# Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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# Supplementary materials

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## C. Protocol methods

### Design

This was a multisite test-negative case-control design study among HCP. Sites collaborated with occupational health clinics in participating healthcare facilities to identify HCP at the time of SARS-CoV-2 testing or received line lists of HCP who have already been tested. Cases and non-cases were defined based on results of SARS-CoV-2 testing, and detailed information on demographics, illness, exposures for SARS-CoV2, and medical and vaccination history was collected via HCP interview.

### Participating healthcare facilities

Selection of healthcare facilities to participate was at the discretion of the project partners, although partners sought to engage healthcare facilities with healthcare workforces that provide geographic, socioeconomic, racial and ethnic diversity. Healthcare facilities that could participate in the project included (but were not limited to) hospitals, emergency departments, long-term care facilities, or outpatient clinics.

### Key definitions

#### Healthcare personnel (HCP):

HCP refers to all paid and unpaid persons serving in healthcare settings who have the potential for direct or indirect exposure to patients or infectious materials, including:

- body substances

- contaminated medical supplies, devices, and equipment
- contaminated environmental surfaces
- contaminated air

For example, this includes any employee or contractor of a healthcare facility such as staff physicians, resident physicians, advanced practice providers (PA/NP), nurses, patient care technicians/nursing assistants, pharmacists, social workers, respiratory therapists, physical therapists, clerks and administrative staff, security personnel, dieticians, cafeteria staff, environmental services/custodial staff, managers and administrators, research staff, volunteers, transport, and health sciences students (medical, nursing, pharmacy, dentistry, or others, as available). HCP of any job classification in any department of participating healthcare facilities were eligible for enrollment, regardless of exposure to patients or vaccination status.

### HCP case:

A HCP case is defined as a HCP with ≥ 1 positive SARS-CoV-2 test result during the project period, with or without known exposures in healthcare or community settings. During the HCP interview, clinical signs and symptoms of illness will be captured during the period of time ranging from 14 days before to 14 days after the positive SARS-CoV-2 test collection date to distinguish symptomatic from asymptomatic infections, and those with at least one symptom present were included. A “positive SARS-CoV-2 test” includes reverse transcriptase (RT)-PCR (or other laboratory-based NAAT) or antigen tests performed on nasal or oral swabs (or similar upper respiratory specimen types, including saliva), sputum or other lower respiratory secretions.

*HCP cases with recurrentSARS-CoV-2 were excluded:* HCP cases who are subsequently identified as having had collection of a positive SARS-CoV-2 RT-PCR or antigen test at least 60 days after the symptom onset date or (if asymptomatic) after the first positive RT-PCR or antigen test collection date of the prior SARS-CoV-2 infection during the project period were not eligible for re-inclusion in this VE evaluation.

### HCP controls:

A HCP controls were defined as a symptomatic or asymptomatic HCP who tested negative for SARS-CoV-2 with or without known exposures in healthcare or community settings. A negative test for SARS-CoV-2 was defined as an RT-PCR test performed on nasal or oral swabs (or similar upper respiratory specimen types, including saliva), sputum or other lower respiratory secretions. Negative antigen tests alone, WITHOUT a confirmatory negative RT-PCR test, were NOT included in the control definition.

### Additional notes regarding HCP eligibility for inclusion:

- Because HCP may have multiple tests for SARS-CoV-2 over time, it is possible for a HCP non-case to be selected randomly for inclusion multiple times (based on multiple negative tests) during the course of the investigation.
- A HCP control who reported symptoms consistent with SARS-CoV-2 infection (despite having a negative test) during their interview is NOT ELIGIBLE to be included again in the project as a control until those symptoms have been resolved for at least 4 weeks.

- If a HCP control was selected again for inclusion as a control later during the project period, project staff reviewed the initial interview form to determine whether the control had symptoms at that time. When contacting the HCP control to re-interview them, project staff first talked with the HCP control to determine when the previous illness resolved before proceeding with the full interview. If the illness did not resolve at least 4 weeks prior to the re-interview, the HCP control was not eligible for re-inclusion.

- HCP who were included as controls and later tested positive for SARS-CoV-2 may be included as cases. However, once a HCP has met the case definition by testing positive for SARS-CoV-2 infection, that HCP was no longer eligible to be included in the project as a control.
- HCP who participated in a COVID-19-related vaccine trial may be included, but detailed information about enrollment and vaccine allocation was required.
- HCP who were unable to confirm test results using an acceptable method were excluded

## Case and control selection, and compensation

Case and control finding could vary by project partner and by healthcare facility. Options for identification of HCP cases and controls utilized by participating healthcare facilities included (but were not limited to) the following:

**1) At time of testing** – HCP who are tested by the healthcare facility in which they work (for example, in the occupational health clinic or a facility-sponsored testing center) can be recruited at the time of specimen collection for SARS-CoV-2 RT-PCR or antigen testing;

**2) At time of reporting test results** – HCP who report test results to their occupational health clinic can be recruited at the time of test result report (must be within 60 days of test collection); or

**3) Through HCP volunteering** – Through e-mails, signs posted in staff patient care areas, screensavers in medical centers, and other employee-directed communication, HCP who are tested outside the health system will be able to submit their test results for participation in the project (must be within 60 days of test collection).

Control HCP were matched to cases by site and week of test date. Within any given week and study site, any HCP testing positive for SARS-CoV-2 (cases) and those who tested negative (controls) and agreed to complete a survey or be interviewed were matched, with an overall target ratio of 3 controls per case. An algorithm to enroll controls from among the eligible controls using random selection if the control accrual exceeded 3 times the cases during any given week was utilized.

At the discretion of project partners and according to local policies, HCP cases and controls could receive compensation for their participation in the project.

## Data collection

### Initial interview and HCP interview report form (IRF):

Data collection began as soon as possible following receipt of HCP SARS-CoV-2 test results through telephone interviews with HCP cases or controls using an IRF or through self-reporting by HCP cases or controls using a secure, electronic IRF (e.g., REDCap survey). For the purposes of this protocol, "interview" and IRF include telephone interview and IRF completion or completion of a self-administered electronic IRF. Each HCP case or controls was contacted by project staff up to five times to schedule a future time for the interview or to conduct the interview.

If a HCP case or control was unable to be interviewed due to illness or incapacitation, or if the HCP case or control was deceased, project staff had to attempt to interview the HCP's primary caregiver or next of kin to serve as the HCP's proxy. Project staff were to identify the person who is most familiar with the HCP's medical history to serve as the proxy, and state-specific guidelines were to be followed for determining which individual has legal authority to provide information on behalf of the deceased or incapacitated HCP.

Project partners were responsible for ensuring that partner-initiated communications with HCP or their proxies comply with applicable privacy and information security standards. Interviews were conducted by partners' project staff (unless an electronic tool was used). Partners that chose to administer an electronic questionnaire included standard, introductory language via email or text to HCP or their proxies .

Variable categories in the IRF included case status, demographics, underlying medical conditions, roles in healthcare facilities, workplace and community exposures, household income, education level, medical and vaccination history (including vaccines against SARS-CoV-2 and influenza), hospitalizations or outpatient visits related to the current illness episode (for symptomatic HCP seeking care), and providers from whom the HCP has received vaccinations, including vaccines against SARS-CoV-2. The survey and interview were available to HCP cases and non-cases in English and Spanish.

Partners' project staff obtained verbal or electronic consent from HCP during the initial interview to review HCP medical records and vaccination records.

### Follow-up interview:

HCP cases and controls who were interviewed <14 days after the collection date of their SARS-CoV-2 test and were asymptomatic at that time were re-contacted 14 or more days after the collection date of their SARS-CoV-2 test and the IRF was updated if they became symptomatic after the initial interview and during the 14 days after their test collection date. HCP cases who remained asymptomatic 14 days after the collection date of their positive SARS-CoV-2 test were not included in VE analyses. Asymptomatic controls were retained in the VE analysis.

## Medical record review:

Medical record reviews were completed for all HCP cases or controls who reported having sought medical care for the current episode of illness as reported on the IRF. Project staff completed a supplemental review of hospital and/or outpatient medical records, as appropriate. Medical Record Review Form  was used to abstract information from HCP medical records on clinical signs and symptoms of illness, laboratory tests for SARS-CoV-2 (test type, date, result), vaccination history, and underlying medical conditions.

## Vaccination history:

To ensure complete capture of SARS-CoV-2 vaccination history for HCP cases and non-cases, project staff queried various sources of information, as appropriate and available at each site, including the state Immunization Information System (IIS) and/or a new vaccine tracking platform (known as the Vaccine Administration Management System, VAMS). Project staff also accessed HCP case or non-case records from vaccine providers (as reported on the IRF from the HCP interview) to capture vaccine type, date of administration, lot number, manufacturer and any information associated with the vaccination event.  Vaccination history was recorded using a Vaccine record review form .

### D. Vaccination status definitions

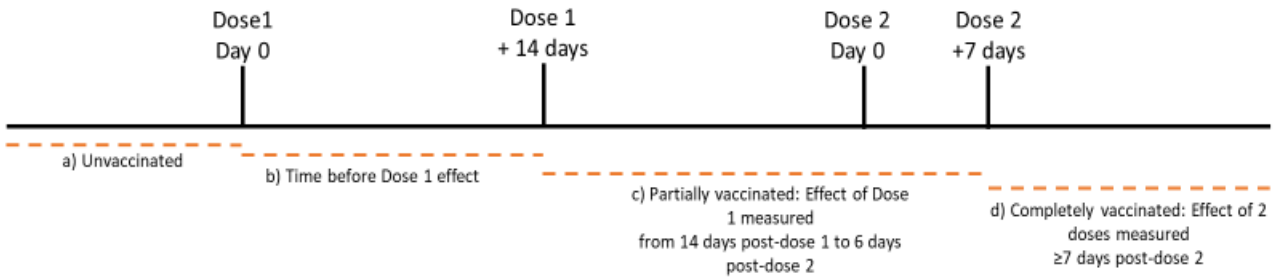
HCP vaccination status was defined at the time of their SARS-CoV-2 test date.

a) Unvaccinated: zero doses of COVID-19 vaccines by the test date

b) Time before dose 1 effect: measured from day 0–13 after the first dose

c) Partially vaccinated: measured from 14 days after the first dose through 6 days after the second dose

d) Completely vaccinated: measured ≥7 days after the second dose (consistent with the Pfizer-BioNTech clinical trial)

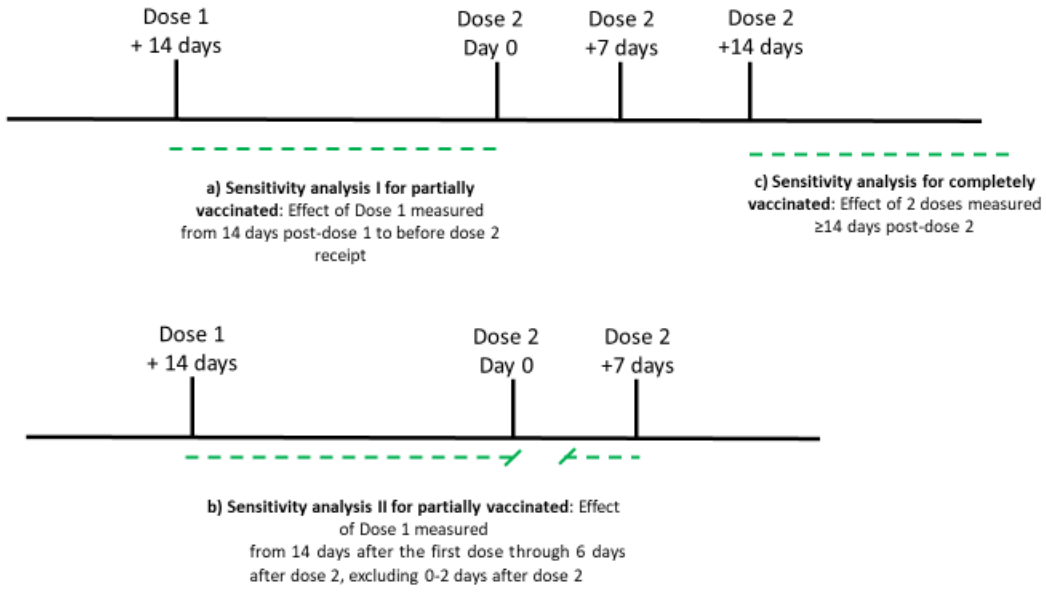


Sensitivity analysis:

a) Sensitivity analysis I for partially vaccinated (to exclude potential early post-dose 2 vaccine effects): from 14 days after the first dose before the receipt of the second dose

b) Sensitivity analysis II for partially vaccinated (to evaluate potential influence of vaccine-related reactions leading to HCP testing): from 14 days after the first dose through 6 days after the second dose, excluding participants tested 0-2 days after the second dose

c) Sensitivity analysis for completely vaccinated: measured ≥14 days after the second dose (consistent with the Moderna clinical trial)



## E. Statistical analyses

### Sample size

Sample size calculations were made using 80% power with a range of precision for VE estimates of 0.3–0.6. To generate a range of sample size estimates vaccine coverage was assumed to range from 30–70% of HCP. To reach 80% power at 30% coverage assuming a VE of 70%, a range of 60–190 SARS-CoV-2 cases with 3 non-cases per case will be needed. As the vaccine coverage increases, the number of cases required to demonstrate 70% effectiveness decreases (e.g., at 70% coverage, between 30–100 SARS-CoV-2 cases will be needed to demonstrate a VE of 70%) (Table 1). The number of cases needed under each assumption increases with <3 non-cases enrolled per case. Given the short window available to assess vaccine effectiveness and to minimize the target number of cases, the goal should be to enroll at least 3 non-cases per case to increase power. Enrollment will continue until at least one of the following criteria is reached: 1) vaccine coverage among eligible HCP population reaches 80%, or 2) the site enrolls the minimum number of cases and non-cases based on sample size estimated given the vaccine coverage achieved. The optimal time for completing the majority of enrollment for the VE evaluation is when vaccine coverage is between 30% and 80% of the included HCP population.

**Table 1: Sample Size Estimates for VE Evaluation**

| Vaccine coverage among HCPs | Number of HCP cases needed if VE=30%* | Number of HCP cases needed if VE=60%* | Number of HCP cases needed if VE=70%* |
|---|---|---|---|
| 30% | 160–620 | 80–280 | 60–190 |
| 50% | 120–460 | 50–180 | 35–120 |
| 70% | 130–500 | 45–160 | 30–100 |

*Assuming a 1:3 case: control ratio

## Analysis

Data were aggregated across project partners and healthcare facilities and analyzed at CDC using SAS version 9.4 (SAS Institute, Cary, NC). Primary analysis included HCP cases who develop any symptoms of COVID-like illness. Secondary analyses included HCP cases who met Pfizer-BioNTech or Moderna randomized control trial case definitions (Table S3)

Descriptive analyses were performed comparing demographic and clinical characteristics and risk factors for HCP cases and controls included in the analysis. We used the standardized difference comparing the difference in means in units of the pooled standard deviation. For dichotomous variables, the standardized difference was defined as:

$$d = \frac{(\hat{p}_{cases} - \hat{p}_{controls})}{\sqrt{\frac{\hat{p}_{cases}(1-\hat{p}_{cases}) + \hat{p}_{controls}(1-\hat{p}_{controls})}{2}}}$$

where $\hat{p}_{cases}$ and $\hat{p}_{controls}$ denotes prevalence of each characteristic among cases and controls, respectively.

For continuous variable (age), the standardized difference was defined as:

$$d = \frac{(\bar{x}_{cases} - \bar{x}_{controls})}{\sqrt{\frac{s^2_{cases} + s^2_{controls})}{2}}}$$

Where $\bar{x}_{cases}$ and $\bar{x}_{controls}$ denotes sample mean of the age for cases and controls, respectively, and $s^2_{cases}$ and $s^2_{controls}$ denotes sample variance of the age in cases and controls, respectively.

To measure VE, we estimated the odds ratio for vaccination (receipt of SARS-CoV-2 vaccine compared to no vaccine) among cases vs. non-cases, using conditional logistic regression, adjusting for potential confounders. We estimated VE as follows:

VE = (1 - adjusted odds ratio for vaccination) x 100%

The variables evaluated as potential confounders met a priori confounder definition (i.e. potentially associated with both exposure and outcome of interest). These variables were evaluated individually (with only vaccination status) in the model. In addition, we included all potential confounders in the full model and evaluated the effect of exclusion of each variable from the full model on the estimate for vaccination status. The final model retained only those variables resulting in >10% change in estimate with either approach.

The primary analysis evaluated the effectiveness of a complete vaccination vs. no vaccine, and partial vaccination vs no vaccine for both mRNA vaccines and by vaccine type. A secondary analysis evaluated the effectiveness for subgroups of HCP by age group, race/ethnicity, job category, and presence of underlying conditions. In order to obtain subgroup-specific VE estimates, we used the entire dataset to evaluate individual interaction between a factor of interest (e.g, diabetes) and vaccine status by adding the interaction term into the conditional logistic model adjusting for confounders included in the primary analyses model. Regardless of whether interaction variables were significant or not, we estimated VE and confidence intervals for those with and without a factor of interest (in the main paper only estimates with the factor present are reported). We repeated secondary analyses using unconditional logistic regression, and because the case-control match was broken, adjusted analyses for study site and week of test date (as well as confounders as in the main analysis model). The results obtained using unconditional logistic model were similar those in the main analysis using conditional logistic regression for all subgroup analyses.

To evaluate potential for waning of vaccine effect, we estimated VE by time since the receipt of the second dose. We stratified vaccinated with 2-doses of mRNA category by time since the receipt of the second dose into 2-week intervals. Vaccine effectiveness for each of these categories was measured as compared to unvaccinated using conditional logistic regression.

## F. Supplemental tables

Table_S1. List of Participating Organizations

| Study Partner | Site | HCP cases enrolled | HCP controls enrolled |
|---|---|---|---|
| CDC Arctic Investigations Program (AIP)* | Alaska Native Tribal Health Consortium (ANTHC) | 16 (1) | 48 (1) |
| | Yukon-Kuskokwim Health Corporation (YKHC) | 19 (1) | 59 (2) |
| Emerging Infection Program (EIP) † | Zuckerberg San Francisco General Hospital, San Francisco, CA | 9 (<1) | 29 (<1) |
| | Colorado EIP | 65 (4) | 164 (5) |
| | Connecticut EIP | 45 (3) | 101 (3) |
| | Georgia EIP | 15 (1) | 54 (2) |
| | Maryland EIP | 79 (5) | 196 (6) |
| | North Memorial Health Hospital, Robbinsdale, and Maple Grove Hospital, Maple Grove, Minnesota | 9 (<1) | 15 (<1) |
| | New Mexico EIP | 42 (3) | 47 (1) |
| | University of Rochester Medical Center, Rochester, NY | 217 (15) | 396 (11) |
| | Oregon EIP | 41 (3) | 84 (2) |
| | Tennessee EIP | 30 (2) | 106 (3) |
| Preventing Emerging Infections through Vaccine Effectiveness | Baystate Medical Center, Springfield, MA | 29 (2) | 78 (2) |
| | Brigham and Women's Hospital, Boston, MA | 29 (2) | 81 (2) |
| | Jackson Memorial Hospital, Miami, FL | 13 (<1) | 21 (<1) |

| | | | |
|---|---|---|---|
| Testing (Project PREVENT) | Olive View-UCLA, Los Angeles, CA | 6 (<1) | 14 (<1) |
| | Thomas Jefferson University, Philadelphia, PA | 156 (11) | 204 (6) |
| | Truman Medical Centers, Kansas City, MO | 18 (1) | 40 (1) |
| | University of Alabama Hospital, Birmingham, AL | 53 (4) | 35 (1) |
| | University of California San Francisco-Fresno, Fresno, CA | 24 (2) | 46 (1) |
| | University of Chicago, Chicago, IL | 11 (<1) | 60 (2) |
| | University of Iowa, Iowa City, IA | 38 (3) | 94 (3) |
| | University of Massachusetts Memorial Medical Center, Worcester, MA | 93 (6) | 255 (7) |
| | University Medical Center, Louisiana State University, New Orleans, LA | 2 (<1) | 7 (<1) |
| | University of Mississippi Medical Center, Jackson, MS | 48 (3) | 92 (3) |
| | University of Washington, Seattle, WA | 7 (<1) | 19 (<1) |
| | Valleywise Hospital, Phoenix, AZ | 20 (1) | 17 (<1) |
| Safety and Healthcare Epidemiology Prevention Research Development (SHEPheRD Program) | Duke University, Durham, NC | 56 (4) | 337 (10) |
| | Johns Hopkins University, Baltimore, MD | 31 (2) | 117 (3) |
| | Rush University, Chicago, IL | 80 (5) | 267 (8) |
| | University of Utah, Salt Lake City, UT | 77 (5) | 188 (5) |
| | Washington University, St. Louis, MO | 89 (6) | 90 (3) |
| | University of Wisconsin, Madison, WI | 15 (1) | 88 (3) |

*CDC Arctic Investigations Program (AIP) sites include the Alaska Native Tribal Health Consortium (ANTHC) and the Yukon-Kuskokwim Health Corporation (YKHC). In Alaska, the project is being implemented through a collaboration between the Alaska Native Tribal Health Consortium (ANTHC), Southcentral Foundation (SCF), Yukon-Kuskokwim Health Corporation (YKHC), and CDC AIP.

† Emerging Infections Program (EIP) sites includes a mix of hospitals and long-term care facilities selected within the state surveillance area

Table S2. Clinical characteristics and vaccination status of healthcare personnel who tested positive for SARS-CoV-2 and had one or more symptom of COVID-like illness (cases) and those who tested negative (controls), 33 U.S. sites, January-May 2021.

| **Characteristic** | **Cases (No.=1482)** | **Controls (No.=3449)** |
|---|---|---|
| | **No. (%)** | **No. (%)** |
| **Reported symptoms of illness** | | |
| Fever (measured temp. ≥100°F or subjective) | 640 (43) | 684 (20) |
| Cough (dry and/or productive) | 867 (59) | 798 (23) |
| Shortness of breath | 425 (29) | 204 (6) |
| Chills | 650 (44) | 694 (20) |
| Muscle pain | 721 (49) | 745 (22) |
| Altered sense of smell or taste | 860 (58) | 108 (3) |
| Sore throat | 560 (38) | 1067 (31) |
| Diarrhea | 367 (25) | 441 (13) |
| Nausea or vomiting | 296 (20) | 468 (14) |
| Headache | 994 (67) | 1368 (40) |
| Congestion | 841 (57) | 806 (23) |
| Runny nose | 655 (44) | 851 (25) |
| Loss of appetite | 339 (23) | 139 (4) |
| Chest pain/tightness | 289 (20) | 169 (5) |
| Abdominal pain | 134 (9) | 201 (6) |

| | | |
|---|---|---|
| Red bruised toes or feet | 12 (1) | 8 (0.2) |
| No symptoms reported | 0 | 891 (26) |
| **Sought medical care**[†] | 326 (22) | 521 (15) |
| **Hospitalized**[†] | 29 (2) | 34 (1) |
| **Presence of one or more underlying condition or risk factor increasing risk of severe COVID-19**[§] | 1133 (76) | 2583 (75) |
| Obesity (BMI ≥30 or listed in medical record) | 533 (36) | 1078 (31) |
| Overweight (BMI 25-29 or listed in medical record) | 429 (29) | 970 (28) |
| Asthma | 208 (14) | 623 (18) |
| Hypertension | 216 (15) | 486 (14) |
| Diabetes mellitus[¶] | 69 (5) | 160 (5) |
| Immunocompromising condition** | 64 (4) | 126 (4) |
| Heart disease | 31 (2) | 109 (3) |
| Cerebrovascular disease | 3 (0.2) | 7 (0.2) |
| Neurologic condition | 12 (1) | 37 (1) |
| Chronic kidney disease | 5 (0.3) | 24 (1) |
| Chronic obstructive pulmonary disease (COPD) | 5 (0.3) | 17 (1) |
| Other chronic lung disease | 18 (1) | 39 (1) |
| Chronic liver disease | 10 (1) | 21 (1) |
| Thalassemia/ sickle cell disease | 0 (0) | 4 (0.1) |
| Current or former smoker | 291 (20) | 705 (20) |
| Pregnancy (proportion out of female HCP) | 62 (4) | 91 (3) |
| **Received flu vaccine for the current respiratory season**[††] | 1208 (82) | 2829 (82) |

| **COVID-19 Vaccine Status** | | |
|---|---|---|
| Unvaccinated | 812 (55) | 890 (26) |
| Received ≥1 dose prior to test date | 670 (45) | 2559 (74) |
| By interval from last dose to test date | | |
| One dose, < 14 days | 357 (24) | 602 (17) |
| One dose, ≥14 days | 114 (8) | 502 (15) |
| Two doses, <7 days | 29 (2) | 370 (11) |
| Two doses, 7-13 days | 11 (1) | 174 (5) |
| Two doses, ≥14 days | 159 (11) | 911 (26) |
| By vaccine type | | |
| Pfizer-BioNTech | 520 (78) | 2030 (79) |
| Moderna | 140 (21) | 500 (20) |
| Other vaccine[§§] | 10 (1) | 29 (1) |

[†] HCP who sought care for the current episode of illness were seen in an outpatient setting, emergency department, urgent care, or hospital. Among hospitalized cases, 5 cases required supplemental oxygen, 3 cases were admitted to intensive care unit, and 2 were intubated. Among hospitalized controls, 1 HCP was admitted to intensive care unit and required supplemental oxygen.

[§]Conditions associated with definite or potential increased risk of severe COVID-19 disease were based on CDC criteria (https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html)

[¶]Among HCP who reported diabetes mellitus, 1 case and 3 controls (<1% of all cases or controls) reported type 1, 19 cases (1% of all cases) and 21 controls (<1% of all controls) had type 2, and 49 cases (3%) and 136 controls (4%) did not specify a type

**Immunocompromising conditions include immunosuppressive medication (e.g., corticosteroids, chemotherapy, or other immunosuppressive medications), solid organ transplant, hematopoietic stem cell transplant, HIV, or active cancer (current cancer or in treatment or diagnosed in last 12 months).

††Influenza vaccination status was based on self-report or medical or vaccine record review

§§Other COVID-19 vaccines included AstraZeneca (2 case-patients and 1 control), Janssen (8 case-patients and 28 controls)

Table_S3. Characteristics of healthcare personnel (HCP) who tested positive for SARS-CoV-2 and had one or more symptom of COVID-like illness (cases) by vaccination status

| | **Completely vaccinated cases*** **(No.=167)** **No. (%)** | **Partially vaccinated cases†** **(No.=140)** **No. (%)** | **Unvaccinated cases** **(No.=812)** **No. (%)** |
|---|---|---|---|
| **Characteristic** | | | |
| Median age (range), years | 37 (20-67) | 40 (22-67) | 35 (18-69) |
| **Age group, years** | | | |
| 18-49 | 130 (78) | 106 (76) | 646 (80) |
| 50-64 | 34 (20) | 33 (24) | 149 (18) |
| ≥ 65 | 2 (1) | 1 (1) | 7 (1) |
| Missing | 1 (1) | 0 | 10 (1) |
| **Sex** | | | |
| Male | 31 (19) | 31 (22) | 115 (14) |
| Female | 135 (81) | 108 (77) | 690 (85) |
| **Race/ethnicity** | | | |
| Hispanic/Latino | 16 (10) | 12 (9) | 98 (12) |
| White, Non-Hispanic | 127 (76) | 103 (74) | 467 (58) |
| Black, Non-Hispanic | 6 (4) | 7 (5) | 161 (20) |

| | **Completely vaccinated cases* (No.=167) No. (%)** | **Partially vaccinated cases† (No.=140) No. (%)** | **Unvaccinated cases (No.=812) No. (%)** |
|---|---|---|---|
| Asian & Pacific Islander, Non-Hispanic | 11 (7) | 9 (6) | 42 (5) |
| American Indian/Alaska Native, Non-Hispanic | 6 (4) | 5 (4) | 16 (2) |
| Multiple/Other, Non-Hispanic | 1 (1) | 4 (2) | 28 (3) |
| **Reported symptoms of illness** | | | |
| Fever (measured temp. ≥100°F or subjective) | 46 (28) | 50 (36) | 378 (47) |
| Cough (dry and/or productive) | 69 (41) | 66 (47) | 513 (63) |
| Shortness of breath | 31 (19) | 29 (21) | 270 (33) |
| Chills | 49 (29) | 51 (36) | 385 (47) |
| Muscle pain | 56 (34) | 57 (41) | 413 (51) |
| Altered sense of smell or taste | 74 (44) | 71 (51) | 502 (62) |
| Sore throat | 66 (40) | 53 (38) | 315 (39) |
| Diarrhea | 26 (16) | 28 (20) | 231 (28) |
| Nausea or vomiting | 21 (13) | 24 (17) | 180 (22) |
| Headache | 98 (59) | 89 (64) | 568 (70) |
| Congestion | 106 (63) | 81 (58) | 443 (55) |
| Runny nose | 93 (56) | 76 (54) | 334 (41) |
| Chest pain/tightness | 21 (13) | 24 (17) | 189 (23) |
| Loss of appetite | 19 (11) | 21 (15) | 214 (26) |

| | **Completely vaccinated cases*** **(No.=167)** **No. (%)** | **Partially vaccinated cases†** **(No.=140)** **No. (%)** | **Unvaccinated cases** **(No.=812)** **No. (%)** |
|---|---|---|---|
| Abdominal pain | 12 (7) | 13 (9) | 88 (11) |
| Red bruised toes or feet | 1 (1) | 2 (1) | 7 (1) |
| **Sought medical care**§ | 29 (17) | 33 (24) | 194 (24) |
| **Hospitalized** | 4 (2) | 1 (1) | 21 (3) |
| **Presence of one or more underlying condition or risk factor increasing risk of severe COVID-19**¶ | 118 (71) | 110 (79) | 620 (76) |
| Obesity (BMI ≥30 or listed in medical record) | 49 (29) | 47 (34) | 315 (39) |
| Overweight (BMI 25-29 or listed in medical record) | 44 (26) | 50 (36) | 210 (26) |
| Asthma | 21 (13) | 20 (14) | 112 (14) |
| Hypertension | 22 (13) | 17 (12) | 123 (15) |
| Diabetes mellitus** | 10 (6) | 4 (3) | 35 (4) |
| Immunocompromising condition†† | 15 (9) | 8 (6) | 24 (3) |
| Heart disease | 5 (3) | 3 (2) | 12 (1) |
| Other chronic lung disease | 2 (1) | 1 (1) | 11 (1) |
| Chronic liver disease | 3 (2) | 1 (1) | 3 (0.4) |
| Current or former smoker | 32 (19) | 21 (15) | 160 (20) |
| Pregnancy (proportion out of female HCP) | 1 (1) | 5 (4) | 52 (6) |

[*]Partially vaccinated cases include HCP who received a single dose of an mRNA vaccine during the interval from 14 days after the first dose through 6 days after the second dose.

[†] Completely vaccinated cases include HCP who received 2 doses of an mRNA vaccine ≥7 days after the receipt of the second dose (consistent with the Pfizer clinical trial).

[§] HCP who sought care for the current episode of illness were seen in an outpatient setting, emergency department, urgent care, or hospital

[¶]Conditions associated with definite or potential increased risk of severe COVID-19 disease per CDC (https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html)

[**]Among HCP cases who reported diabetes mellitus, 0 cases reported type 1, 13 cases had type 2, and 35 cases did not specify a type

[††]Immunocompromising conditions included immunosuppressive medication use (e.g., corticosteroids, chemotherapy, or other immunosuppressive medications), solid organ transplant, hematopoietic stem cell transplant, HIV, or active cancer (current cancer or in treatment or diagnosed in last 12 months).

Table_S4. Estimated effectiveness of mRNA COVID-19 vaccines among healthcare personnel by presence of various symptoms and vaccine type, 33 U.S. sites, January -May 2021.

| | **Cases (No.= 1472) No. (%)** | **Controls (No.=3420) No. (%)** | Vaccine effectiveness by number of doses and by interval from last vaccine dose to test date | |
|---|---|---|---|---|
| Received any COVID-19 vaccine by vaccination status | | | Unadjusted * | Adjusted*[†] |
| Among **febrile** cases | | | | |
| Partially vaccinated[§] | 51 (8) | 253 (37) | 93.3 (90.0-95.5) | 92.2 (88.2-94.9) |
| Completely vaccinated[¶] | 47 (7) | 168 (25) | 94.3 (90.8-96.4) | 94.2 (90.2-96.5) |
| Among **afebrile** cases | | | | |
| Partially vaccinated[§] | 92 (11) | 478 (17) | 72.4 (63.5-79.1) | 70.5 (60.3-78.1) |
| Completely vaccinated[¶] | 123 (15) | 917 (33) | 86.8 (81.9-90.4) | 86.8 (81.5-90.6) |
| Among cases meeting Pfizer– BioNTech randomized control trial case definition** | | | | |
| Partially vaccinated[§] | 118 (9) | 519 (27) | 85.3 (80.9-88.7) | 83.9 (78.7-87.9) |
| Completely vaccinated[¶] | 134 (10) | 577 (31) | 91.6 (88.4-93.9) | 91.5 (87.9-94.0) |
| Among cases NOT meeting Pfizer- BioNTech randomized control trial case definition** | | | | |
| Partially vaccinated[§] | 25 (16) | 353 (23) | 51.3 (18.2-71.0) | 46.5 (7.9-69.0) |
| Completely vaccinated[¶] | 36 (23) | 508 (33) | 74.6 (57.5-84.8) | 75.0 (56.9-85.5) |

| | | | | |
|---|---|---|---|---|
| Among HCP cases meeting Moderna randomized control trial case definition[††] | | | | |
| Partially vaccinated[§] | 128 (9) | 583 (26) | 84.6 (80.1-88.1) | 83.7 (78.6-87.6) |
| Completely vaccinated[¶] | 145 (10) | 701 (32) | 91.9 (88.8-94.1) | 92.0 (88.7-94.3) |
| Among HCP cases NOT meeting Moderna randomized control trial case definition[††] | | | | |
| Partially vaccinated[§] | 15 (16) | 289 (23) | 31.3 (-32.9, 64.5) | 19.3 (-61.0, 59.5) |
| Completely vaccinated[¶] | 25 (26) | 384 (31) | 59.3 (23.7-78.3) | 58.5 (19.3-78.6) |
| Anticipated level of patient contact based on job categories [§§] | | | | |
| Substantial direct patient contact | | | | |
| Partially vaccinated[§] | 101 (11) | 621 (28) | 84.3 (79.2-88.1) | 82.2 (76.2-86.8) |
| Completely vaccinated[¶] | 119 (13) | 740 (34) | 91.2 (87.9-93.6) | 91.1 (87.4-93.7) |
| Moderate direct patient contact | | | | |
| Partially vaccinated[§] | 9 (5) | 75 (19) | 84.0 (65.3-92.7) | 80.3 (55.4-91.3) |
| Completely vaccinated[¶] | 22 (13) | 123 (31) | 85.5 (72.3-92.4) | 85.5 (71.3-92.7) |
| Minimal direct patient contact | | | | |
| Partially vaccinated[§] | 24 (7) | 139 (20) | 74.2 (57.4-84.3) | 74.3 (56.3-84.9) |
| Completely vaccinated[¶] | 23 (7) | 185 (26) | 91.8 (85.1-95.4) | 92.4 (85.8-96.0) |
| Undefined direct patient contact | | | | |
| Partially vaccinated[§] | 5 (9) | 25 (21) | 64.9 (-6.1, 88.4) | 75.7 (23.0-92.4) |
| Completely vaccinated[¶] | 3 (6) | 24 (20) | 90.4 (52.5-98.0) | 92.5 (58.6-98.7) |

* Vaccine effectiveness was calculated as one minus the matched odds ratio for partially or completely vaccinated, compared to unvaccinated and estimated using a conditional logistic regression model accounting for matching by site of enrollment and week of test date; effectiveness for all categories estimated using unvaccinated as a reference group.

† Odds ratio is adjusted for age, race/ethnicity, presence of underlying conditions, and close contact with COVID-19 patients in the workplace, or persons with COVID-19 outside of the workplace

§For partially vaccinated effectiveness of a single dose was measured during the interval from 14 days after the first dose through 6 days after the second dose.

¶ For completely vaccinated effectiveness of 2 doses was measured ≥7 days after the receipt of the second dose.

** Pfizer-BioNTech randomized control trial case definition was as follows: participants with at least 2 of the following symptoms: fever (subjective or measured), chills, muscle aches/fatigue or malaise, headache, sore throat, or altered sense of smell or taste OR at least one of the following: cough, shortness of breath, or clinical or radiographic evidence of pneumonia; partially or completely vaccinated HCP case-patients who did not meet this case definition had the following symptoms: congestion (n=31, 51%), runny nose (n=27, 44%), headache (n=14, 23%), altered sense of smell or taste (n=12, 20%), sore throat (n=6, 10%), diarrhea (n=6, 10%), nausea or vomiting (n=2, 3%), chills (n=1, 2%), muscle pain (n=1, 2%), abdominal pain (n=2, 3%)

[††] Modena randomized control trial case definition was as follows: participants with the presence of at least one of the following symptoms: fever, cough, shortness of breath, chills, muscle pain, loss of taste or smell, sore throat, diarrhea, or vomiting; partially or completely vaccinated HCP case-patients who did not meet this case definition had the following symptoms: congestion (n=23, 58%), runny nose (n=23, 58%), headache (n=16, 40%).

[§§] Job categories with anticipated substantial direct patient contact included: physician, physician assistant, nurse practitioner, registered nurse, licensed practical nurse, other nurse, certified nursing assistant, patient care technician or assistant, medical assistant, COVID-19 tester, phlebotomist, home health personnel, emergency medical services, physical therapist or assistant, rehabilitation aide, occupational therapist, speech-language pathologist, respiratory therapist, radiology technician, dental healthcare provider, and surgical, medical, or emergency technician. Job categories with anticipated moderate direct patient contact included: environmental services personnel, food services personnel, patient transport personnel, non-physician behavioral health provider, chaplain, care coordinator, translator, health educator, genetic counselor, dietician, and research personnel. Job categories with anticipated minimal patient contact included: administrative or ward clerk, symptom checker, telehealth trainer, facilities maintenance equipment and sterile technician; medical equipment sales; laboratory personnel; and pharmacists. Undefined patient contact included others who could not be classified into any of the above categories or those with missing information.