

# **Evaluating SARS-CoV-2 Vaccine Effectiveness Among Health Care Personnel During Early Phase Vaccination**

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**COVID-19 Response Vaccine Task Force,  
Centers for Disease Control and Prevention**



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## INTRODUCTION

Since the World Health Organization was first notified of a cluster of respiratory infections in Wuhan City, China on December 31, 2019 [1], the novel coronavirus, SARS-CoV-2, has caused more than 7,500,000 infections and 211,000 deaths in the United States and more than 35,000,000 infections and 1,000,000 deaths worldwide as of October 7, 2020. Overall, 20–30% of cases in the United States have required hospitalization[2], resulting in substantial burden on healthcare personnel (HCP) and U.S. healthcare systems.

Healthcare personnel (HCP) are at risk of contracting SARS-CoV-2 during their interactions with patients with suspected or confirmed infection with SARS-CoV-2 (COVID-19) or patients with unrecognized infection[3]. A key component of controlling the pandemic and protecting the U.S. healthcare workforce is deployment of a safe and effective SARS-CoV-2 vaccine. Evaluating the effectiveness soon after introduction of vaccine is a routine public health activity aimed to inform any revision of vaccine recommendations based on real-world experience in the early period of vaccine availability. Multiple vaccines are currently being evaluated in clinical trials. In the U.S., vaccines are expected to become available in limited supply starting November or December of 2020. SARS-CoV-2 vaccines are expected to be distributed during early phases of introduction to front-line HCP. This early phase distribution of one or more vaccines provides an opportunity to evaluate the effectiveness of these vaccines in preventing symptomatic COVID-19 and to learn how these vaccines work in a real-world setting before widespread distribution to the general public but after favorable Phase III results are released.

### Key Personnel and Partners

- Centers for Disease Control and Prevention:
  - Principal investigator = Tamara Pilishvili, PhD MPH
  - Coordinator = Ryan Gierke, MPH
  - Co-investigators:
    - Katherine Fleming-Dutra, MD MPH
    - Jennifer Farrar, MPH
- Emerging Infections Program sites (<https://www.cdc.gov/ncezid/dpei/eip/index.html>)
- Project COVERED sites (<https://medicine.uiowa.edu/emergencymedicine/research/covid-evaluation-risk-emergency-departments-covered-project/study-overview>)

- Safety and Healthcare Epidemiology Prevention Research Development (SHEPherD) Program organizations (<https://www.cdc.gov/hai/research/safehealthcare.html>)

## Funding

Partners are supported by CDC through cooperative agreements (Emerging Infections Program, Project COVERED) or through contracts (SHEPherD).

## Objectives

### Primary:

- 1) Evaluate post-introduction effectiveness of a complete schedule of the SARS-CoV-2 vaccine in preventing laboratory-confirmed symptomatic COVID-19 among HCP.

### Secondary:

- 1) Evaluate post-introduction effectiveness of the SARS-CoV-2 vaccine in preventing severe disease among HCP with laboratory-confirmed symptomatic COVID-19;
- 2) Evaluate effectiveness by HCP age groups and in subgroups with comorbidities;
- 3) Evaluate effectiveness by various groups of HCP job categories and clinical practice settings;
- 4) Evaluate effectiveness by vaccine product (if more than one product is in use) and for a single dose (if a 2-dose schedule is recommended).

## METHODS

### Design

This project will be completed using a multisite test-negative case-control design in HCP over a period of a 6-month period or longer, depending on vaccine uptake and sample size needs. This study design has been well described in influenza vaccine evaluation, and it can be used in post-introduction vaccine evaluation for SARS-CoV-2 [4]. Sites will collaborate with occupational health clinics in participating healthcare facilities to identify HCP at the time of SARS-CoV-2 testing or to receive line lists of HCP who have already been tested. Cases and non-cases will be defined based on results of SARS-CoV-2 testing, and detailed information on demographics, illness, exposures for SARS-CoV2, and medical and vaccination history will be collected via HCP interview.

## Participating healthcare facilities

Selection of healthcare facilities to participate is at the discretion of the project partners, although partners should seek to engage healthcare facilities with healthcare workforces that provide geographic, socioeconomic, racial and ethnic diversity. Healthcare facilities that may participate in the project include (but are 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 will be eligible for enrollment, regardless of exposure to patients or vaccination status.

### HCP case:

A HCP case is defined as a HCP with  $\geq 1$  positive SARS-CoV-2 test result during the project period, with or without known exposures in healthcare or community settings. The presence of symptoms is not included in the case definition; HCP who test positive for SARS-CoV-2 are considered cases regardless of whether they are symptomatic or asymptomatic. However, 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. A “positive SARS-CoV-2 test” includes reverse transcriptase (RT)-PCR or antigen tests performed on nasal or oral swabs (or similar upper respiratory specimen types, including saliva), sputum or other lower respiratory secretions.

*Note regarding HCP cases with recurrent or repeat positive tests for SARS-CoV-2:* 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 are not eligible for re-inclusion in this VE evaluation.

#### HCP non-case:

A HCP non-case is 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 is 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 antibody tests are NOT included in the non-case definition. Negative antigen tests alone, WITHOUT a confirmatory negative RT-PCR test, are NOT included in the VE non-case 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 non-case 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 non-case until those symptoms have been resolved for at least 4 weeks.
  - If a HCP non-case is selected again for inclusion as a non-case later during the project period, project staff should review the initial interview form to determine whether the non-case had symptoms at that time. When contacting the HCP non-case to re-interview them, project staff should first talk with the HCP non-case 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 non-case is not eligible for re-inclusion.

- HCP who were included as non-cases and later test 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 is no longer eligible to be included in the project as a non-case.
- HCP who participated in a COVID-19-related vaccine trial may be included, but detailed information about enrollment and vaccine allocation will be required.
- HCP who were unable to confirm test results using an acceptable method will be excluded

### Case and non-case finding, non-case selection, and compensation

Case and non-case finding may vary by project partner and by healthcare facility. Project staff may need to work directly with a healthcare facility's occupational health department to obtain the names, contact information and test results for all HCP who have been tested for SARS-CoV-2 (see Appendix 1 for an example of variables to be included in the line list). Project staff will seek to minimize the burden on healthcare facility staff to the extent possible.

Other options for identification of HCP cases and non-cases that may be utilized by participating healthcare facilities include (but are 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, but after a project site is approved to enroll HCP); 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).

An algorithm will be developed to enroll non-cases from among the eligible non-cases using random selection if the non-case accrual exceeds 3 times the cases.

At the discretion of project partners and according to local policies, HCP cases and non-cases may be compensated for their participation in the project. Procedures for compensation may vary across project partners depending on local policies. Partners who are already conducting similar HCP

COVID-19-related projects (such as Emerging Infections Program sites) should ensure comparability in HCP compensation across activities.

## Data collection

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

Data collection should begin as soon as possible following receipt of HCP SARS-CoV-2 test results through telephone interviews with HCP cases or non-cases using an IRF (see Appendix 2) or through self-reporting by HCP cases or non-cases 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 non-case will be contacted by project staff up to five times to schedule a future time for the interview or to conduct the interview, unless the HCP case or non-case requests a call back, or if the HCP case or non-case returns the call from the project staff. In these instances, an additional contact attempt (i.e., a sixth call) is permissible. For example, if the project staff person makes contact with a HCP on the fifth call attempt, and the HCP requests a call back the next day, that will be permitted. Contact with HCP cases and non-cases may be via telephone, email or text message at the project partners’ discretion.

If a HCP case or non-case is unable to be interviewed due to illness or incapacitation, or if the HCP case or non-case is deceased, project staff will attempt to interview the HCP’s primary caregiver or next of kin who will serve as the HCP’s proxy. Project staff will try to identify the person who is most familiar with the HCP’s medical history to serve as the proxy, and state-specific guidelines will be followed for determining which individual has legal authority to provide information on behalf of the deceased or incapacitated HCP. If appropriate, a proxy will be identified through review of medical records (including primary care provider records, where available) or contact with someone living at the HCP’s residence.

Project partners are responsible for ensuring that partner-initiated communications with HCP or their proxies comply with applicable privacy and information security standards. Interviews will be conducted by partners’ project staff (unless an electronic tool is used). Interviewers will introduce themselves and the project using a standard, introductory script. Partners that choose to administer an electronic questionnaire will include standard, introductory language via email or text to HCP or their proxies. Partners may make minor modifications to the scripts as needed to meet local needs or requirements. HCP or their proxies will be informed that their participation is voluntary.



Variable categories in the IRF include 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 will be available to HCP cases and non-cases in English and Spanish.

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

As with HCP case and non-case identification, partners may choose to implement a variety of approaches for determining eligibility, obtaining consent, and collecting data, depending on local resources, practices and policies.

#### Follow-up interview:

HCP cases and non-cases who are interviewed <14 days after the collection date of their SARS-CoV-2 test and are asymptomatic at that time will be re-contacted 14 or more days after the collection date of their SARS-CoV-2 test and the IRF will be updated if they became symptomatic after the initial interview and during the 14 days after their test collection date. HCP cases and non-cases who remain asymptomatic 14 days after the collection date of their positive SARS-CoV-2 test will not be included in VE analyses.

#### Medical record review:

Medical record reviews will be completed for all HCP cases or non-cases who report having sought medical care for the current episode of illness as reported on the IRF. Project staff will complete a supplemental review of hospital and/or outpatient medical records, as appropriate. An Extended Medical Record Review Form (Appendix 6) will be 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 will query 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 currently in development (known as the Vaccine Administration Management System, VAMS). Project partners should attempt to query VAMS, at least during early phases of SARS-CoV-2 vaccine roll-out, to record vaccine doses that may not be captured in the IIS until a later point. Project staff may also access 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 will be recorded using a Vaccine record review form (Appendix 7).

### 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.

Project partners may continue enrolling HCP after minimum numbers of cases and non-cases are reached if vaccine coverage has not yet exceeded 80%. 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
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\*Assuming a 1:3 case: control ratio

## Data management

Completed IRFs and HCP line lists will be maintained in project partner offices in secure locations according to applicable local or state regulations. The project staff will enter data from the IRF into a secure, web-based data system, such as REDCap. For partners where the electronic IRF is used, data will be first reported to the project partner and have HCPs’ identifiable information removed before submitting to CDC. Partners may also submit their data to CDC using a secure data upload function through CDC’s Secure Access Management System. Individual-level data will be transmitted to CDC on a bi-weekly basis.

## Healthcare personnel privacy and confidentiality

Project partners are responsible for ensuring that site-initiated electronic communications with HCP comply with applicable information security and privacy standards. The CDC data system will also comply with applicable information security and privacy standards. Direct personal identifiers such as HCP name or contact information (e.g., phone number or email address) will not be transmitted to CDC.

## Analysis

Data will be aggregated across project partners and healthcare facilities and analyzed at CDC using SAS version 9.4 (SAS Institute, Cary, NC) or other appropriate statistical software. Only HCP cases who develop symptoms will be included in the VE analysis. HCP cases must meet Criterion 1 or Criterion 2, below, during a period from 14 days prior to 14 days after test collection date. These criteria were developed in consultation with sites to align with U.S. Food and Drug Administration criteria for vaccine clinical trials, but they are subject to revision during project startup activities.

CRITERIA 1. At least ONE of the following respiratory signs/symptoms:

- Shortness of breath or difficulty breathing;
- Cough; or
- Acute respiratory distress syndrome (ARDS).

CRITERIA 2. At least TWO of the following:

- Fever (within episode of illness);
- Myalgia;
- New olfactory or taste disorder(s);

- Chills;
- Rigors;
- Headache;
- Sore throat.

Descriptive analyses will be performed. Characteristics of HCP cases and non-cases will be compared using chi-square tests or Fisher's exact tests (for categorical variables) or median or Wilcoxon rank-sum tests (for continuous variables).

To measure VE, we will calculate the odds ratio for vaccination (receipt of SARS-CoV-2 vaccine compared to no vaccine) among cases vs. non-cases, adjusting for potential confounders. Vaccine doses received within 14 days before HCP cases' and non-cases' SARS-CoV-2 test collection dates will be excluded from the analysis. We will estimate VE as follows:

$$VE = (1 - \text{adjusted odds ratio for vaccination}) \times 100\%$$

The primary analysis will evaluate the effectiveness of 2 doses of SARS-CoV-2 vaccine (if a 2-dose schedule is recommended) vs. no vaccine. A secondary analysis will evaluate the effectiveness of any vaccine doses vs. no vaccine, or one dose vs. no vaccine. More than one SARS-CoV-2 vaccine may be available during early phases of vaccine introduction among HCPs; analysis will be stratified by vaccine type.

We will conduct interim analyses after approximately 3 months of enrollment to evaluate vaccine coverage among non-cases. If these analyses suggest that we will not have adequate sample size to meet our primary objective, we will consider conducting the evaluation for a longer period.

## PROJECT TIMELINE (preliminary and subject to change)

- November 1, 2020 (or when SARS-CoV-2 vaccine introduced for HCPs): Enrollment and data collection for HCP cases and non-cases begin
- January–February 2021 (if enrollment started in November): Interim analysis of vaccine coverage among VE non-cases; revise sample size estimates and enrollment timelines as needed
- June 2021 (or after 6 months of enrollment or when sample size is reached): Complete VE analysis; report results

## HUMAN SUBJECTS RESEARCH REVIEW

Project partners and CDC will each seek a determination about whether the project constitutes human subjects research. Where necessary, individual participating healthcare facilities will also obtain a human subjects determination. In some instances, partners may need to add additional language to this protocol to address state- and/or partner- or facility-specific IRB considerations, such as those pertaining to HIPAA waivers or waivers of informed consent. Project personnel will ensure that any site-specific additions to the protocol will not affect the project objectives or data collection content or methods. Data generated by this project may be used to inform guidance to healthcare facilities and help protect HCP from COVID-19. Data collection will have no impact on the clinical care or work activities of participating HCP.

## REPORTING AND PUBLICATION

CDC and project partner investigators may communicate the results of this project at scientific meetings or in publications. Given the urgent nature of the data collection, CDC will provide interim data updates to appropriate audiences as needed. Data may be reported in aggregate, across all participating partners, or at the level of individual project partners. Data may also be reported by healthcare facility type, depending on the numbers of participating facilities. Data may be used in partner, state health department, or CDC reports.

## REFERENCES

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## APPENDICES

**Appendix 1: Example of a weekly line list for HCP cases and non-cases**

**Week reporting:** \_\_\_\_\_ **Start date:** \_\_\_\_ / \_\_\_\_ / \_\_\_\_ **End date:** \_\_\_\_ / \_\_\_\_ / \_\_\_\_

**Reported by: (Name)** \_\_\_\_\_

**Healthcare Facility:** \_\_\_\_\_

Last name	First name	DOB	Phone number	Email	Job	Test collect date	Test type	Specimen type	Reason for test	Test result
█	█	█	█	█	RT		PCR		Symptomatic	Positive
█	█	█	█	█	RN		Antigen		Screening	Negative



**Appendix 2:** Interview report form (see attachments)

**Appendix 3:** Proxy form (see attachment)

**Appendix 4:** Medical Record Review form (see attachment)

**Appendix 5:** Vaccination Record Review form (see attachment)