PReventing Emerging infections through Vaccine EffectiveNess Testing—COVID (Project PREVENT)
Project Protocol

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1) Background

As of October 10, 2020, the COVID-19 pandemic has caused over 37 million cases worldwide with over 1 million deaths.[1] It has also led to unprecedented efforts to develop a safe and effective vaccine on an abbreviated timeline through public-industry partnerships.[2] Currently, several SARS-CoV-2 vaccines are nearing completion of Phase III clinical trials, and public release is anticipated in late 2020.

While clinical trials will provide high-quality data on clinical efficacy, they will not provide real-world estimates of effectiveness or comparative effectiveness of competing vaccines. Effectiveness studies are important to confirm the results of clinical trials and estimate the impact of the vaccine on public health.

Front-line health care personnel (HCP) are a particularly high-risk group for COVID-19 exposure.[3-5] As SARS-CoV-2 vaccine is anticipated to be distributed first to front-line HCP, the early distribution of competing vaccines provides an important first-look opportunity to examine the effectiveness of these vaccines in preventing symptomatic COVID-19 infection. It also provides an opportunity to learn about the vaccines before they are widely available to the general public, but after clinical trials can no longer be performed.

2) Objectives

The primary objective of this project is:

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

Secondary objectives include:

1) Estimating the post-introduction effectiveness of SARS-CoV-2 vaccines in preventing severe disease among those with laboratory-confirmed symptomatic COVID-19;
2) Identifying differences in vaccine effectiveness by age group and comorbidity categories;
3) Evaluating vaccine effectiveness in various job categories and clinical practice settings;
4) Estimating the comparative effectiveness of different SARS-CoV-2 vaccines or, for vaccines with 2-dose schedules, 1 vs. 2-doses;
5) Comparing health care and COVID-19 testing practices of HCP within specific job groups;
6) Describing quarantine, isolation, repeat testing, and return-to-work practices among vaccinated and unvaccinated HCP tested for COVID-19;
7) Identifying factors associated with the decision to be vaccinated for SARS-CoV-2; and
8) Evaluating provider behavior changes, use of infection mitigation strategies, and decision-making in response to COVID-19 vaccination.

3) Project Design

This project will be completed using a multicenter test-negative case-control design in front-line HCP over a 6-month period. This design has been well described in influenza vaccine evaluation, and it can be used in post-approval vaccine evaluation for SARS-CoV-2.[6] We plan to collaborate with the

occupational/employee health clinic and the COVID-19 testing center at 16 participating academic medical centers located in urban U.S. cities to capture symptomatic employees at the time of COVID-19 testing. We will define cases and controls according to the results of COVID-19 testing when the participant is symptomatic (and those pre-symptomatic), and we will collect detailed information on vaccination, symptoms, risk profile, and exposures at the time of enrollment.

3.1. Inclusion Criteria

Any employee or volunteer in a participating hospital who was tested for COVID-19 is eligible for inclusion, regardless of their degree of patient exposure or vaccination status. HCP will include all paid and unpaid persons 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; or
- Contaminated air.

HCP of any job classification in any department of participating hospitals will be eligible, including 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, and health sciences students (medical, nursing, pharmacy, dentistry, or others, as available).

All employees retained for full data collection will meet either Criteria 1 or Criteria 2 during a period from 14 days prior to their first COVID-19 test to 14 days after that test. Asymptomatic participants will be screened for symptom development, and only those who develop Criteria 1 or 2 symptoms during the surveillance period will be enrolled in the project. Among those tested, a questionnaire will be used to confirm that the employee is eligible for participation. These clinical illness criteria below were developed in consultation with CDC to align with FDA 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
- Severe respiratory illness with either clinical or radiographical evidence of pneumonia or acute respiratory distress syndrome (ARDS).

OR

CRITERIA 2. At least TWO of the following signs/symptoms:

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

- Sore throat.

Any person who participated in a COVID-19-related vaccine trial may be included, but detailed information about enrollment and allocation will be required.

Eligible employees can be enrolled more than once (if the employee tested negative during a prior enrollment), but after being enrolled they will be ineligible for a period of 4 weeks after the time of enrollment, and they must have had complete resolution of symptoms from the time of the first episode of testing.

3.2. Exclusion Criteria

Any employee who was previously diagnosed with laboratory confirmed COVID-19 infection (RT-PCR, or antigen) will be ineligible (including previous project participants who tested positive during prior participation). Any person unable to confirm test results or vaccine administration using an approved method will also be excluded. Any previously enrolled HCP who did not complete the follow-up survey during a previous enrollment will be ineligible for re-enrollment.

3.3. Case Definition

Cases are defined as those who have a positive SARS-CoV-2 reverse-transcriptase polymerase chain reaction (RT-PCR) or SARS-CoV-2 antigen test deployed in routine local medical or public health clinical practice. Controls are defined as those who have a negative SARS-CoV-2 RT-PCR test(s), with no positive tests within 14 days after the time of their first test (if additional testing is performed). Note that negative SARS-CoV-2 antigen tests alone will not be permitted as a single test sufficient to qualify for inclusion as a control participant (but a positive antigen is sufficient for defining a positive case).

3.4. Case Finding, Subject Identification, and Recruitment

Case finding may vary by site, but every site will submit a Case Finding and Recruitment Plan (Appendix A) to the Clinical Coordinating Center (CCC) for approval prior to being released to enroll. Local project teams will obtain a list of HCP with positive and negative tests to identify and contact potentially eligible employees for enrollment. HCP may be identified in one of five ways:

1) **From occupational health clinics that have tested HCPs** – Local occupational health clinics will provide a complete list of participants with positive and negatives tests for screening. Sites may contact HCP by e-mail, telephone, or in-person recruitment as appropriate (enrollment must occur within 60 days of sample collection, but after a site is released to enroll);
2) **From non-occupational health clinics that have tested HCPs** – For employees who are tested outside their employer (occupational health clinic or employer-sponsored testing center), sites may recruit participants;
3) **From COVID-related hospital admission records** – For employees who are diagnosed with COVID-19 at the time of hospital admission, sites may recruit participants after hospital release (must be within 60 days of test collection, but after a site is released to enroll); or
4) **From employees 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 may be able to submit their test results for participation in the project (must be within 60 days of test collection).

The total pool of eligible employees will be collected with the following procedure. Each site coordinator will obtain a list of employees tested for COVID-19 in any given week. Each week, the DCC will send sites an algorithm to select HCPs to recruit, including a stepwise replacement procedure should selected HCPs be ineligible. Using the selection algorithm, site teams will invite employees to participate by sending them a link to the REDCap approximately 14 days after their test. Any HCPs who are ineligible or decline participation will be excluded and a record of invites, ineligible employees, declines, non-responses, and participants will be maintained by the site team

Eligible HCPs may be selected as follows but will be site dependent based on testing rates:

1. All of those with a positive test result will be invited to participate.
2. A sample of those each week with a negative test result will be invited to participate. This sample will be randomly selected from all negative tests for the week, and will be selected to be approximately 3 times the number of positive tests reported in a given week.

After eligible HCPs are selected, they will be invited by the site team to participate by e-mail. If an HCP declines to participate, a replacement eligible HCP will be automatically selected. If an eligible HCP does not respond, a reminder e-mail will be sent at 2 days and 4 days. Anyone who has not responded within 1 week will be contacted personally by a site coordinator by e-mail, telephone, or both. If an eligible HCP has not responded within 1 week, the supervisor will be contacted to confirm the employee is not admitted to a hospital. After confirming that the employee is not critically ill and has not responded for 1 week, the site coordinator will replace that eligible HCP to approach the next eligible HCP. Recruitment procedures should be developed to minimize differences between recruitment of cases and controls to limit bias in the project conclusions.

All eligible HCPs will be directed to the project wide web site and data collection forms with contact information for a local site PI. All employees tested at their employee testing clinic will also receive a letter from the local site PI explaining the project and encouraging participation (if an employee is selected).

All sites should maintain a record of eligible HCPs approached for the project who did not enroll in the project, and also the number of tested employees not approached for enrollment. This screen failure log should be deidentified, but should include the following data elements as available: job category, age, sex, test result. Summary data from this log will be reported weekly to the Data Coordinating Center (DCC). Details of this process will be included in the Case Finding and Recruitment Plan.

3.5. Procedures and Data Collection

Two possible strategies for data collection are available: 1) participant self-reported data; and 2) structured interviews with project participant or a proxy. All participants will have the opportunity to provide data by interview, and project staff will be prepared to collect information at the time of contact for people who are identified by telephone or in-person contact.

A central REDCap database will be developed by the DCC and will be used at all sites for project data collection. Two sets of participant forms will be used: 1) forms for participants providing data through online entry; and 2) forms for study coordinators who record information provided by participant interviews. Data access to the forms will be enabled for the following groups: 1) participants; 2) site

investigators and project oversight staff; and 3) coordinators, project assistants, and others who are validating data elements and conducting data collection activities.

All data collection activities may be completed either in English or Spanish. Consent documents, REDCap questionnaires, and communication can be selected to be in either language, and project personnel will be available to conduct both English and Spanish interviews. Sites that do not have Spanish-speaking project staff will have interviews for Spanish speaking participants done by the CCC.

Arm 1: Participant Self-Reported Data Collection

1) Employees will be notified by a written letter (distributed to people being tested at testing sites) at the time of testing. That letter will include a link to the project web site and general information about the project. Graphics for posters, screensavers, and other employee-facing communication will be posted around the medical center.
2) After test results are reported from employee health, testing data will be pooled with self-reported testing. A selection algorithm will identify within each site all the positive tests (n) and a randomly selected sample of negative tests (3n). Each selected HCP will receive an e-mail invitation to participate 14 days after their test result.
3) Employees will be presented information about the project in their e-mail solicitation, then they will be able to agree to participate or decline. After employees click on the link indicating participation, they will answer **eligibility questions** to confirm that they meet criteria for inclusion in the project. They will also provide contact information for pre-completion of forms and ways for project staff to contact them.
4) After confirming eligibility, they will be presented with an **electronic informed consent document**. Eligible employees will sign this consent document electronically.
5) After informed consent, the data structure will present the **baseline enrollment form**. This form will include questions about symptoms, demographics, testing, comorbidities, and vaccination history. For participants who are being tested at work, the data provided will allow the project team to access test results and vaccine information, but for participants self-reporting outside test or vaccination results, a portal will allow for uploading verification source documents or a photograph of relevant documents.
6) For situations in which medical record requests are indicated, REDCap will output data on needed medical record release forms and will automatically send these forms pre-completed through DocuSign by e-mail. Participants will electronically sign the forms and return them to the project team.
7) Four weeks after testing, participants will receive a follow-up e-mail and text message with a **follow-up survey**. That survey will include additional questions about symptoms, severity of illness, care required, subsequent testing, return to work, and other parameters important to assessing disease course. After the follow-up survey is completed, participation will end. If participants are unable to respond to this survey because they are admitted to the hospital, the project team will follow participant progress and collect data after hospital discharge through 28 days from their COVID-19 test. This follow-up data collection may be triggered from within the data system for participant self-reported data, or it may be conducted by interview with either the participant or a proxy.
8) Any data that requires clarification or confirmation will be resolved and documented by additional electronic or telephone communication between local project staff and local participants. An emergency contact and supervisor will be collected at the time of project enrollment to capture information in the event of severe illness.

Arm 2: Participant or Proxy Interview

1) If participants contacted by project team members elect to complete an interview, the interview will be scheduled and participants will be sent an **electronic informed consent document** alone to complete. This consent document will cover both participation and data release permission for vaccine records, testing records, and medical records. Follow up emails using the DocuSign portal will use an identical technique as described above.
2) No additional data will be collected within REDCap from the participant, and the rest of the data collection will occur through a structured interview. Medical, vaccine, and testing records will be collected from source documentation, or will be shared through secure e-mail as necessary.

3.5. Data Sources

Chart review methods will be guided by detailed data collection practices in the *Manual of Procedures*. Those practices will specify training, order of abstraction (to maintain blinding), and dual data collection/verification procedures on some critical parameters. The purpose of these methods is to minimize bias and maximize the robustness of our data.

Test Results: We will verify all test results (type of test/assay, date of test, result) from at least one of the following sources (a participant's self-report of the test result alone will be insufficient):

1) medical record of the occupational health/employee health or health system;
2) medical record of the primary care physician or another testing center; or
3) participant-submitted photograph of test result or official test result report (screenshot or PDF file with test result).

A project team member from each site will verify and attest to each result in REDCap. If medical records are obtained, source documents will be uploaded into REDCap, and a determination will be recorded (along with the identifier of the person making the determination) that the test meets the requirements of the project. If data are obtained from an employer or clinic through a bulk download process for which verification of methods have already been performed, then the project team attestation will meet the requirements for verification. Multiple documents may be provided for multiple tests, and all tests performed within the 14-day period after the index test will be recorded. For participants with source documents that provide verification, those requirements include the following:

1) The document must be provided as an official result from a health care provider, employee health clinic, or testing center;
2) The document must include a definitive identifier that links it with the project participant;
3) The document must show the date of the test;
4) The document must confirm identifying information about the organization or agency reporting the test;
5) The document must show the type of assay performed (e.g., RT-PCR). If the type of assay cannot be confirmed, the issuer may be contacted by project personnel to confirm the type of assay; and
6) The document must definitively report the test result. Samples that are positive for COVID-19 may be reported as "Positive," "Present," or "+." Any other result should be confirmed with the DCC or the issuing provider.

Vaccine Data: We will verify vaccine data (date, product, manufacturer, lot number, number of doses) from at least one of the following sources (a participant's self-report of vaccine information alone will be insufficient):

1) medical record of the occupational health/employee health or health system;
2) medical record of the primary care physician or other vaccination center; or
3) state or federal vaccine registry (state Immunization Information System, Vaccine Administration Management System, or other vaccination system).

A project team member from each site will verify each result and attest to that verification within REDCap. If medical records are obtained, source documents will be uploaded into REDCap, and a determination will be recorded (along with the identifier of the person making the determination) that the test meets the requirements of the project. If data are obtained from an employer or clinic through a bulk download process for which verification of methods have already been performed, then the project team attestation will meet the requirements for verification. Please note that verification documents will be collected for ALL COVID-19 vaccines and influenza vaccines. For participants with source documents that provide verification, those requirements include the following:

1) The document must be provided as an official result from a health care provider, employee health clinic, clinical trials office, or vaccination center. If a participant was vaccinated as part of a clinical trial, a letter with trial arm allocation can be used to provide source document verification;
2) The document must include a definitive identifier that links it with the project participant;
3) The document must show the date of the vaccine(s);
4) The document must confirm identifying information about the organization or agency reporting the test; and
5) The document must show the manufacturer or product name of the vaccine administered. This vaccine should list a lot number, which should also be recorded (not required).

For participants requiring inpatient or outpatient COVID-19 treatment, severity of illness will be confirmed through the participant medical record. The local project team will request the medical records from every:

1) Inpatient acute care hospitalization (for any cause) from the date of the test through 28 days after the first test was collected. If a participant was admitted to the hospital during this time, a comprehensive record of the hospitalization should be included (admission note, daily progress notes, discharge summary), even if discharge did not occur by this time. Inpatient and observation visits at an acute care hospital will be included, but skilled nursing care, rehabilitation, long-term acute care hospital admissions, or other post-acute admissions will not be included;
2) Emergency department visit (for any cause);
3) Unscheduled non-emergency episodic outpatient care visit (urgent care, walk-in clinic, etc.); or
4) Outpatient clinic appointment (only in relation to COVID-19 infection)

A project team member at each site will upload these source documents into REDCap and will abstract the record using case abstraction forms in REDCap. Abstraction instructions may be referenced in the *Manual of Procedures*.

Any participant who provides data through an interview will still provide access to records in the same manner, and project site staff will manage the workflow of the verification process similarly.

3.6. Participant Incentives

Each participant will be compensated $25 for completing the baseline enrollment survey, and an additional $25 for completing the follow-up survey. Compensation will be delivered by a check, which will be mailed directly to the participant from the DCC.

4) Site Selection

Sites will be selected from Project COVERED (http://www.covered-study.org) and *EMERGE*ncy IDNet (https://www.emergencyidnet.org/) sites, and other high-volume centers as necessary. We anticipate that 16 sites will be necessary for an adequate sample size (see below). Sites will be selected based on the ability to capture testing data (i.e., where most participants would be tested at employer-sponsored locations that allow access to these results), and on ability to develop highly reliable enrollment systems.

The schedule for site selection and launch activities is as follows:

1) Project protocol distribution – The final draft protocol will be shared with all interested sites by e-mail. Sites will have 1 week to review and send questions or clarifications to the CCC around the time of the All-Site Webinar;
2) All-Site Webinar – At this event, we will share an overview of project activities, a proposed site budget, and the checklist for the Site Readiness Call. We will discuss feasibility at sites and answer questions about the launch. A Launch Schedule will be proposed at this call;
3) Site Readiness Checklist – All sites will submit a Site Readiness Checklist by 2 weeks after the Kickoff Webinar. In completing this checklist, all sites will draft plans detailing recruitment, local COVID-19 testing practices, vaccine distribution, and monitoring that they will share with the CCC at least 48 hours before the Site Readiness Call. Sites will also identify their collaborators from the Employee Health/Occupational Health Clinic and the Testing Center (may be the same individual), and a primary Site PI and Primary Project Coordinator will be identified. Sites will also get local IRB determinations and will confirm data sharing procedures;
4) Site Readiness Call – On the Site Readiness Call, the Site Readiness Checklist will be reviewed and additional questions about resources, procedures, and staff will be discussed;
5) Site Selection – The Project PREVEnT COVID Executive Team will select all sites for the project. Selection will be communicated to all Site PIs. Sites that are unlikely to provide high-quality data will be replaced prior to site launch procedures; and
6) Subcontracts/Data Use Agreements (DUAs) – After sites are selected, subaward contracts will be drafted by the Olive View-UCLA Education and Research Institute (ERI) and distributed to sites along with proposed budgets. Any sites requesting DUAs will work with the DCC directly and will establish those agreements with the University of Iowa.

Based on preliminary interest forms and feasibility data, we anticipate participation by the following 16 sites. These sites have been selected to avoid overlap with other similar CDC surveillance activities. Some sites will enroll from multiple local medical centers within one health system because of overlap with employee health/occupational health coverage. During Site Selection, we may need to replace some sites, which will be done with CDC approval to prevent geographic overlap with other networks.

Site	Location	Estimated Total Number of Employees
Baystate Medical Center	Springfield, Massachusetts	8,000
Brigham and Women's Hospital	Boston, Massachusetts	19,000
Jackson Memorial Hospital	Miami, Florida	9,250
Louisiana State University	New Orleans, Louisiana	4,000
University of Alabama at Birmingham	Birmingham, Alabama	18,000
University of California, Los Angeles	Los Angeles, California	5,000
University of California, Fresno	Fresno, California	9,000
University of Chicago	Chicago, Illinois	10,000
University of Iowa	Iowa City, Iowa	4,200
University of Massachusetts	Worcester, Massachusetts	13,000
University of Mississippi	Jackson, Mississippi	7,000*
University of Texas, Southwestern	Dallas, Texas	26,100
University of Washington	Seattle, Washington	30,000*
Truman Medical Center	Kansas City, Missouri	3,800
Thomas Jefferson University	Philadelphia, Pennsylvania	15,900
Valleywise Health Medical Center	Phoenix, Arizona	2,690
TOTAL HEALTH CARE PERSONNEL POPULATION		184,940

*Some sites have expressed interest but have not been able to confirm surveillance population size. These estimates were derived from publicly available sources.

4.1. Project Launch Schedule

After site selection is complete, sites will get contracts and DUAs (if necessary) approved, hire staff, and implement their proposed recruitment process. Once the first vaccine is available in the U.S. market, all sites will start measuring and reporting vaccine coverage weekly. During this period, site ramp-up activities will continue until enrollment begins. Once vaccine coverage reaches 30% (across all HCP within the entire health system), sites will be launched to start enrollment. We will launch sites individually as they reach this surveillance milestone in consultation with our CDC collaborator team.

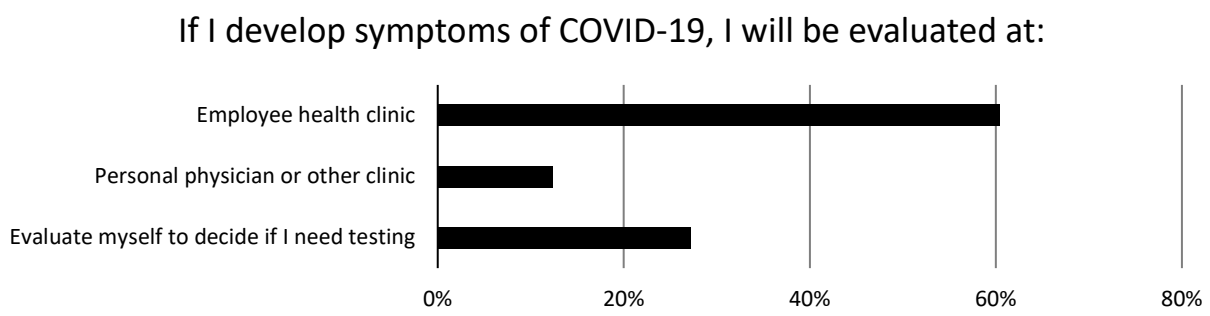
Enrollment will continue until at least one of the following criteria is reached:

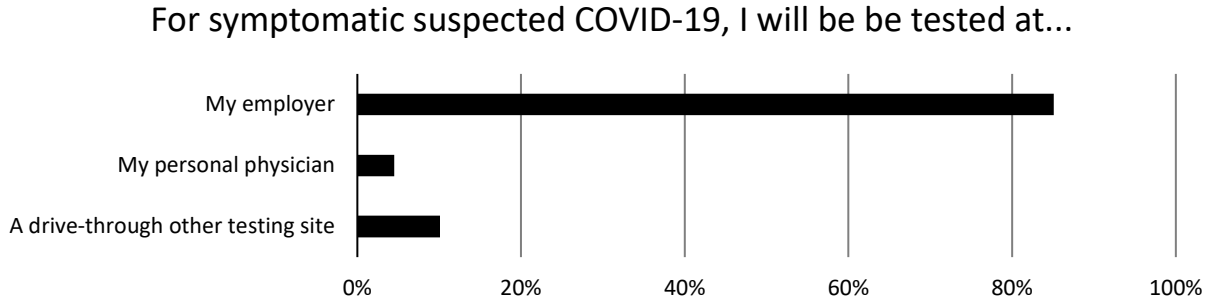
1) Vaccine coverage within the site population reaches 80%;
2) The targeted sample across all Project PREVENT COVID sites meets the predetermined sample size; or
3) The targeted sample across all CDC-funded networks completing the harmonized protocol meets the predetermined sample size.

The decision to stop the project will be managed through the Project PREVENT Executive Committee. The optimal time for enrollment for vaccine effectiveness evaluation is when vaccine coverage is between 30% and 80% of the included HCP population.

5) Preliminary Testing Data

To better understand the process of testing across a network of academic medical centers, a survey was distributed to all 1600 participants of Project COVERED (emergency department HCP) in 20 medical centers (n=846 responses). Because of the short timeline, these results were responses collected within the first 3 days after survey distribution.





Among those who would be tested outside their employer (only 15%), 63% would self-report all test results to their employee health clinic (with an additional 23% self-reporting positive test results). We also asked site PIs to discuss this proposed design with local employee health clinics. Among 11 responses (within 3 days), these procedures were feasible at all sites.

6) Human Subjects

Each site IRB will make an independent determination about whether project activities constitute human subjects research, but each IRB will be asked to evaluate in the context of public health surveillance and vaccine program evaluation. A letter from the CDC will accompany that application enumerating the support and funding for the project. The protocol will be submitted to the human subjects advisor in CDC's National Center for Immunization and Respiratory Diseases (NCIRD) for human subjects determination at CDC.

Prior to project startup, the University of Iowa and Olive View-UCLA IRBs will review the protocol, and these determinations will be shared with all participating sites. Each site IRB will make an independent determination about whether project activities constitute human subjects research, and data use agreements will be executed with the DCC as required by individual sites.

The risks to participant HCP are minimal and include 1) the time required to complete surveys, and 2) inadvertent release of protected health care information, which will be kept secure and will only be reported in aggregate. The surveillance poses no more than minimal risk of COVID-19 exposure because all surveys will be conducted electronically, and testing will be done locally in accordance with clinical infection prevention guidelines. No identifiable project data will be shared with employers or public health authorities. Data will be reported in aggregate, and no sites will be identified in reports.

All participant and patient protected health information will be maintained in a confidential, password-protected secure electronic database. Paper records will be maintained at each site in locked cabinets

maintained behind locked doors according to local or state regulations. All records will be scanned and uploaded to REDCap, and once the quality of a scanned document is confirmed and verification has occurred, paper records may be destroyed using methods acceptable for identifiable protected health information. Data will be managed centrally by the DCC prior to transmission of deidentified data to CDC using a secure data upload function through CDC's Secure Access Management System or via REDCap. Individual-level data will be transmitted to CDC on a bi-weekly basis. No personal identifying information will be transmitted to CDC.

7) Communications Plan and Data Release

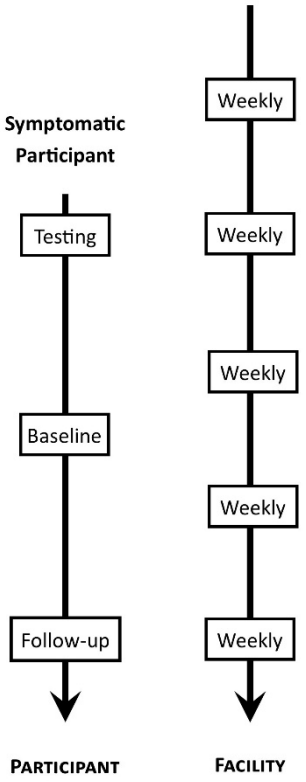
As data collection tools are built, question sets and harmonized data collection instruments will be reviewed by CDC and approved prior to initiating data collection. A project web site will be developed for participant communication, site team communication, and public reporting. The protocol will be publicly released on the project web site, and data collection tools will be released on the NIH Public Health Emergency and Disaster Research Response (DR2) system. A project overview webinar will be scheduled for representatives of all potentially interested sites to present project procedures and answer questions about participation. CDC representatives will be invited to this call.

During the project period, the project team will organize a meeting with CDC every 2 weeks and, during this meeting, enrollment data, vaccination coverage, testing and vaccine verification data, proportion of total tests captured, and interim progress will be presented. Deidentified data will be transmitted to CDC every 2 weeks for interim analysis using a common data format.

The main vaccine effectiveness result will be reported by CDC. Additional results and subsequent manuscripts are planned for publication by the project team in peer-reviewed journals after review and approval by CDC. A Data Use Policy will be developed and released that will permit de-identified data sets to be released to investigator teams, and a Publications and Presentations policy will guide reporting of results. We will develop a dissemination plan guiding release of findings.

8) Data Management

All forms will be completed electronically using REDCap case report forms, developed and managed centrally at the DCC. Participants who complete their data collection by interview will have their data entered into REDCap by project staff. Informed consent documents will be completed electronically and maintained within the REDCap database. Survey links for employees will be sent via email and/or text message. Each site PI and coordinator will have access to site-specific data and will conduct site-level completion monitoring, data entry, and data validation. Medical records data, vaccine data, and data validation requests will be managed by site coordinators and entered into the project-wide record, and all source documents will be stored and verified within the REDCap database. Any clarification of data elements may require local project staff to contact participants by telephone or e-mail. A summary of forms and data collection timelines is included below.



For any participant hospitalized at the time of the final follow-up survey, the final follow-up (including medical record review) will be delayed until after hospital discharge.

A weekly facility survey will collect information on total number of tests performed at a site, local vaccine coverage, total number of people approached for participation, and any changes in local testing or vaccination practices.

8.1. Data Analysis

To measure vaccine effectiveness, we will use a test-negative case control design. This design has been shown to limit bias compared with traditional case-control studies when vaccination is nonrandom.[7] We will consider a SARS-CoV-2 PCR, with accompanying symptoms consistent with COVID-19, to be the qualifying event.

The primary vaccine effectiveness analysis will be done at CDC using pooled data from multiple sites. Additional secondary analysis will be conducted by the DCC.

8.2. Covariate Adjustment

We will include in our data collection for multivariable modelling factors associated with COVID-19 infection, including:

1) job type and schedule;
2) known COVID-19 clinical or nonclinical exposures;

3) personal protective equipment use;
4) community transmission;
5) COVID-19 vaccine history (type, number of doses);
6) influenza vaccine history;
7) number of prior COVID-19 evaluations and an index of health care use;
8) personal living and commuting conditions;
9) household and community exposures;
10) hospital-level factors;
11) site; and
12) local COVID-19 activity (from public health reports).

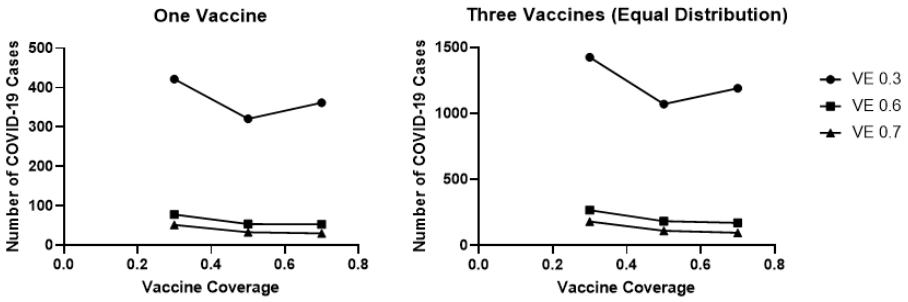
By collecting important covariates, we will account for factors that make COVID-19 infection more or less likely so as to isolate the independent association between SARS-CoV-2 vaccination and COVID-19 diagnosis. We will include the type of SARS-CoV-2 vaccine (manufacturer) as a categorical variable, so that we can determine the relative effectiveness of various vaccines in preventing infection.

8.3. Severity of Illness Analysis

We will use a similar multivariable logistic regression model to predict severe disease. In this model, we will additionally include HCP comorbidities that could be associated with severe disease to measure the role of vaccination in reducing severe disease, among those who are infected.

8.4. Sample Size Estimate

To estimate the required sample size, we predicted infections in a cohort of employees with nonrandom vaccine coverage. We built our sample size estimate using the number of COVID-19 cases during the period of observation required to demonstrate vaccine effectiveness (α=0.05, β=0.20, m=3:1, multiple vaccines will be equally distributed). For the estimate with 3 vaccines, we applied a Bonferroni correction for multiple comparisons:



Using a 3:1 case-control design, the total number of enrolled participants will be 4 times the number of cases listed in the figure above. We will develop an algorithm to select controls from among the available controls using random selection if our control accrual exceeds 3 times our cases.

To detect 60% vaccine effectiveness with 3 vaccines (adjusting for multiple comparisons) and 50% vaccine coverage with 0.5% COVID-19 acquisition probability, we estimate that we need at least 68,000 employees under surveillance. With one vaccine that is 30% effective and 0.5% COVID-19 cumulative incidence, we estimate that we need 119,000 employees under surveillance.

We estimate that our network will have 167,740 HCP under surveillance. If 8% have previously been infected with COVID-19 (estimated at 4.3% in Project COVERED, range by site 0-20%), then we will be observing 154,300 HCP. With that network, we anticipate being able to measure the effectiveness of a single vaccine of 0.3 (30-70% vaccine coverage, 0.5% COVID-19 acquisition) or the effectiveness of 3 vaccines with vaccine effectiveness of 0.5 (30-70% vaccine coverage, 0.5% COVID-19 acquisition).

We plan interim analyses performed by CDC throughout the surveillance period to refine our estimate of vaccine coverage in the network and the COVID-19 acquisition rate. If our estimate of COVID-19 acquisition is incorrect, then we will change our period of observation in consultation with CDC. We selected conservative estimates to ensure that we have robust estimates of vaccine effectiveness.

Currently, we plan to enroll 1,500 positive cases if at least 3 vaccines are available.

9.0. Project Team and Oversight

Project PREVENT COVID will be directed by the same leadership team that is currently conducting Project COVERED. Olive View-UCLA will be the Clinical Coordinating Center and prime award, and the University of Iowa will be the Data Coordinating Center.

- Nicholas Mohr, MD, MS (co-PI) – Professor of Emergency Medicine, Anesthesia Critical Care, and Epidemiology, University of Iowa Carver College of Medicine
- David Talan, MD (co-PI) – Professor of Emergency Medicine and Infectious Diseases, David Geffen School of Medicine at UCLA and University of Iowa Carver College of Medicine
- Anusha Krishnadasan, PhD (Project Manager and Director, Clinical Coordinating Center) – Epidemiologist, David Geffen School of Medicine at UCLA
- Karisa Harland, PhD (Director, Data Coordinating Center) – Epidemiologist, University of Iowa Carver College of Medicine
- Patrick Ten Eyck, PhD (Biostatistician) – Biostatistician, University of Iowa Carver College of Medicine
- William Mower, MD, PhD (Biostatistician) – Professor of Emergency Medicine, David Geffen School of Medicine at UCLA

10.0. Timeline and Budget

Using the infrastructure of Project COVERED, we anticipate that Project PREVEnT COVID will cost approximately $4.88 million. Based on our experience with Project COVERED, we anticipate project launch to occur 8 weeks from funding decision.

11.0 References

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7. Shi M, An Q, Ainslie KEC, Haber M, Orenstein WA. A comparison of the test-negative and the traditional case-control study designs for estimation of influenzavaccine effectiveness under nonrandom vaccination. *BMC Infect Dis.* 2017;17(1):757.