

Arizona Healthcare, Emergency Response, and Other Essential Workers Surveillance (Az Heroes) Study

Version 1.3
December 5, 2020



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1. Abstract/Executive Summary

Coronavirus disease 2019 (COVID-19) is a disease caused by the emergent and rapidly spreading severe acute respiratory syndrome coronavirus (SARS-CoV-2) [1, 2]. The World Health Organization declared the COVID-19 outbreak a global pandemic on March 11, 2020 [3]. Despite the efforts by states and the federal government to limit transmission, the number of cases continues to grow rapidly, and healthcare systems are struggling to manage patients who need life-saving care.

Many questions about COVID-19 urgently need to be answered, including infection and re-infection rates, illness characterization, risk and protective factors, differences between symptomatic and asymptomatic individuals, and efficacy of interventions and vaccination when they become available. In the midst of the global public health emergency brought about by a new coronavirus, tools and infrastructure available to fill these critical gaps in knowledge and practice must be developed and implemented as quickly as possible. Healthcare personnel (HCP) and first responders (FR) are among those with the highest risk for COVID-19. Characterization of the risk factors and infection features in these populations will help inform our understanding of this infection and may help us protect them and their patients as they respond to the pandemic. Because HCP/FR are especially likely to be exposed to respiratory viruses and are among the priority targets for a pandemic vaccine once it is available, this population is a high priority for early studies of both the incidence and characterization of SARS-CoV-2 infection and COVID-19 illness. In addition, the HCP/FR population is ideal for studying the immune response to SARS-CoV-2 virus infection because of their early exposure and the feasibility of obtaining timely blood specimens. A protocol unique to this population is therefore needed to obtain early and critical information regarding incidence, characterization of illness, frequency and severity of repeat infection, frequency of asymptomatic infection, and humoral and cell-mediated immune responses.

Our primary objectives for this current proposal, the Arizona Healthcare, Emergency Response, and Other Essential workers Surveillance (AZ HEROES) study, are to: 1) estimate the incidence of asymptomatic and symptomatic re-infection in Arizona healthcare personnel, first responders and other essential workers; and 2) establish patterns of serologic immunity over time in previously and newly infected sero-positive individuals, including neutralizing antibody levels. Secondary objectives include describing illness severity, risk factors for infection and re-infection, healthcare utilization, and relative risk compared to influenza.

We will enroll 4,000 participants within 4 months. Sampling of eligible participants from the AZ COVID-19 Antibody Testing Initiative will be driven by the demographics of Arizona (approximately 50% women, 25% Hispanic, and 5% Native American) and the goal of enrolling 60% healthcare personnel, 30% first responders, and 10% frontline essential workers. For the purposes of planning and budgeting, we anticipate recruiting 2,000 sero-positive and 2,000 sero-negative study participants, but the final distribution of sero-positives and sero-negatives enrolled may be adjusted based on the needs of the CDC and NIH.

The initial study period will be 12 months. Participants enrolled in our cohort will self-collect respiratory specimens weekly and at acute illness onset during the study period. Those specimens will be delivered and analyzed by the laboratory contracted by CDC. Participants will also complete weekly surveys tracking general health, symptoms, social and occupational exposure risks, and healthcare utilization for those with symptoms or confirmed disease. Participants will provide blood specimens for serology at study enrollment, 4-5 months post-enrollment, 9 months post-enrollment, and as needed to assess convalescent serum antibody levels approximately 28 days following a positive PCR test. Antibody testing will be performed at the UA using the same ELISA developed for statewide testing. Aliquots of all study serum will also be stored and shipped to CDC and NIH for further analysis. In addition to serology, surveillance activities will be aligned with the current Research on the Epidemiology of COVID-19 in Emergency Response & Healthcare Personnel (RECOVER) study, and other ongoing CDC surveillance projects. Recruitment, enrollment, consent, weekly survey, and participant testing data will be collected and stored utilizing REDCap. CDC and NIH best practices will be followed for recruitment, consent, data management, and data sharing. An optional second year will provide for monitoring of the durability of immune response over a longer time period and potential evaluation of vaccine response.

2. Investigators

University of Arizona

Centers for Disease Control and Prevention, Influenza Division, NCIRD

Centers for Disease Control and Prevention, Division of Healthcare Quality and Promotion, NCEZID

3. Background

COVID-19 is a recently emergent disease, caused by SARS-CoV-2, a betacoronavirus from the SARS family [1]. The disease originated in Wuhan China at the end of 2019 and within 3 months quickly spread to the rest of the world [2]. The World Health Organization declared the COVID-19 outbreak a global pandemic on March 11, 2020 [3, 4]. As of May 10th, the number of confirmed cases worldwide is nearly 4 million, with more than 274,000 deaths [5]; in the U.S. the disease is present in all states with over 1.3 million confirmed cases and nearly 79,000 deaths [6]. Despite the increasingly aggressive efforts by governments to implement “social distancing” measures to limit transmission, the number of cases continues to grow rapidly in the U.S. and worldwide, posing an ongoing and serious threat to human health and society.

The main symptoms of COVID-19 include fever, cough, and shortness of breath [2], although other symptoms, such as loss of taste and smell, have also been reported [7]. The disease presents with varying degrees of severity [8] and a high percentage of infected individuals are thought to be asymptomatic. Certain population groups are at high risk of SARS-CoV-2 infection or of severe disease, including healthcare personnel and first responders.

Healthcare personnel (HCP) and first responders (FR) are at high-risk because they are on the front lines of the COVID-19 pandemic. A recent editorial in the Lancet estimated 3,300 SARS-

CoV-2 infections and at least 22 deaths among HCP in China, and a 20% rate of infection among this group in Italy [9]. As of April 9th, in the United States, there were more than 9,000 confirmed cases among HCP. However, this number is likely an underestimate due to missing data. Furthermore, work-related risks and exposures may differ from the general public, placing HCP and FR at higher risk for severe infections. Per- and polyfluoroalkyl substances (PFAS) are a component of some fire suppression foams, a known contaminant in some drinking water supplies around the U.S., and have been associated with a reduced immune response [10]. A recent study found increased serum levels in a population of firefighters as compared with the general population, which may impact the severity of COVID-19 infection.

Additional data are needed to confirm findings about the impact of potentially important factors (e.g., disparities in race and ethnicity or underlying health conditions among HCP) [11]. While anecdotal evidence of risk for HCP is persuasive, few research studies in this population have been published so far [12]. Further research is needed as it is critical to ensure the health and safety of our HCP/FR workforce. Surveillance is necessary for monitoring the impact of COVID-19 and to better inform infection prevention and control practices. Improving surveillance through routine reporting will benefit all workers during the COVID-19 pandemic [11].

During a pandemic, the CDC is responsible for monitoring related illnesses, describing the epidemiology of the virus infection and the burden of disease across the spectrum of illness, and monitoring and evaluating public health interventions. The CDC needs to provide guidance and information to clinicians, public health officials, and the public on pharmacological and non-pharmacological interventions, infection control measures, and the epidemiology of the pandemic virus. Therefore, in addition to surveillance and non-research field investigations, research platforms will be necessary to collect information to support CDC's mandate during a pandemic.

The importance of public health research has been reviewed by the Office of the Assistant Secretary for Preparedness and Response, Department of Health and Human Services [13]. Prepositioned protocols and studies, with prior IRB approval and study details and instruments vetted, will optimize our ability to perform relevant public health research during a pandemic. During the 2009 influenza pandemic, many important studies to guide public health decision making were delayed or not performed due to the lack of prior planning.

A meta-analysis of studies of seasonal influenza estimated that about 1 in 5 HCP are infected with influenza each year [13]. Due to their close contact with patients and the public, HCP and FR may also transmit influenza viruses to others. In fact, less than half of influenza virus infections may be symptomatic [13, 14] and HCP often work while ill [15-17], which further increases the risk of secondary transmission. In the event of a pandemic, there are likely to be multiple public health questions surrounding the effectiveness of pandemic vaccines in preventing COVID-19 illness, medical utilization, and missed work. Vaccine effectiveness (VE) may differ for different pandemic vaccines and vaccine strategies. Because this cohort will include HCP and FR who will likely be among the first recipients of a pandemic vaccine, this

protocol will provide one of the earliest measures of the effectiveness of the pandemic influenza vaccine to prevent laboratory-confirmed pandemic influenza infections, including those infections that result in both mild (i.e., non-medically-attended) and more severe illness.

Approximately 4,000 healthcare professionals (HCP), first responders (FR), and other essential workers (EW) that have close contact with the general public as part of their routine occupational duties will be enrolled in a prospective cohort to be followed for up to two years. Participants will be primarily recruited out of the statewide SARS-CoV-2 serological testing program, the AZ COVID-19 Antibody Testing Initiative, that is recruiting 250,000 Arizonans including HCP, FR, and EW. The study protocols will follow CDC-approved processes, structured on the current COVID-19 Research on the Epidemiology of COVID-19 in Emergency Response & Healthcare Personnel (RECOVER) study, for which the Principal Investigator (PI) for this current proposal is the site PI for firefighters in Arizona and Florida.

An enrollment survey will collect demographics, health history and status, knowledge of and attitudes about SARS-CoV-2, workplace and home infection control practices, and occupational exposure to SARS-CoV-2. All participants will provide blood samples in a local laboratory at enrollment, mid-point, and end-point for the study year for serologic testing. Participants who develop SARS-CoV-2 infections during the surveillance period will provide an additional sample 28 days after symptom onset. Serologic testing will occur at the UA. In addition to serology, all participants will provide weekly self-collected respiratory samples appropriate for providing a diagnosis of SARS-CoV-2 and influenza (during influenza season). If an individual develops symptoms related to SARS-CoV-2, they will collect an additional respiratory sample on the date of symptom onset. Respiratory samples will be analyzed utilizing the CDC-designated reference laboratory for PCR testing. AZ HEROES will prepare and distribute self-collection kits to the study participants. Participants will send their respiratory samples to the PCR reference laboratory.

Enrolled participants will participate in active surveillance via weekly surveys. They will be contacted weekly via secure SMS text messages asking them to provide information about their health, changes in their occupational or personal SARS-CoV-2 exposure, and a rotating series of questions capturing their attitudes and beliefs surrounding SARS-CoV-2. Participants will be instructed to notify staff if they develop symptoms. Any individual that identifies they have symptoms consistent with SARS-CoV-2 in a weekly survey or by contacting staff will complete additional information including the participant's symptoms, severity, duration, self-reported medical treatment, during- and post-illness function, and details about the resolution of their illness.

3.1 Abbreviations

CDC	Centers for Disease Control
EW	Essential workers
FR	First responders
HCP	Health care personnel

IRB	Institutional Review Board
PFAS	Per- and polyfluoroalkyl substances
PCR	Polymerase chain reaction
RR	Relative Risk
UA	University of Arizona

3.2 Objectives

1. Estimate the incidence of PCR+ SARS-CoV-2 re-infection (among adults with prior infection as indicated by SARS-CoV-2 antibodies)
 - a. Estimate for all PCR+ (regardless of symptoms) and separately for symptomatic vs. not
 - b. Estimate the incidence of sero-conversion not associated with PCR-positivity (“serology-only”) among prior infected vs. not
2. Assess the relative risk (RR) of PCR+ SARS-CoV-2 among those with prior infection vs. those without prior infection
 - a. Estimate this in total (regardless of symptoms) and separately for symptomatic vs. not
3. Compare the severity and duration of PCR+ COVID-19 among those with repeated versus novel infections.
4. Describe the serologic immune response to PCR+ SARS-CoV-2 event
 - a. Sero-conversion from pre-PCR+ sera to convalescent sera
 - b. Compare those with or without symptoms at PCR-positivity
 - c. Compare this among those with prior infection vs. without; examine correlates of protection
5. Describe the kinetics and duration of serologic immunity over time following PCR+ event
 - a. Stability (or waning) of antibodies over subsequent blood draws
 - b. Compare this among those with prior infection vs. without
6. Describe the sociodemographic, occupational, health, and other risk factors associated with increased risk of PCR+ COVID-19 and prolonged disease and/or functional impairment.
7. Determine the association of serum PFAS concentrations with the endpoints measured above.

Vaccine effectiveness activities are:

1. Assist in the evaluation of the immunogenicity of pandemic SARS-CoV-2 vaccines by collecting sera from participants before and after vaccination and performing serologic and cellular immune response testing.
2. Assess the effectiveness of SARS-CoV-2 vaccines in preventing SARS-CoV-2 infection and COVID-19 illness. Examine VE for different vaccine exposures, including different vaccine types and full vs. partial adherence to recommended vaccine doses and timing. Specifically, estimate VE against:
 - a. rRT-PCR-confirmed SARS-CoV-2 with COVID-19 illness;
 - b. rRT-PCR-confirmed SARS-CoV-2 with other symptomatic illness not meeting COVID-19 criteria;

- c. Asymptomatic rRT-PCR-confirmed SARS-CoV-2 infections.
3. Examine if VE is modified by socio-demographic characteristics, occupation, health status, or other risk factors.
4. Examine if vaccine modifies illness severity, duration, and infectiousness (or viral shedding) among essential responders with breakthrough infection despite vaccination.
5. Characterize the knowledge, attitudes, and practices (KAPs) related to new COVID-19 vaccines and examine the associations between KAP and subsequent vaccination behaviors (including vaccine refusal, hesitancy, or incomplete adherence to vaccination recommendations) among essential responders.
6. Determine the association of serum PFAS concentrations on SARS_CoV-2 infection, COVID-19 illness, and SARS-CoV-2 antibodies.

4. Methods

4.1 Overview of Study Design

Approximately 4,500 healthcare professionals (HCP), first responders (FR), and other essential workers (EW) that have close contact with the general public as part of their routine occupational duties will be enrolled in a prospective cohort to be followed for up to two years. Participants will be primarily recruited out of the statewide SARS-CoV-2 serological testing program, the AZ COVID-19 Antibody Testing Initiative, that is recruiting 250,000 Arizonans including HCP, FR, and EW.

The study protocols will follow CDC-approved processes, structured on the current COVID-19 Research on the Epidemiology of COVID-19 in Emergency Response & Healthcare Personnel (RECOVER) study, for which the Principal Investigator (PI) for this current proposal is the site PI for firefighters in Arizona and Florida.

An enrollment survey will collect demographics, health history and status, knowledge of and attitudes about SARS-CoV-2, workplace and home infection control practices, and occupational exposure to SARS-CoV-2. All participants will provide blood samples in a local laboratory at enrollment, mid-point, and end-point for the study year for serologic testing. Participants who develop SARS-CoV-2 infections during the surveillance period will provide an additional sample 28 days after symptom onset. Serologic testing will occur at the UA.

In addition to serology, all participants will provide weekly self-collected respiratory samples appropriate for providing a diagnosis of SARS-CoV-2 and influenza (during influenza season). If an individual develops symptoms related to SARS-CoV-2, they will collect an additional respiratory sample on the date of symptom onset. Respiratory samples will be analyzed utilizing the CDC-designated reference laboratory for PCR testing. AZ HEROES will prepare and distribute self-collection kits to the study participants. Participants will send their respiratory samples to the PCR reference laboratory.

Enrolled participants will participate in active surveillance via weekly surveys. They will be contacted weekly via secure SMS text messages asking them to provide information about their

health, changes in their occupational or personal SARS-CoV-2 exposure, and a rotating series of questions capturing their attitudes and beliefs surrounding SARS-CoV-2. Participants will be instructed to notify staff if they develop symptoms. Any individual that identifies they have symptoms consistent with SARS-CoV-2 in a weekly survey or by contacting staff will complete additional information including the participant's symptoms, severity, duration, self-reported medical treatment, during- and post-illness function, and details about the resolution of their illness.

4.2 Study Population

SARS-CoV-2 sero-positive and sero-negative participants will be recruited from the AZ COVID-19 Antibody Testing Initiative. As of June 4, >12,000 participants had been enrolled in the Initiative, with a sero-positive rate of 1.25 % among healthcare personnel. Individuals participating in the Initiative are asked to confirm they are willing to participate in additional research. Additionally, the baseline questionnaire for the Initiative includes information about occupation, demographics, SARS-CoV-2 exposure, and contact information.

In addition, with permission from the sponsor and partners, populations targeted for serology testing outside of the ATI may be targeted for enrollment. These agencies may include the from the Arizona Department of Health Services (ADHS) and independent corporations such as Banner Health.

4.3 Eligibility Criteria

Inclusion criteria

- Aged 18 to 85 years old
- Has smartphone access or internet access
- Has a mailing address
- Works at least 20 hours per week
- Plans to remain in Arizona for next 12 months
- Has not received the COVID-19 vaccine
- Job duties include activities that can result in direct contact with co-workers, patients, or the public more than 50% of the time
- Confirmation of meeting definitions for work as healthcare personnel, first responder, essential worker, or frontline worker

Exclusion criteria

- Enrolled in a SARS-CoV-2 vaccine or interventional trial;
- Previously requesting that s/he not be contacted regarding research studies;
- Working less than an average of 30 hours per week;
- Unwilling to provide verbal and/or electronic confirmation of consent;
- Unwilling to self-report occupation, work responsibilities, and prior COVID-19 illness;
- Unable to conduct study activities in English or Spanish

4.4 Recruitment

Once participants in the AZ COVID-19 Antibody Testing Initiative have received their antibody results, those who have agreed to participate in additional research will be automatically placed into a REDCap database, which will constitute the AZ HEROES sampling frame. Participants will be sampled randomly within strata defined by occupation, sero-positive/sero-negative status, sex, age group, and race/ethnicity. For the purpose of planning and budgeting, the research team intends to recruit 2,000 sero-positive and 2,000 sero-negative participants into the study.

Potential participants will be called by trained clinical research coordinators utilizing a standardized script. A study recruitment and retention dashboard will be developed for continual evaluation of study goals in terms of participant recruitment by serologic status demographic variables that reflect recruitment targets for vulnerable populations. The recruitment and retention dashboard will be built using the RShiny flexdashboard package using deidentified study data (Chang and Borges Ribeiro 2018).

As needed to reach specific AZ HEROES recruitment goals for minority populations, we will work with other COVID-19 testing programs to recruit both sero-positive and sero-negative participants. The UA works closely with multiple American Indian nations, and the AZ HEROES team will be working with these communities to establish opportunities for participation in the current proposal. A particular set of workers at high risk of exposure is casino workers, as casinos provide both employment and financial income for many of the American Indian nations within Arizona. UA MEZCOPH researchers have also been contacted by Hispanic restaurant business owners and employees, who are interested in obtaining serological testing, providing an opportunity to expand serological testing in these essential workers if they are not already covered by the AZ COVID-19 Antibody Testing Initiative. In addition, limited testing using point-of-use SARS-CoV-2 antibody kits has been performed by clinical providers for some Phoenix area firefighters. The site PI has worked closely with these providers and firefighters, providing an additional opportunity for focused minority subject recruitment. In May 2020, the Arizona Department of Health Services also initiated a statewide antibody testing program for HCP at 147 skilled nursing facilities. There may be opportunities for additional recruiting among this population of HCP who know their SARS-CoV-2 serologic status, should additional targeted recruiting be necessary to meet recruitment goals.

4.4.1 Identify Potential Participants

We will recruit a total of 4,000 participants into the AZ HEROES study. Fifty percent will have a seronegative (SN) status upon enrollment and 50% will have a seropositive (SP) status.

The samples sizes for **Health Care Workers (HCW)**, **First Responders (FR)** and **Essential Workers (EW) broken into two categories**. We will be oversampling for participants identifying as Hispanic/Latino and will include all Native Americans (current 2% of serology sample).

Table 1. Sampling from seronegative database (first 1000 seronegatives).

Age Group	Race	Sex	HCW (n=400)	FR (n=300)	EW ¹ (n=150)	EW ² (n=150)
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18-39 Years of Age (50%)	White/Non- Hispanic (50%)	Female (50%)	50	38	19	19
		Male (50%)	50	38	19	19
	Hispanic/Native American (50%)	Female (50%)	50	38	19	19
		Male (50%)	50	38	19	19
40-64 Years of Age (50%)	White/Non- Hispanic (50%)	Female (50%)	50	38	19	19
		Male (50%)	50	38	19	19
	Hispanic/Native American (50%)	Female (50%)	50	38	19	19
		Male (50%)	50	38	19	19

EW¹ Public-Facing Frontline Workers; EW² Essential Operations & Infrastructure

Trigger for re-evaluation: less than 10 in any strata or greater than 70, 50 or 30 in either HCW, FR, or either EW category, respectively; or more than 35% of any substrata of HCW and FR and 60% of either substrata of EW1 or EW2.

Table 2. HCP, FR, and EW substrata

Health Care Personnel
Inpatient
Ambulatory/Outpatient
Intentional (Institutional (residential care, long term care, assisted care and skilled nursing facilities, including residential facilities and rehab facilities)
First Responders
Fire Service/EMS
Law Enforcement
Corrections
Essential Workers (Public-Facing Frontline Workers)
Hospitality, Retail & Food Service
Other frontline (grocery, childcare/education, transportation, government clerks and services)
Essential Workers (Essential Operations & Infrastructure)
Essential operations (agriculture/food processing, 911 operators, delivery/warehouse)
Essential infrastructure (utilities, custodial/environmental services, waste collectors, and other facilities/maintenance staff)

4.4.2 Recruitment Methods

For the purposes of planning and budgeting, we anticipate employing a three-phased recruitment approach, similar to, but with a few modifications, to the RECOVER cohort. The first phase (Wave 1) will focus on sampling (according to the stratified process described above) and enrolling individuals from a retrospective sampling frame with retrospective AZ

COVID-19 Antibody Testing Initiative participants. The second phase (Wave 2) will focus on enrolling subjects as they enroll in the AZ COVID-19 Antibody study within the sampling strata described above. The third phase (Ongoing Recruitment) will be used to replace participants who have dropped out of the study. Refinements to this approach will be developed based on ongoing discussions with CDC and the external expert advisory group.

Wave 1 Recruitment:

- Stratified random sampling, recruitment, and enrollment of HCP/FR/EW from a sampling frame retrospectively populated with data from the AZ COVID-19 Antibody Testing Initiative

Wave 2 Recruitment:

- Stratified random sampling, recruitment and enrollment of HCP/FR/EW to achieve selective oversampling of select strata.

Ongoing Recruitment:

- Participants who voluntarily withdraw from the study will be replaced by a newly recruited participant within the original participant's sampling strata until mid-study blood collection in the second year of the study is completed.

4.4.3 Screening

Study staff will track study recruitment efforts using the Recruitment Screening Log (Appendix A: Aggregate Recruitment Log). In accordance with the phased recruitment approach detailed above, study sites will contact potential participants from the pre-formed rosters via email or phone to determine eligibility. Participating sites may partially determine eligibility through pre-screening a portion of eligibility questions via online survey or conducting the full screening interview by email, phone or live video conference (Appendix B: Screening Survey). If the participant is found to be eligible, study staff will obtain and document individual informed consent for study procedures as per the local institution's IRB.

4.4.4 Informed Consent

To facilitate informed consent during a period of enforced social distancing and/or shelter-in-place orders, sites may employ a virtual informed consent process. Once a potential participant screens as eligible for the study, study staff will review study materials and the consent form (Appendix C: Consent Form) with the potential participant by phone. Upon complete review of these materials, documentation of participant consent will be provided by the participant utilizing a REDCap-based consent form. All participants will provide consent to be in the study. This consent will include authorization to provide the following:

- Permission to be contacted for acute illness surveillance and study surveys.
- Self-collected respiratory mucosal specimens, including but not limited to nasal swabs and saliva samples, as appropriate for SARS-CoV-2 detection in accordance with FDA guidance and approval.

- Blood (serum) samples drawn at enrollment and the approximate midpoint and end of each study year, and in the event of an infection, a convalescent sample approximately 4 weeks after illness onset or rRT-PCR detection,

In addition to the activities detailed in the general consent form for the main study, the informed consent will provide an opportunity to accept or decline participation in future research.

4.4.5 Data Collection

Most research activities will occur through electronic communications (email, text, and internet-based surveys), telephone contacts, or via postal or express mail minimizing direct contact between study staff and participants. All surveys are designed to be self-administered electronically and online, either via the internet accessed by computer or smart phone. All surveys may also be administered by telephone or mail should participants be unable or become unwilling to access them online.

4.4.6 Enrollment Activities

4.4.6.1 Enrollment Survey

Following the provision of informed consent, participants will be asked to complete the online Enrollment Survey (Appendix D: Enrollment Survey) which will assess the following through self-report:

- Occupational use of personal protective equipment;
- Socio-demographic characteristics (sex, age, race, ethnicity, marital status, household composition, and socio-economic status);
- Health status and behaviors (smoking history, self-rated health, sleep quality, and productivity);
- Self-reported chronic medical conditions (for participants without medical records) and influenza vaccination history;

4.4.6.2 Orientation and Instruction

Shortly after enrollment, participants will be provided with a set of materials for the self-collection of a respiratory specimen. Participants will be given enough supplies for at least one month of weekly specimen collection and an active illness specimen. Participants will be provided with instructions for collecting, storing and submitting to a specified facility drop-off location or shipping the specimens according to FDA guidance and the specifications listed in Section 5.6.1.

4.4.6.3 Enrollment Serum Collection

Participants will be asked to provide a 40ml blood sample at baseline to inform the evaluation of immune responses to infection. These samples may be provided as part of the overall enrollment process and will be collected as close to the start of study activities as possible. Information on each blood sample collection will be documented using the Blood Sample Collection Form (Appendix E: S1 Blood Collection Form).

4.4.7 Active Surveillance for Acute Illness

Active surveillance for acute illness will be conducted throughout the study period. Participants will be prompted to begin surveillance as quickly as possible after study enrollment. The primary means for detecting acute illnesses during the study period will be through a Weekly Active Surveillance system using Twilio + REDCap text messaging. All text messaging scripts are outlined in Appendix H: Surveillance Messaging Scripts. Each week, all participants will be contacted to ascertain the development of symptoms and reminded to collect a weekly specimen (Appendix I: Surveillance Specimen Collection Form). Participants will have an elected or assigned routine day for communication and specimen collection. Specifically, the participant is asked if they have experienced one or more of the following in the past 7 days:

- Fever
- Cough
- Shortness of breath
- Sore throat
- Diarrhea
- Muscle or body aches
- Change in smell or taste

An acute illness can be identified by indicating symptoms within the last week or by contacting study staff. If a participant reports they are not ill, they will be asked additional questions and reminded to submit their weekly specimen to the laboratory through standard procedures (Appendix I: Weekly Specimen Collection).

Once an acute illness is identified, participants will be asked to identify qualifying symptoms from a more detailed symptom checklist, confirm date of onset, and if symptoms are still ongoing (Appendix K: Acute Illness Survey). If the symptoms are currently ongoing, participants will be prompted to collect specimens using the Illness Specimen Kit (Appendix J: Acute Illness Specimen Collection) and send them to the laboratory using standard procedures. Regardless of illness, participants should collect their weekly surveillance specimen on their assigned day. If the participant reports illness and/or collects the Illness Specimen Kit on their assigned routine specimen day, they will not be asked to collect their weekly specimen again.

Weekly surveys for ill participants will be modified to assess continuing illness, ability to conduct normal activities, and a reminder to contribute their weekly specimen. This message will continue every week until the participant reports they are no longer experiencing illness symptoms or until a new unrelated illness is reported.

Participants who report continuing illness symptoms on the first weekly messaging that is ≥ 7 after illness onset will be asked to complete the Illness Update Survey (Appendix L: Illness Update Survey) which assesses symptom onset and severity for this persistent illness.

Once the participant reports they are no longer experiencing illness symptoms, they will be asked to report the number of days since symptoms ended and current recovery progress. Participants will also be prompted to complete the Appendix M: Illness Recovery Survey to assess symptoms and additional illness information. Until a participant reports return to normal activities, the weekly surveillance messaging will continue to ask about recovery progress. Once a participant reports a return to normal activities, the weekly messaging will return to the standard questions.

4.7.8 Vaccination

Pandemic vaccination status will be assessed through multiple methods to ensure complete and near real-time data capture, which is a critical component for scheduling post-vaccination blood collection and monitoring for additional vaccine dose receipt.

4.7.8.1 Immunization Information Systems

We will query the state immunization information system (IIS) or registry to obtain COVID-19, influenza, and pneumococcal vaccination status.

4.7.8.2 Vaccination Reporting

Participants will be asked to report COVID-19 vaccination to study staff in advance of scheduled vaccination or as soon as soon as possible after receipt. Pandemic COVID-19 vaccination status will further be assessed through brief surveys sent to participants after vaccine becomes available (Appendix O2: SARS-CoV-2 Vaccination Update Survey).

Whether COVID-19 vaccination is identified by direct contact from participants or in response to the vaccination surveys, participants will be asked to send vaccine documentation. Examples of documentation include a digital photo of the vaccination receipt or vaccine fact sheet (handout) delivered at vaccination. These documents can also be scanned and sent by email or SMS text.

4.4.9 Follow-up Surveys

4.4.7.1 Follow-up Survey 1

A brief online survey administered at the study-year midpoint (Appendix O: Mid-Study Survey), approximately 4 to 6 months after study year start, and at the end of each study year (Appendix R: End of Year Survey) will provide opportunities to update exposure, influenza vaccination receipt, and health status information that may have changed since enrollment timing.

4.4.7.2 Interim Blood Collection

Participants will have 40ml of blood collected at the approximate midpoint (Appendix P: S2 Mid-Study Blood Collection Form) and at the end of each study year (Appendix S: S3 Blood Collection Form). Information on each blood sample collection will be documented using the Blood Sample Collection Form (Appendix S: S3 Blood Collection Form). In the event of a qualifying illness infection, a convalescent sample will be

collected (Appendix N: S2 Convalescent Blood Collection Form) as described in Sections 5.6.2.

4.5 Specimen Collection

4.5.1 Respiratory Mucosal Samples

Respiratory mucosal specimens will be self-collected and shipped according to the most up-to-date guidance from FDA and CDC. Approved specimen collection methods may include options for specimen types, including respiratory specimens or saliva specimens. There are a variety of approved nasal swabs (e.g., flocked, foam) that can be shipped in several approved transport media, without medium, or in saline.

During this study, a standard respiratory specimen is defined as a participant-collected anterior or mid-turbinate nasal swab using a flocked swab or equivalent based on available data about SARS-CoV-2 detection. Additional specimen types such as saliva samples and foam nasal swabs may be collected with identification of acute COVID-19-like illness. If emerging data indicate that other specimen types such as saliva or foam swabs are comparable or superior to current standard specimens or procurement of flocked nasal swab supplies is not possible, the study will modify the choice of standard respiratory specimen accordingly. Any modifications to sample collection will be determined and approved jointly by the study team and CDC.

Participants will be asked to self-collect a respiratory specimen each week regardless of symptoms throughout the study period. If a participant identifies that they have an acute illness, they will self-collect a standard respiratory specimen and an additional sample (e.g., nasal swab and a saliva sample). Ideally, the sample would be collected no later than 24 hours from the weekly text notification or illness onset. As noted in Section 5.5.1.2, participants will receive training to self-collect a respiratory specimen. At the start of surveillance, participants will be given a “self-collection kit” that includes illustrated instructions, and at least one month-worth of prepared supplies for routine, weekly specimen collection and for acute illness specimen collection, based on availability of supplies at each site. The supplies will include the appropriate collection items for the specimen types (e.g., nasal swab), cryovials (labeled with the participant/specimen ID), and interior specimen packing materials, with room temperature transport medium, and packaging materials for shipping the specimen. During summer months, we expect all shipments will have to include a cold pack to avoid extremely high temperatures during shipment. Study staff will track the use of kits and ship replacements to participants as needed.

The study team may designate drop-off locations for kits within their facilities or in accordance with FDA guidance, respiratory specimens may be shipped by participants via express mail to the central reference laboratory. Study and laboratory staff can track shipments via online tracking software available from express mail services.

4.5.2 Serum and Blood Specimens

All participants will contribute 40 mL of whole blood at least three times, including at enrollment, approximate midpoint and end of each study year. They will provide a blood sample at a Sonora Quest Laboratory or other participating lab in the participant's area. In the event of a qualifying illness infection, a convalescent sample will be collected approximately 4 weeks (range 21 and 60 days) after illness onset. If a participant does not develop symptoms, but SARS-CoV-2 is detected in a weekly surveillance specimen, the date of rRT-PCR detection will be used. If the participant has a convalescent blood specimen drawn within the 4 weeks prior to the timing of the planned midpoint or end of year collection times, the planned specimen will not be collected.

Whole blood will be collected and processed by the study site laboratory using CDC guidelines for serum collection. The serum specimen will be divided into aliquots labeled with the same study identification number (Study ID) and specimen ID on all tubes, and an aliquot ID unique to each tube. All specimens will be stored in a -70 degree C or colder freezer and shipped to central study laboratories approved by CDC for serologic testing (Section 5.7.3). All samples will be logged into REDCap using the Blood Sample Collection Forms (Appendices E, N, P and S).

4.6 Laboratory Assessments

4.6.1 Molecular Assays

The CDC-approved, CLIA-approved reference laboratory Marshfield Laboratory will perform a CDC-specified rRT-PCR assay to ascertain infection with SARS-CoV-2. Marshfield will not be engaged in research or have access to participant identifiers. Testing will be completed using CDC protocols and with primers, probes, and reagents provided by the CDC. Additional testing for other common respiratory pathogens including influenza, parainfluenza viruses, human metapneumovirus, adenoviruses and other coronaviruses may also be conducted. Additional virus characterization including measuring of sub-genomic virus RNA (sgRNA) may also be conducted, especially among participants with prolonged viral shedding. Remaining aliquots of all study specimens will be sent to a CDC-designated facility for additional virus characterization (including but not limited to viral isolation, and novel severity markers), banking and storage; no specimens will contain personal identifiers.

4.6.2 Reporting of SARS-CoV-2 rRT-PCR Results

The reference laboratory will provide daily updates to the central data management system and study staff of rRT-PCR results. All participants will be informed of the results.

Molecular diagnostic results will not always be available during the period when participants are acutely ill. Participants will be informed that:

- Results are not meant to replace recommended clinical and/or occupational molecular tests;
- False positive and false negative results are possible;

- Receiving a negative diagnostic result should not alter their preventive behaviors, given that results are specific to the date and time they are collected and current assays may not be sensitive to all infections;
- Participants should consult their personal primary care provider if they have questions, concerns, or any medical needs related to their illness;
- They should follow their employer's guidelines for reporting illnesses and returning to work.

There are potential benefits from reporting results to participants and minimal risks. Because participants are HCP or FR, confirmation of SARS-CoV-2 infection may aid them in making decisions to prevent secondary exposure to family members, co-workers, patients, and/or members of the public.

If participants receive their test results they will be informed that the result is from a research laboratory and is not meant to replace necessary clinical tests, and that false positive and negative results are possible; participants should consult their personal HCP if they have questions, concerns, or any medical needs related to this illness. Further, they should follow their employer's guidelines for reporting illnesses and returning to work.

4.6.2.1 Humoral immunity assays

Serologic work will be conducted by UA. Serum specimens will be tested with CDC-approved serologic assays. Leftover serum will be stored at -20oC or colder for additional testing in the future. A 0.5 ml serum aliquot from participants at enrollment and end of year will be stored for analysis of per- or polyfluoroalkyl substances (PFAS) compounds. Current assays for concentrations of nine PFAS (n-PFOA, Sb-PFOA, n-PFOS, Sm-PFOS, PFHxS, PFDeA, PFNA, Me-PFOSA-AcOH and PFUA) are available and will be conducted by a CDC-designated laboratory. The end of study year samples will be kept for potential future analysis of longitudinal changes in PFAS concentrations.

5. Statistical Considerations

5.1 Statistical Analysis

Nonlinear mixed effects models will be used to describe individual and group mean trajectories in neutralizing antibody titers over time, and the time of the decrease in titer will be estimated by the change points of the fitted trajectories. We will classify and identify subgroups of cases by self-reported severity, healthcare utilization, exposures, and duration of symptoms collected in Activity 4. These models will help elucidate the patterns of serologic immunity over time that can be used to differentiate re-infection from initial infection as well as provide necessary information on timing and efficacy of future vaccine trials.

These studies will include all seropositive patients at baseline, 500 seronegative subjects as controls, as well as all cases of novel disease that occurs in the seronegative population that test positive for by PCR for the virus (primary infection) during follow-up.

A similar workflow will be applied for all subjects that score positive for the first time by PCR for the virus (primary infection), using their post-infection blood samples. These subjects will then be added to the sero-positive cohort for longitudinal follow-up.

6. Data Entry and Management

A study database will be maintained in REDCap on site. Tracking databases with patient identifying information and contact information will be kept securely according to the standard operating procedures of the local site with respect to cybersecurity, privacy, patient confidentiality, and compliance with applicable HIPAA regulations. Any study-related papers with personal identifiers will be stored in a locked cabinet in the research offices.

All survey data will be entered directly into the study REDCap database through the use of online surveys and/or the text messaging interface. Study site staff will enter response data directly into the REDCap database if surveys are administered by telephone or in person interviews. The questions in the approved forms will appear on the REDCap data website rather than in paper form.

All study related documents and samples will contain a unique identifier per person. Data entry screens will provide some quality assurance thorough the use of logic and range checks and automated skip patterns. Additional quality checks of the data will be performed on a weekly basis including checks for out-of-range values and missing data.

Laboratory results will be entered directly into the REDCap study database from the study reference laboratory, including results from rRT-PCR assays and serologic assays. If a reference laboratory is not able to enter data directly, the laboratory will be provided a laboratory results reporting template that will be merged with study data using the Specimen ID.

7. Human Subjects Issues

7.1 IRB Review

Prior to study implementation, the protocol, informed consent form, participant education and recruitment materials, data collection instruments and other documents associated with the protocol shall be approved by the UA institutional review board (IRB), which complies with 45 CFR 46. Subsequently, all protocols must be re-reviewed at least annually. All protocol amendments will be approved by the IRB prior to implementation. The study site is responsible for preparation and submission of all documents and periodic reports as required by the IRBs.

US CDC determined (May 20, 2015) that the information collection activities conducted under this project qualify for the NCVIA-conferred Paperwork Reduction Act (PRA) waiver as they come under the activities authorized under the NCVIA at section 2102 (a)(7) of the Public Health Service Act (42 U.S.C. 300aa-2(a)(7)).

7.2 Informed Consent

Informed consent information will be reviewed by telephone after sending information through postal mail or email to each prospective participant. Virtual consent will follow institutional

best practices. After reviewing this information, participants will provide consent utilizing REDCap. After the consent form is signed, participants will be sent an electronic copy of the consent form for their records.

Study staff will emphasize the voluntary nature of the study, the possible benefits and outcomes, alternatives to participation, confidentiality of participation, and the participant's right to refuse and/or withdraw from the study at any time. It will be explained to participants that discontinuation of participation or choosing not to participate will not affect their professional standing.

7.3 Confidentiality

Each participant will be given a unique study ID which will be used on all study materials and specimens. Multiple forms of contact information, including telephone, email, mailing address and information from close contacts (e.g., spouse or other family members) likely to know how to reach the participant should the study lose contact will be collected.

Only descriptive information included in the contact lists (non-identifiable demographic information and occupation) will be recorded for potential participants who cannot be contacted, are ineligible, or are eligible but refused participation, in order to examine potential participation or selection biases. Stated reasons for refusal will also be recorded.

Participation rates will be monitored by sex, age group, and occupation. If participation rates are significantly lower among a specific subgroup, efforts during the final phases of recruitment will focus on expanding recruitment for these under-represented groups.

All study data, laboratory specimens, reports, study data collection, study procedure, and administrative forms will be identified by a coded number only to maintain participant confidentiality. All study data will be stored separately from study records that contain names or other personal identifiers (such as locator forms and informed consent forms). All databases will be secured with password protected access systems.

Forms, lists, logbooks, appointment books, and any other listings that link Study IDs to other identifying information must be stored in a separate, locked file in an area with limited access. If participant names and corresponding Study IDs are entered into a computer database, this database must be password protected and must be maintained in a directory separate from any study specific data.

7.4 Benefits

Participants will not personally benefit from participating in this study. There are potential benefits for reporting COVID-19 test results to participants. Given the contact of participants with the community, confirmation of COVID-19 illness, when results are available, may aid them in making decisions to prevent secondary exposure to family members, co-workers, patients, and/or members of the public. However, the timeliness of notification of COVID-19

test results to participants will depend on reference lab capacity. Test results may not be available in time to provide guidance relevant to the index illness.

7.5 Remuneration

No remuneration of study participants will be provided.

7.6 Risks

Study investigators are committed to protecting personal health information through the maintenance of privacy and security of each subject's personal information in this study. To protect confidentiality, we will use a study assigned number instead of personal information on study forms and we will store data in locked files and/or secured computers. Any data collected that could identify individual participants will be destroyed per institutional guidelines after study termination. If information from this study is presented publicly or published in a medical journal, individuals will not be identified by name or by any other personally identifiable information.

Participants may experience mild discomfort associated with blood collection and the self-administered nasal swab sample collection. There is some limited risk associated with blood sample collection required for this study.

7.7 Communicable Disease Reporting Requirements

State or local health department regulations may require reporting of incident cases of SARS-CoV-2 infections. Local investigators at each study site will be responsible for contacting their local public health departments to ensure study procedures comply with all reporting requirements.

7.8 Protocol Completion or Termination

Study staff will complete a protocol completion or termination form for each participant at the time the participant either completes all protocol procedures or at the time of termination if early termination occurs (Appendix T: Status Change Form). Deviations will be reported to the UA IRB according to reporting requirements in consultation with CDC.

8. References

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9. Appendices

- Appendix A: Consent Form
- Appendix B: Screening Survey
- Appendix C: Enrollment Survey
- Appendix D: Active Surveillance SOP
- Appendix E: Acute Illness Survey
- Appendix F: Illness Update Survey
- Appendix G: Illness Recovery Survey
- Appendix H: Acute Illness Specimen Collection Form
- Appendix I: Weekly Illness Specimen Collection Form
- Appendix J: S1 Blood Collection Form
- Appendix K: S2 Blood Collection Form
- Appendix O: Follow-up Survey
- Appendix O2: Vaccination Survey