)	0.071
3	1095/1528 (71.7%)	1584/2119 (74.8%)	0.070
4	175/1528 (11.5%)	232/2119 (10.9%)	0.016
Days since last monovalent mRNA dose			
0-	7/1528 (0.5%)	6/2119 (0.3%)	0.029
90-	61/1528 (4.0%)	69/2119 (3.3%)	0.039
180-	144/1528 (9.4%)	185/2119 (8.7%)	0.024
270-	360/1528 (23.6%)	386/2119 (18.2%)	0.132
360-	473/1528 (31.0%)	727/2119 (34.3%)	0.072
450-	483/1528 (31.6%)	746/2119 (35.2%)	0.076
Days since bivalent mRNA dose			
0-	112/443 (25.3%)	228/791 (28.8%)	0.080
60-	331/443 (74.7%)	563/791 (71.2%)	0.080

Characteristic	Case-participants No. with characteristic / Total (%)	Control-participants No. with characteristic / Total (%)	Standardized mean difference
Bivalent mRNA product			
Pfizer-BioNTech	337/443 (76.1%)	593/791 (75.0%)	0.026
Moderna	106/443 (23.9%)	198/791 (25.0%)	0.026

[a.] Among persons with symptoms; some participants had initially tested for other reasons listed.

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

Table 3:

Characteristics of healthcare personnel with COVID-19 by whether they received a bivalent dose

Characteristic	Did not receive bivalent mRNA COVID-19 dose	Received bivalent mRNA COVID-19 dose	SMD
Age group, years			
18–29	603/2413 (25.0%)	205/1234 (16.6%)	0.207
30–39	816/2413 (33.8%)	404/1234 (32.7%)	0.023
40–49	469/2413 (19.4%)	235/1234 (19.0%)	0.010
50	525/2413 (21.8%)	390/1234 (31.6%)	0.224
Sex			
Male	366/2413 (15.2%)	258/1234 (20.9%)	0.150
Female	2047/2413 (84.8%)	976/1234 (79.1%)	0.150
Race and ethnicity[a]			
White, non-Hispanic	1668/2413 (69.1%)	990/1234 (80.2%)	0.257
Black, non-Hispanic	276/2413 (11.4%)	66/1234 (5.3%)	0.221
Hispanic	297/2413 (12.3%)	79/1234 (6.4%)	0.204
Other, non-Hispanic	172/2413 (7.1%)	99/1234 (8.0%)	0.034
Educational level			
No college degree	413/2413 (17.1%)	98/1234 (7.9%)	0.280
College degree	1697/2413 (70.3%)	798/1234 (64.7%)	0.121
Doctoral or professional degree	303/2413 (12.6%)	338/1234 (27.4%)	0.377
Number of underlying health conditions[b]			
0	529/2413 (21.9%)	329/1234 (26.7%)	0.111
1	1065/2413 (44.1%)	516/1234 (41.8%)	0.047
2	819/2413 (33.9%)	389/1234 (31.5%)	0.052
If symptoms reported, fever present[c]			
No	1236/2350 (52.6%)	768/1193 (64.4%)	0.241
Yes	1114/2350 (47.4%)	425/1193 (35.6%)	0.241
Any COVID-19 close contact in 14 days before symptom onset or positive test[d]	1157/2413 (47.9%)	595/1234 (48.2%)	0.005
At work, patient	605/1759 (34.4%)	302/946 (31.9%)	0.014
At work, not a patient	426/1629 (26.2%)	191/868 (22.0%)	0.059
Outside work	548/2187 (25.1%)	302/1115 (27.1%)	0.042
Known prior infection[e]			
No	1313/2413 (54.4%)	770/1234 (62.4%)	0.162
Yes, >12 months ago, or before Omicron predominance	481/2413 (19.9%)	151/1234 (12.2%)	0.211
Yes, 12 months *and* after Omicron predominance	619/2413 (25.7%)	313/1234 (25.4%)	0.007
Vaccination status on test date			
Received monovalent doses only	2413/2413 (100%)	0/1234 (0%)	-
Received bivalent dose	0/2413 (0%)	1234/1234 (100%)	-
Number of monovalent mRNA doses			
2	519/2413 (21.5%)	42/1234 (3.4%)	0.570

Characteristic	Did not receive bivalent mRNA COVID-19 dose	Received bivalent mRNA COVID-19 dose	SMD
3	1744/2413 (72.3%)	935/1234 (75.8%)	0.080
4	150/2413 (6.2%)	257/1234 (20.8%)	0.437

[a.] For Hispanic ethnicity, participants were asked whether Hispanic or Latino.

[b.] Number of underlying conditions, using categories defined in Supplementary Table 2.

[c.] Among symptomatic case-participants, 632/1,085 (58.2%) who did not receive a bivalent dose reported fever, compared with 207/443 (46.7%) who did receive a bivalent dose; among symptomatic control-participants, 482/1,265 (38.1%) who did not receive a bivalent dose reported fever, compared with 218/750 (29.1%) who did receive a bivalent dose.

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

[e.] Prior infection defined as self-reported positive SARS-COV-2 nucleic acid amplification test or antigen test result >90 days before test date; Omicron predominance defined based on national estimates as on or after 12/19/2021.

Table 4:

Estimated Vaccine Effectiveness of a bivalent mRNA dose against symptomatic SARS-CoV-2 infection among U.S. healthcare personnel

Characteristic	Median days since bivalent dose (interquartile range)	No. case-participants who received a bivalent dose / No. eligible (%)[a]	No. control-participants who received a bivalent dose / No. eligible (%)	Adjusted vaccine effectiveness (95% CI)[b]
Bivalent product[c]				
Any mRNA	93 (56,138)	443/1528 (29.0%)	791/2119 (37.3%)	**34.1 (22.6–43.9)**
Pfizer BioNTech	94 (56,139)	337/1422 (23.7%)	593/1921 (30.9%)	**34.0 (21.1–44.7)**
Moderna	89.5 (55,134)	106/1191 (8.9%)	198/1526 (13.0%)	**34.6 (13.9–50.3)**
Days since bivalent dose				
7–59	37 (22,48)	112/1197 (9.4%)	228/1556 (14.7%)	**54.8 (40.7–65.6)**
60	115 (87,153)	331/1416 (23.4%)	563/1891 (29.8%)	**21.6 (5.6–34.9)**
Days since last monovalent dose				
67–359	68 (36,112)	125/572 (21.9%)	200/646 (31.0%)	**42.9 (23.3–57.5)**
360	100 (64,145)	318/956 (33.3%)	591/1473 (40.1%)	**29.3 (14.9–41.3)**
Number of monovalent doses				
Two	80 (45,119)	14/258 (5.4%)	28/303 (9.2%)	**43.8 (−13.4–72.1)**
Three	94 (58,139)	330/1095 (30.1%)	605/1584 (38.2%)	**31.4 (17.5–42.9)**
Four	89 (48,135)	99/175 (56.6%)	158/232 (68.1%)	**42 (10.7–62.4)**
Age group in years				
<50	94 (55.5,139)	285/1107 (25.7%)	559/1625 (34.4%)	**33.5 (19.9–44.8)**
50	92 (56,137)	158/421 (37.5%)	232/494 (47.0%)	**31.4 (8.8–48.5)**
Underlying health conditions[d]				
No	97 (58,144)	111/353 (31.4%)	218/505 (43.2%)	**41.4 (20.3–56.9)**
Yes	91 (55,134)	332/1175 (28.3%)	573/1614 (35.5%)	**31.6 (18.0–42.9)**

[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 being eligible to have received a bivalent dose, if 67 days after the last monovalent mRNA dose, and as receiving a bivalent dose if 7 days after a bivalent mRNA dose and no additional doses were received. Analyses are restricted to participants with complete covariate information.

[b.] Vaccine effectiveness was calculated using conditional logistic regression, accounting for clustering by four-week enrollment period and U.S. census region. Adjusted estimates included additional covariates: age group, sex, race and ethnicity, highest educational level, known community exposure to SARS-CoV-2, prior infection, days since referent dose (most recent monovalent dose). Models comparing estimates by subgroup included an interaction term.

[c.] For each product, analysis of bivalent vaccine effectiveness excluded recipients of a different bivalent product.

[d.] Number of underlying conditions, using categories defined in Supplementary Table 2.