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

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1) Background

In January 2021, Project PREVENT launched a test-negative case-control vaccine effectiveness study of health care personnel (HCP) at 15 medical centers. Over 16 months, we enrolled 11,900 participants, contributing to data that demonstrated real-world effectiveness of COVID-19 vaccination.[1,2]

Starting in summer 2021, some data suggested that vaccine effectiveness waned over time.[3,4] In addition, new variants were associated with increasing COVID-19 case counts, especially among the unvaccinated, but also among vaccinated due to immune evasion. Vaccine effectiveness and the role of boosters for prevention of Delta and Omicron variant infections was unclear. Therefore, there was increased priority to continue to evaluate vaccine effectiveness among HCP through the previously successful methods used in Project PREVENT. Due to the increased number of variables that could affect vaccine effectiveness compared to the period when Project PREVENT was conducted, we project the need for larger sample of participants to ensure the rigor of estimates derived from Project PREVENT II.

Since we initiated PREVENT, there have been changes to COVID-19 testing practices. Fewer HCP are being tested exclusively through their employers and vaccines are more widely available to the general public. Since Project PREVENT, some HCP have received subsequent primary or booster vaccination doses, some have become infected, and now some have been treated with anti-viral medications. Thus, data collection tools that we built in early 2021 are now outdated.

This proposal, Project PREVENT II, is intended to continue HCP surveillance in a case-control design but with updated methods to continue to monitor HCP infections during the continued pandemic.

2) Objectives

The primary objective of this project is to evaluate SARS-CoV-2 vaccine effectiveness in preventing laboratory-confirmed symptomatic COVID-19 among HCP, specifically focusing on the effect of vaccine boosters and temporal changes in vaccine effectiveness.

Secondary objectives include:

1) identifying differences in vaccine effectiveness by age group and comorbidity categories,
2) evaluating vaccine effectiveness within job categories and clinical practice settings,
3) estimating the comparative effectiveness of different SARS-CoV-2 vaccines, vaccine schedules, and time periods between doses,
4) evaluating vaccine effectiveness as related to participant reported history of past infection,
5) measuring effectiveness of SARS-CoV-2 vaccine boosters,
6) elucidating the role of vaccination in preventing prolonged symptoms of COVID-19, and
7) evaluating vaccine effectiveness for illness related to emerging variants.

3) Project Design

This project will be completed using a multicenter case-control design among front-line HCP over a 9-month period. This design has been well described in influenza vaccine evaluation.[5] We plan to collaborate with the occupational/employee health clinics and COVID-19 testing centers at up to 20 participating academic medical centers located in urban U.S. cities to capture employees at the time of COVID-19 testing. We will define cases and controls according to the results of COVID-19 testing. At the time of enrollment, we will collect detailed information on vaccinations, symptoms, risk profile, and exposures.

3.1 Inclusion Criteria

A screening questionnaire will be used to confirm that the HCP is eligible for participation.

Any employee or volunteer in a participating hospital who was tested for COVID-19 in the prior 60 days 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, and
- 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).

HCP who test positive for COVID-19 must have at least one of the following symptoms during a period from 14 days prior to their first COVID-19 test to 14 days after that test.

- Abdominal pain;
- Bruised toes or feet;
- Changes in ability to smell or taste;
- Chest pain or chest tightness;
- Chills;
- Cough;
- Diarrhea;
- Fatigue (unusual feeling of tiredness);
- Fever (greater than 100°F or 37.8°C);
- Headache;
- Loss of appetite;
- Myalgia (muscle aches);
- Nausea (sick to your stomach) or vomiting;

- Rhinorrhea (runny nose);
- Rigors (sudden feeling of cold with shaking);
- Severe respiratory illness, including pneumonia;
- Shortness of breath or difficulty breathing;
- Sinus or nasal congestion; and
- Sore throat.

For HCP who test negative for COVID-19, no symptoms are required for enrollment. Eligible employees can be enrolled more than once, but after being enrolled and completing follow-up activities, they will be ineligible for a period of 6 weeks and must have had complete resolution of any symptoms from the time of the first episode of testing.

Any HCP who participated in a COVID-19-related vaccine trial may be included, but detailed information about enrollment and allocation will be required. For this project, HCP who had prior COVID-19 infection >90 days before their COVID-19 index date (i.e., symptom start date for symptomatic HCP and test date for asymptomatic HCP) may be enrolled.

3.2 Exclusion Criteria

The following will be excluded:

1) HCP that are unable to confirm test results or vaccine administration using an approved method (see section 3.7);
2) Previously enrolled HCP who did not complete any follow-up surveys during a previous enrollment;
3) HCP who do not intend to be working, studying, or volunteering in the participating health care facility for at least 6 weeks after enrollment;
4) HCP who do not speak English or Spanish; and
5) HCP who work remotely from home (defined as not working at least 1 day in a healthcare facility over the last 2 weeks, as defined above).

3.3 Case and Control Definition

Cases are defined as participants 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. Positive home antigen tests will be permitted (with photograph of the test type). Controls are defined as those who have a negative SARS-CoV-2 NAAT test(s), with no positive tests within 14 days after the time of their first test (if additional testing is performed). Note that an HCP with a negative SARS-CoV-2 antigen test alone will not qualify for inclusion as a control participant (but a positive antigen is sufficient for defining as a case).

3.4 Recruitment, Selection, and Invitation

Each site will submit a Recruitment Plan to the Clinical Coordinating Center (CCC) for approval prior to being allowed to enroll. All sites will keep a record (i.e., screening log) of the HCP who were tested, selected, and invited to the project, and HCP who declined participation. This screening log should be deidentified and 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 Recruitment Plan.

Recruitment

Sites may recruit HCP by e-mail, telephone, or in-person as appropriate. Recruitment procedures should be developed to minimize differences between recruitment of cases and controls. Potentially eligible HCP will be identified from local employee health records for recruitment in one of two ways:

1) Local employee health departments will provide the site team with a weekly list of HCP who were tested or reported outside testing for COVID with their test results. If employee health departments are able to release HCP names, but not test results, this is acceptable but only if the site team is able to achieve at least a 50% response rate from tested HCP with their test result, and
2) Sites where the local employee health department prefers not to release lists of HCP tested to the site team, may also work with an appointed contact (or contacts) within the employee health department to invite HCP to the project.

Note, HCP lists will be maintained at the site and will not be shared with the coordinating sites or CDC. The above methods of recruitment are required, but site teams may also use the following methods to supplement recruitment of HCP.

1) From non-employee health clinics that have tested HCPs – For employees who are tested outside their employer (employee health clinic or employer-sponsored testing center); or
2) From employees volunteering – Through e-mails, signs posted in staff patient care areas, screensavers, 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 (within 60 days of test collection).

Selection

The site coordinator or employee health contact will compile the list of employees tested for COVID-19 and each week, and sites will use an algorithm developed by the DCC to select participants to recruit, using a stepwise replacement procedure should selected HCPs be ineligible. Two weeks after the HCPs' test, using the selection algorithm, site teams will invite employees to participate by sending them a link to the REDCap database. Any HCP who are ineligible or declines participation will be replaced and a record of those invited, ineligible, declining, not responding, and participating will be maintained by the site team. The algorithm will be developed to slightly over-select controls because the recruitment rate is expected to be lower among participants who are not SARS-CoV-2 infected.

Based on site testing rates, HCP may be selected to participate as follows:

1) All those with a positive test result, and
2) A sample of those with a negative test result will be invited to participate each week. This sample will be randomly selected from all negative tests to yield approximately 3 times the number of positive tests reported. Based on experience from PREVENT I and to reduce workload, we will over-sample controls, aiming for 1:4 allocation ratio.

Invitation to project

After HCPs are selected, they will be invited to participate by e-mail or text message (if possible). The invitation will include a letter or flyer from the local site PI explaining the project, contact information of

site PI for questions, a link to the project website (www.prevent-project.org) for further information, and a link to the main project REDCap screening form. In addition, the HCP will be given the option to immediately decline participation before moving forward. If an HCP declines to participate, a replacement HCP should be selected and invited to the project. If an HCP does not respond to the project invitation, 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 e-mail, telephone, or both. If the HCP has not responded after 1 week, the site coordinator will select and invite a replacement HCP (if available).

3.5 Screening, Consent, and Enrollment

All HCP who receive a project invitation will receive a link to the main project screening form. After clicking on the link but prior to being presented with the screening form, the HCP will be given the option to stop and not continue. If the HCP decides to continue with screening, they will answer eligibility questions to determine if they meet inclusion and exclusion criteria. If they are eligible, they will be presented with an electronic consent form. If they agree to participate, they will be asked to type in their name to provide their consent to participate in the project and will be enrolled in the project. If they decline to participate, they will not proceed further.

3.6 Participant 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 data collection. Two sets of participant forms will be used: 1) forms for participants providing data through online entry; and 2) forms for site 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.

Sites will be able to accommodate employees who prefer to complete the surveys in Spanish. These will be conducted by scheduled interview with one of the Spanish-speaking site coordinators. After confirming eligibility, the site coordinator will use a Spanish version of the consent form to obtain verbal consent from the participant prior to conducting surveys. The site coordinator will enter the participant's responses into REDCap.

<u>Participant Self-Reported Data Collection</u>

1) After informed consent is provided, the data system will present the **baseline enrollment form**. This form will include questions about symptoms, demographics, testing, comorbidities, vaccination history, and health care utilization.
2) All participants will be asked to provide their test result and vaccination records for verification by the site team. For participants tested at work, the data provided will allow the local site team to access test results and vaccine information through their employee health department, 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.

3) Participants who report health care utilization 14 days prior through 14 days after their symptom onset will be asked permission to access their records for verifications. For situations in which medical record requests are indicated, data needed for medical record release forms will be recorded in REDCap. Site staff will electronically request these forms to be sent to participants pre-completed through *DocuSign* by e-mail. Participants will electronically sign the forms and return them to the site team.
4) At 6 weeks, 12 weeks, and 6 months after their initial symptoms or testing, participants will receive an e-mail and text message with **follow-up surveys** at those time points. The surveys will include questions about symptoms, severity of illness, care required, subsequent testing, timing of return to work, and other parameters important to assessing disease course. After the follow-up surveys are completed, participation will end. This follow-up data collection may be triggered from the data system for participant self-reported data, or it may be conducted by interview with either the participant or a proxy.
5) 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. Information regarding an emergency contact and the employee's supervisor will be collected at the time of project enrollment in the event that the participant experiences severe illness.

<u>Participant or Proxy Interview</u>

1) If a participant contacted by site team members elects to complete an interview, the interview will be scheduled and the participant will be sent an **electronic informed consent document** to complete. This consent document will cover both participation and permission for data release permission of vaccine, testing, 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 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.

3.7 Data verification

Site teams will ensure complete and accurate data collection, including obtaining, abstracting, and verifying medical chart data, testing results and vaccine records. Chart review methods will be guided by detailed description of 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 critical parameters. The purpose of these methods is to minimize bias and maximize the robustness of the data. A clinical lead will guide training and review of chart review across all sites, and chart abstractors will pass a simple quiz before being released to collect data.

COVID 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, except in the case of home self-administered tests):

1) medical record of the occupational health/employee health or health system,
2) medical record of the primary care physician or testing center,
3) participant-submitted photograph of test result or official test result report (screenshot or PDF file), or
4) participant-submitted photograph of the test type (box, etc.) for a home test.

A site team member 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 project requirements. 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 requirement for verification. Multiple documents may be provided for multiple tests, and all COVID 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 test date,
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 SARS-CoV-2 may be reported as "Positive," "Present," or "+." Any other result should be confirmed with the DCC or the issuing provider.

COVID 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 vaccination center, or
3) state or federal vaccine registry (state Immunization Information System, Vaccine Administration Management System, or other vaccination system).

The site team will capture all vaccine doses (including booster doses). A site team member will verify each result and attest to that verificationin 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 vaccination 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 requirement for verification. For participants with source documents that provide verification, those requirements include the following:

1) The document must be provided as an official vaccination 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 vaccination date(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. The vaccine lot number should also be recorded if possible (not required).

For participants requiring inpatient or outpatient COVID-19 treatment, severity of illness will be confirmed through review of the participant's medical record. The local project team will request the medical records from 14 days prior to onset of symptoms through 14 days after symptom onset for every:

1) Inpatient acute care hospitalization (for any cause except mental health or substance use/abuse). 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, and discharge summary [if applicable]), 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 visits (for any cause),
3) Unscheduled non-emergency episodic outpatient care visits (urgent care, walk-in clinic, etc., for any cause); and
4) Outpatient clinic appointments (only in relation to COVID-19 infection)

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

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

3.8 Participant Incentives

Each participant will be compensated $25 for completing each survey. If they complete all 4 surveys, they will receive $100 for their participation. 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 PREVENT (http://www.prevent-project.org) and *EMERGE*ncy ID NET (https://www.emergencyidnet.org/) sites, and other high-volume centers as necessary. 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.

Site Qualification – To be considered as a site, sites must:

1) conduct the project using public health surveillance exception to human subjects research,
2) obtain waiver of consent or opt-out consent strategies to contact and invite tested HCP to the project. The site team will maintain HCP testing data at their site and it will not be shared with the main coordinating sites, and
3) have at least results from 50% of HCP tested for COVID-19 available for screening and recruitment (e.g., from employee health).

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 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, which 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), Site PI, and Primary Project Coordinator. Sites will also get local IRB determinations and will confirm data sharing procedures,
4) Site Readiness Call – During 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 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 OV-UCLA site 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 selection from the sites listed below. These sites have been selected to avoid overlap with other similar CDC surveillance activities and are based on performance in PREVENT I and *EMERGE*ncy ID NET projects. We anticipate enrollment from this number of sites to exceed PREVENT I enrollment because of new site qualification guidelines for consent 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	12,500
Brigham and Women's Hospital	Boston, Massachusetts	17,900
Duke University	Durham, North Carolina	23,400
Jackson Memorial Hospital	Miami, Florida	11,800
Johns Hopkins Hospital	Baltimore, MD	10,000
Olive View-UCLA Medical Center	Los Angeles, California	4,700
Thomas Jefferson University	Philadelphia, Pennsylvania	32,000
University Health/ UMKC	Kansas City, Missouri	6,870
University Medical Center/LCMC	New Orleans, LA	12,700
University of Alabama	Birmingham, Alabama	18,500
University of California, Los Angeles	Los Angeles, California	32,000
University of San Francisco, Fresno	Fresno, California	9,100
University of Chicago	Chicago, Illinois	15,000
University of Iowa	Iowa City, Iowa	16,000

University of Massachusetts	Worcester, Massachusetts	17,000
University of Mississippi	Jackson, Mississippi	9,000
University of New Mexico	Albuquerque, NM	10,000
University of Utah	Salt Lake City, UT	20,000
University of Washington	Seattle, WA	12,760
Valleywise Medical Center	Phoenix, AZ	4,000
TOTAL HEALTHCARE PERSONNEL POPULATION		**295,230**

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. Many sites are currently conducting PREVENT I, so will be able to continue working on PREVENT II when it is launched.

Enrollment will continue for a 9-month period. The decision to stop the project will be managed through the Project PREVENT Executive Committee in consultation with CDC collaborators.

5) 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 consider the project in the context of public health surveillance and vaccine evaluation, as was deemed similarly by the CDC IRB and site IRBs for PREVENT I. A letter from the CDC will accompany that application indicating 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, as occurred for PREVENT I.

Prior to project startup, the University of Iowa and 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, compliant with local or state regulations. All records will be scanned and uploaded to REDCap, and once the quality of a scanned document is confirmed and verified, paper records will 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.

6) 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 and 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, 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.

CDC will report the main vaccine effectiveness results. 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 shared with investigator teams, and a Publications and Presentations policy will guide reporting of results. We will develop a dissemination plan guiding release of findings.

7) Data Management

All forms will be completed electronically using REDCap case report forms, which will be 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 data entry and validation, and completion monitoring. Medical record and 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.

For any participant hospitalized at the time of a follow-up survey, the 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 each site, local vaccine coverage, total number of people approached for participation, and any changes in local testing practices.

7.1. Data Analysis

To measure vaccine effectiveness, we will use a case-control design. This design has been shown to limit bias compared with traditional case-control studies when vaccination is nonrandom.[6] 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. Secondary analysis will be conducted by the DCC. Additional analyses will be conducted of:

1) Time from vaccination to illness,
2) Booster vaccinations,
3) Time between vaccinations (for mRNA vaccines), and
4) Vaccine types.

7.2. Covariate Adjustment

For multivariable modelling, we will collect information on factors associated with COVID-19 infection, including:

1) job type,
2) known COVID-19 clinical or nonclinical exposures,
3) COVID-19 vaccine history (type, number of doses),
4) hospital-level factors,
5) site, and
6) 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.

7.3. Severity of Illness Analysis

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

7.4. Sample Size Estimate

With the expanded justification for the aims of PREVENT II, this will require an increase in the sample size. We expect that we will be comparing vaccine effectiveness between (1) a 2-dose mRNA vaccine series, (2) 2 doses plus a booster, (3) 2 doses plus 2 boosters of existing mRNA vaccines, and (4) 2-3 doses of existing mRNA vaccines plus a new formulation targeting novel SARS-CoV-2 variants. We want to ensure that we are able to detect differences in vaccine effectiveness in these 4 cohorts, and we are able to achieve substantial precision of our vaccine effectiveness estimates. In our sample, we are planning to calculate relative vaccine effectiveness (compared with the 2-dose mRNA series only), since the population of unvaccinated HCP is expected to be very low.

We calculated the sample size using the World Health Organization Sample Size Calculator for Evaluation of COVID-19 Vaccine Effectiveness Studies.[7] We plan to compare participants who have received a novel booster to those who received the 2-dose mRNA series only. We assume that the relative vaccine effectiveness is at least 50%, and that we want to estimate precision of the estimate ±5%. Based on our experience with early COVID-19 vaccine uptake in 2021, we expect that 25% of controls will have received the novel booster vaccine. With 1:3 matching, this sample will require 15,332 participants, so we will budget for 15,000 participants (because we have enriched the sample for cases during period of surge, which improves our power).

This larger sample will also allow us to measure the effect of prior infection, variant-specific vaccine effects, the impact of comorbidities, and variation in vaccine and booster timing.

We estimate that our expanded network will have at least 270,000 HCP under surveillance. Our sample requires 3,800 SARS-CoV-2-positive participants, which will require approximately 1.4% of HCP under observation to be diagnosed with COVID-19. We think that a 1.4% infection rate over the next year is reasonable, given observed infection rates in PREVENT I sites with a largely vaccinated population during the first 14 months of PREVENT I observation.

8.0 Project Team and Oversight

Project PREVENT II will be directed by the same leadership team that is currently conducting Project PREVENT I. UCLA will be the prime award site, Olive View-UCLA Education and Research Institute will be the Clinical Coordinating Center, 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 Medicine/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, Olive View-UCLA Education and Research Institute
- Karisa Harland, PhD (Director, Data Coordinating Center) – Epidemiologist, University of Iowa Carver College of Medicine
- J. Priyanka Vakkalanka, PhD (Assistant Director, Data Coordinating Center) – Epidemiologist, University of Iowa Carver College of Medicine

9.0. Timeline and Budget

Using the infrastructure of Project PREVENT I, we anticipate that Project PREVENT II for one year of surveillance will cost approximately $13.6 million (including the previously requested $4.6 million). Based on our experience with Project PREVENT I, we anticipate project launch to occur within 6 weeks from funding decision.

10.0 References

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