Applied Research to Address the Coronavirus (COVID-19) Emerging Public Health Emergency

Research on the Epidemiology of SARS-CoV-2 in Essential Response Personnel (RECOVER)

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1. Abstract/Executive Summary

Severe acute respiratory syndrome coronavirus (SARS-CoV-2), the virus causing the coronavirus disease 2019 (COVID-19) pandemic was first detected in the United States in January 2020 [1], and by February 2020, the first cases resulting from community transmission were identified [2, 3]. The World Health Organization declared the COVID-19 outbreak a global pandemic on March 11, 2020 [4]. 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.

From February 12–April 9, an estimated 19% cases reported to CDC were among healthcare personnel (HCP) [5, 6]. Essential responders, including HCP, first responders (FR), and other frontline workers (FW) 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, co-workers, and customers as they respond to the pandemic. Because essential responders perform public-facing duties or may work in close proximity of co-workers placing them at a higher risk of being exposed to COVID-19, they are among the priority targets for vaccination, once available and are a high priority for early studies of both the incidence and characterization of SARS-CoV-2 infection and COVID-19 illness.

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. The essential responder 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.

The Research on the Epidemiology of SARS-CoV-2 in Essential Response Personnel (RECOVER) protocol has two primary objectives: 1) To determine the frequency of symptomatic and asymptomatic SARS-CoV-2 infection using both molecular and serologic methods; and 2) to determine the frequency of SARS-CoV-2 reinfections among essential responders who are seropositive to SARS-CoV-2 and/or with documented prior PCR-confirmation of SARS-CoV-2 infection. Secondary objectives include estimating incidence, identifying risk factors for infection and manifestation as symptomatic or asymptomatic, describing symptomology and outcomes of infection and re-infection, medical-attendance, immune response, examining antibody correlates of protection against SARS-CoV-2 re-infection, duration of viral shedding, and assessing knowledge, attitudes and practices (KAPs) related to SARS-CoV-2 and COVID-19. The study was also designed to rapidly implement procedures to evaluate vaccine KAPs and

effectiveness and the immune response to vaccination.

The design is a prospective, longitudinal cohort study of approximately 3,000 essential responders across five sites. Cohort participants will be contacted on a once weekly basis to assess symptoms and contribute self-collected respiratory specimens sent to a central laboratory for real-time RT-PCR (rRT-PCR) testing for SARS-CoV-2. Blood specimens will be collected from participants at least three time points, including a convalescent serum from participants with PCR-confirmed infections. Post-vaccination serum collection and monitoring will be conducted to evaluate vaccine effectiveness and duration of the vaccine-induced immune response.

2. Investigators

2.1 Collaborating Study Sites

Baylor Scott and White Health
Kaiser Permanente Northwest
St. Luke's Hospital
University of Arizona
University of Miami
University of Utah

2.2 Centers for Disease Control and Prevention

Influenza Division, NCIRD
Division of Bacterial Diseases, NCIRD
Division of Healthcare Quality and Promotion, NCEZID

2.3 Abt Associates

Project Director
Study Lead
Project Manager
Data Lead

3. Background

COVID-19 is a recently emergent disease, caused by SARS-COV-2, a betacoronavirus from the SARS family [5]. The disease originated in Wuhan China at the end of 2019 and within 3 months quickly spread to the rest of the world [6]. The World Health Organization declared the COVID-19 outbreak a global pandemic on March 11, 2020 [4, 7]. As of May 10th, the number of confirmed cases worldwide is nearly 4 million, with more than 274,000 deaths [8]; in the U.S. the disease is present in all states with over 1.3 million confirmed cases and nearly 79,000 deaths [9]. 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 [6], although other symptoms, such as loss of taste and smell and rash, have been identified as unique manifestations of infection [10]. The disease presents with varying degrees of severity [11] and a high percentage of infected individuals are thought to be asymptomatic.

Essential responders, including healthcare personnel (HCP) and first responders (FR), and other frontline workers (FW) are at high-risk because they are on the front lines of the COVID-19 pandemic ensuring continuity of healthcare and services to the country. 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 [12]. 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 essential responders at higher risk for severe infections. For example, 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 [13]. 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) [14]. While anecdotal evidence of risk for HCP is persuasive, few research studies in this population have been published so far [15]. A meta-analysis of studies of seasonal influenza estimated that about 1 in 5 HCP are infected with influenza each year [16]. 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 [16, 17] and HCP often work while ill [18-20], which further increases the risk of secondary transmission. Further research is needed as it is critical to ensure the health and safety of our essential 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 [14].

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. The essential responder 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.

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. 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 [16]. 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.

In this protocol, standardized active surveillance screening and testing protocols will systematically identify symptoms of COVID-19 among enrolled cohort members and test specimens with CDC-approved SARS-CoV-2 assays. By enrolling a cohort of essential responders as soon as possible after the identification of a pandemic virus, we will be able to estimate the incidence of laboratory-confirmed SARS-CoV-2 infection and COVID-19 illness. We will collect information to describe clinical features of COVID-19, including severe (i.e., hospitalization and death), less-severe (ambulatory care only) and non-severe (non-medically-attended illness) outcomes. We will further contribute to studies describing full burden of COVID-19, including estimating the proportions of severe and mild illness subsequent to infection, characteristics of illness and individuals that prompt seeking of medical care, and the occurrence and sequelae (if any) of asymptomatic infection. In addition, this protocol will allow for the evaluation of humoral immune responses to SARS-CoV-2 infection and compare across symptomatic and asymptomatic infections, and primary infection vs. reinfection. Optional serology studies will further assess various cellular immune responses with assays conducted on peripheral blood mononuclear cells (PBMCs) harvested at the same time points. Because this cohort will include essential responders 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 SARS-CoV-2 vaccine to prevent laboratory-confirmed SARS-CoV-2 infections, including those infections that result in both mild (i.e., non-medically-attended) and more severe illness. If a pandemic vaccine becomes widely available during the study period, this protocol will aim to measure the VE against SARS-CoV-2 infection and COVID-19 illness.

In summary, the RECOVER protocol will enroll a cohort of essential responders, and prospectively identify participants with symptoms of COVID-19 and assess whether SARS-CoV-2 infection is present.

The protocol will address the identification of asymptomatic and symptomatic primary infections and reinfections. Using observational study designs, the information collected will be used to estimate laboratory-confirmed SARS-CoV-2 incidence. In addition, the timely launch of a cohort study focused on essential responders will provide an opportunity to address other gaps in knowledge, including characterizing the humoral and cellular immune responses to SARS-CoV-2 infection and vaccine once available.

3.1 Abbreviations

AZ	University of Arizona
BSWH	Baylor Scott and White Health
CDC	Centers for Disease Control and Prevention (United States)
CMI	Cell-mediated immune
COVID-19	Coronavirus disease 2019
EMR	Electronic medical record
EMT	Emergency medical technicians
FDA	U.S. Food and Drug Administration
FR	First responders
HCP	Healthcare personnel
HIPAA	Health Insurance Portability and Accountability Act
ICD-10	International Classification of Diseases (version 10)
IRB	Institutional Review Board
KAP	Knowledge, attitudes, and practices
KPNW	Kaiser Permanente Northwest
PBMC	Peripheral blood mononuclear cells
PFAS	Per- and polyfluoroalkyl substances
PRA	Paperwork Reduction Act
QA/QC	Quality Assurance and Quality Control
rRT-PCR	Real time Reverse Transcriptase Polymerase Chain Reaction assay
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
sgRNA	Sub-genomic virus RNA
SL	St. Luke’s Hospital in Duluth, Minnesota
SMS	Short message service
UT	University of Utah and Intermountain Healthcare
VE	Vaccine effectiveness

4. Objectives

4.1 Primary Objectives

This prospective cohort study of essential responders has two primary objectives:

1. Determine the frequency of SARS-CoV-2 virus infection and COVID-19 illness among essential responders using both molecular and serologic diagnostics, specifically:
    a. Symptomatic COVID-19 illness associated with laboratory-confirmed SARS-CoV-2 infection, and
    b. Asymptomatic laboratory-confirmed SARS-CoV-2 infections.
2. Identify and describe SARS-CoV-2 reinfections among essential responders with prior rRT-PCR-confirmed SARS-CoV-2 infection and/or SARS-CoV-2 serum antibody detection.

4.2 Secondary Objectives

This cohort study will also provide data relevant to secondary objectives, including:

1. Assess the incidence of primary symptomatic and asymptomatic laboratory-confirmed SARS-CoV-2 infections by examining observed frequencies within the context of characterized source populations of essential responders.
2. Examine the individual, occupational, and environmental predictors of SARS-CoV-2 infection and of asymptomatic infection versus symptomatic COVID-19 illness.
3. Describe the clinical characteristics and outcomes associated with COVID-19.
    a. Determine the duration and severity of illness and examine the socio-demographic and health characteristics associated with prolonged or severe illness.
    b. Determine the impact of COVID-19 on indicators of functioning, including missed work, ability to complete normal work and home activities, and working while ill.
    c. Determine the proportion of COVID-19 illnesses that are medically attended and examine the factors associated with seeking medical care and treatment.
4. Compare illness characteristics and duration among essential responders with primary vs. re-infection with SARS-CoV-2.
5. Evaluate the kinetics of immune responses to SARS-CoV-2 infection by comparing immune indicators from sera collected before or during illness with those collected after illness.
6. Examine antibody correlates of protection against SARS-CoV-2 re-infection.
7. Examine the duration of viral shedding associated with symptomatic COVID-19 illness.
    a. Examine the inter-individual variability in the magnitude and duration of shedding.
    b. Assess the infectiousness of prolonged virus shedding.
8. Identify essential personnel familiarity with PPE and other infection control measures or facility

policies related to SARS-CoV-2, COVID-19, and pandemic response.

9. Compare molecular diagnosis relying on different respiratory mucosal specimen types (e.g., anterior nasal swabs vs. saliva).
10. Examine the association between serum concentrations of per- and polyfluoroalkyl substances (PFAS) and the manifestation of COVID-19 illness and immune response to SARS-CoV-2 infections including risk of re-infection and COVID-19 vaccine effectiveness.

4.3 Pandemic Vaccine Objectives

11. 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.
12. 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.
13. Examine if VE is modified by socio-demographic characteristics, occupation, health status, or other risk factors.
14. Examine if vaccine modifies illness severity, duration, and infectiousness (or viral shedding) among essential responders with breakthrough infection despite vaccination.
15. 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.
16. Determine the association of serum PFAS concentrations on SARS_CoV-2 infection, COVID-19 illness, and SARS-CoV-2 antibodies.

4.4 Optional Objectives

Study sites may also incorporate other related objectives into the cohort study. These represent optional sub-studies which may require additional data and/or specimen collection. We expect additional optional objectives to arise within the scope of this activity that cannot be fully anticipated within the context of COVID-19 pandemic and local and national public health response. Any such activity that is not detailed within the protocol and consent would require protocol and institutional review supplements and as appropriate separate re-consent for participants for the specific activities. The following activities are optional for participants and require written opt-in consent:

1. Examine the kinetics of immune response to SARS-CoV-2 infection through serial sampling of sera.

2. Examine the kinetics of viral shedding associated with SARS-CoV-2 infection and COVID-19 illness.
3. Examine individual heterogeneity in the use and host response to COVID-19 therapeutics and vaccines.
4. Examine cell-mediated immune responses of B, CD4 and CD8 T-cells to SARS-CoV-2.
5. Estimate the secondary attack rate of SARS-CoV-2 virus infection within a household.
6. Estimate the effectiveness of available vaccines or antiviral prophylaxes and treatments to prevent secondary transmission within the household as they become available.

5. Methods

5.1 Overview of Study Design

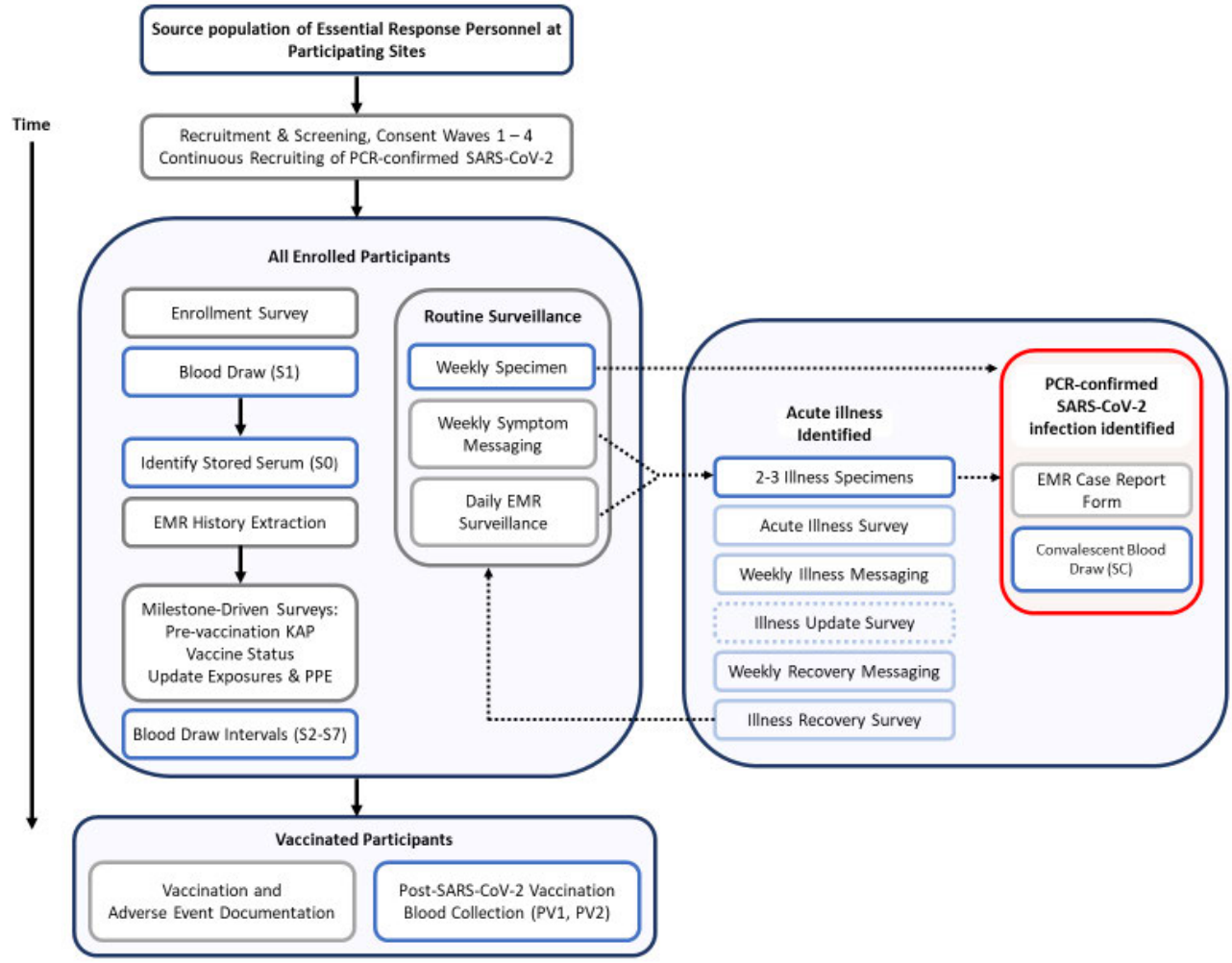
Approximately 3,000 essential response personnel, including HCP, FR, and FW, that have close contact with patients or individuals in the general public as part of their routine occupational duties will be enrolled in a prospective cohort to be followed for up to two years. Essential responders who have prior rRT-PCR-confirmed infection will also be recruited for participation. Information on socio-demographics, occupational responsibilities, exposure to patients or the public, health status, and knowledge and attitudes about SARS-CoV-2 infection control practices will be collected by self-report through an enrollment survey. In some sites with electronic medical record (EMR) availability, information on socio-demographic characteristics, current medical conditions, medical history, medical care utilization, and influenza and pneumococcal vaccination history will be extracted with the participant's permission. Collection of blood specimens will occur at study enrollment and at approximately 3-month intervals to allow for variation in enrollment date for participants. In addition, essential responders who experience an immune-modifying event, including SARS-CoV-2 infection or vaccination, will have blood drawn approximately 21-28-daysafter infection or vaccination.

Active surveillance will be conducted weekly to identify acute illness symptoms via secure SMS text messages. Participants will also be asked to notify study staff if they develop symptoms during the week. Each week regardless of symptoms and when an acute illness is identified, participants will provide a respiratory or mucosal specimen appropriate for diagnosis of SARS-CoV-2 and influenza testing (when influenza is in circulation). When illnesses are identified, participants will describe their symptoms, illness severity, duration, and impact on functioning through resolution of their illness, and in EMR sites, clinical information will be extracted from any medical visits occurring between onset and resolution. Sites may also use employment records to inform absenteeism. For the shipping of self-collected specimens, this study will operate within the guidance of the FDA regarding the use of express mail, facility drop-off, courier services or other methods.

All participants will be asked to complete additional brief surveys according to major pandemic milestones, such as asking KAP and vaccine-intention related questions prior to vaccine availability, obtaining influenza or SARS-CoV-2 vaccine documentation post-vaccination, and updating information on participant health, work responsibilities, and attitudes and practices associated with infection control

and prevention measures at the approximate midpoint and end of each study year. Where possible, EMR extraction will be conducted to update medical condition status and identify medical visits for influenza and SARS-CoV-2 infections. Figure 1 below provides a schematic of the study components.

Figure 1. Schematic of Major Study Components



5.2 Study Population

Cohort members will be recruited in partnership with partner institutions in the United States including health systems, hospital-based facilities and one existing multi-center cohort of FR:

- Baylor Scott and White Health (BSWH),
- Kaiser Permanente Northwest (KPNW),
- St. Luke's Hospital in Duluth, Minnesota (SL),
- University of Utah and Intermountain Healthcare (UT),
- Two participating Fire Fighter Cancer Cohort Study sites:

- University of Arizona in Tucson, Arizona (AZ)
- University of Miami, Miami, Florida (FL).

These health system and hospital-based partners (study sites) have experience recruiting cohorts of HCP and have ready access to both relevant medical care and employment records. Most of these study sites also serve as the 'medical home' to a large proportion of the local community population, and essential responders who receive care from the site institutions will also be recruited. The use of an existing cohort of FR has similar benefits in that the population is well-characterized. The use of these populations has several advantages:

- Individuals will be easier to contact and more likely to agree to participate given the availability of correct contact information and an existing relationship between research partners and potential participants;
- Enrollment of a large number of participants within the same work facility and/or community facilitates estimation of incidence among individuals with similar exposures;
- Recruitment from closed systems such as healthcare facilities opens the opportunity to calculate participation rates and examine potential participation biases related to age, gender, occupation, location, or other basic socio-demographic information;
- Vaccination status for some participants can be documented via a review of their medical and employee (for HCP and some FR and FW) records;

5.3 Eligibility Criteria

Inclusion criteria

- Age ≥18 years;
- Currently working in a healthcare, first responder or other occupation that cannot be done from home or alone;
- Have direct face-to-face contact, defined as being within 3 feet, or about arm's length, with co-workers, patients or the public as part of full-time (≥30 hours/week) job responsibilities;
- In sites with EMR availability, participants with membership in site institution medical plan or ongoing medical encounter data captured consistently 12 months prior to enrollment;
- Plan to remain in the area for the next 12 months;
- For HCP, FR and FW recruited without an institutional medical system, willingness to provide medical history directly through a health-related questionnaire;
- Access to the internet and a phone with text messaging capabilities;
- Willingness to complete weekly symptom assessments via text messaging;
- Willingness to be contacted periodically by study staff via SMS, email, and/or telephone as part of study activities;
- Willingness to self-collect respiratory specimens on a regular basis, and when prompted for study purposes, and to send specimens using approved guidance for drop-off or shipping, once per week for the surveillance period;

- Willingness to self-collect additional respiratory specimen types (approved by FDA for COVID-19 detection) if experiencing a qualifying symptomatic illness or upon rRT-PCR-confirmation of an asymptomatic infection;
- Willingness to provide blood samples at 3 planned time points per year during the study period, and in the event of an infection, a convalescent sample approximately 4 weeks after illness onset or rRT-PCR detection.

Exclusion criteria

- Participation in a clinical trial of investigational or receipt of approved prevention therapies for SARS-CoV-2 infections, such as prophylactic antiviral medications, vaccination, or other immune system modifying interventions in the past 3 months;
- Work less than an average of 30 hours per week;
- Unwilling to provide verbal and/or electronic confirmation of consent;
- The individual has previously requested that s/he not be contacted regarding research studies;
- Unwilling to self-report occupation, work responsibilities, and prior COVID-19 illness.

5.4 Recruitment

Recruitment and attrition prevention activities will occur at local study sites. Because the study objectives focus on essential responders with a variety of socio-demographic characteristics and occupational responsibilities, this study will employ a phased, stratified recruitment approach to ensure there is sufficient variability in sex, age and occupational categories within the cohort. This approach will open the opportunity to examine risks associated with heterogeneity in socio-demographic characteristics and improve the ability to compare and collapse data across study sites if necessary. This systematic approach is also intended to minimize convenience sampling, which can introduce known and unknown biases.

Sites may use a combination of methods to recruit essential responders, including engagement of previously established cohorts that have consented to be contacted for future studies, such as the BSWH and KPNW participants in the 2018-19 and 2019-20 studies titled “Immunogenicity of egg-based, cell culture-based and recombinant antigen Influenza Vaccines in Healthcare Workers” and volunteers for participation in the protocol “Effectiveness of influenza vaccines in preventing pandemic influenza virus infection among healthcare personnel, first responders, and school personnel”. Participants may be recruited from previously established cohorts including the AZ and Florida (through a collaboration with the University of Miami) cohort study titled “Fire Fighter Cancer Cohort Study.”

5.4.1 Identify Potential Participants

Prior to the start of recruitment, study sites will need to produce a list of all potential participants for internal site-specific use to define the population denominator from which the cohort will be recruited

and in later stages of the study to inform estimates of incidence in the context of this source population. This list should include the following information:

- Age group
- Sex
- Occupation category

This list will be cross-tabulated by age group (18-39 years and 40-64 years), sex, and dichotomous occupational category as defined below:

- HCP
  - Primary HCP: physicians, physician's assistants, nurse practitioners, and dentists
  - Support HCP: medical personnel not included in primary, such as assistants, technicians, registered nurses, nursing assistants, occupational therapists, pharmacists, and non-clinical personnel, including but not limited to social workers, reception, etc.
- FR
  - Care or public contact response roles: Emergency Medical Technicians (EMT), fire fighters, law enforcement, security guards or other responders to emergency situations
- FW
  - Frontline workers not in the HCP or FR occupations performing work that cannot be performed at home or without contact with other coworkers or the public, such as grocery store clerks, food services, certain agricultural and manufacturing occupations, hospitality, transportation and construction workers, and school teachers.

Sites should focus recruitment efforts and phases to achieve a minimum number of participants in each occupational category by age and sex to ensure representation of each group. An overall goal of at least 20 participants in each of the major categories is illustrated by Table 1: Illustration of Recruitment Goals by Strata. Aggregate counts of potential enrollees will be recorded in a recruitment log (Appendix A: Recruitment and Screening Log) to track invitations, acceptance and refusal counts.

Table 1. Illustration of Recruitment Goals by Strata

	Female		Male	
	Ages 18-39	Ages 40+	Ages 18-39	Ages 40+
Primary HCP	≥20	≥20	≥20	≥20
Support HCP	≥20	≥20	≥20	≥20
First Responders	≥20	≥20	≥20	≥20
Frontline Workers	≥20	≥20	≥20	≥20

5.4.2 Recruitment Methods

Study sites will employ a multi-phase recruitment approach for initial recruitment to concentrate early efforts on priority groups. Recruitment will be via direct mailings and/or emails and through each site's web sites. See Local Context document for site-specific approaches.

- **Wave 1 Recruitment:**
  - HCP/FR with current or prior rRT-PCR-confirmed SARS-CoV-2 infection;
  - Participants with an available baseline sera sample collected as a part of other research efforts;
  - HCP/FR in difficult-to-fill recruitment strata as listed in Table 1 to meet but not exceed 20 participants per cell.
- **Wave 2 Recruitment:**
  - All other HCP/FR to reach minimum targets in each recruitment strata as listed in Table 1.
- **Wave 3 Recruitment:**
  - All FW to reach minimum targets in each recruitment strata.
- **Wave 4 Recruitment:**
  - Expansion of EMR sites to recruit participants outside of the medical health system. Initiation of wave 4 contingent upon discussion and approval by Abt and CDC investigators.

Study sites will aim to enroll as many participants as possible under each wave. Throughout the duration of the data collection period, sites will also aim to recruit an additional convenience sample of essential responders with rRT-PCR-confirmed SARS-CoV-2 infection who were not previously recruited under Waves 1-3.

- **Ongoing Recruitment:**
  - Participants who voluntarily withdraw from the study will be replaced by a newly recruited participant until mid-study blood collection in the second year of the study is completed.
  - Essential responders with current or prior rRT-PCR-confirmed SARS-CoV-2 infection at any point in the data collection period.

Each site will aim to enroll a total of ≥50 participants with documented, rRT-PCR-confirmed SARS-CoV-2 infection prior to enrollment (enrolled through Waves 1-4 or ongoing recruitment efforts).

5.4.3 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.

5.4.4 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 send the materials to them by email to review. Virtual consent process will vary depending on study site requirements. The consent form (Appendix C: Consent Form) will be reviewed with the potential participant by phone/video visit or at the first study visit (i.e., blood draw) where study staff will document that the participant has read and understood the consent and HIPAA authorization, that they have had all of their questions/concerns about the study answered, and that they have verbally consented to participate in the study. Participants can provide verbal consent in person or by telephone, video conference, or written/electronic signature consent in person or by email or using an online electronic interface. Next, participants will be sent an electronic copy of the consent form and the link to begin the online enrollment survey.

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. Upon complete review of these materials, documentation of participant consent will be written, electronic, or verbal. 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 mid-turbinate nasal swabs and saliva samples, as appropriate for SARS-CoV-2 detection in accordance with FDA guidance and approval.
- Blood (serum) samples drawn at the following times:
    - At enrollment and approximately every 3 months
    - In the event of an infection, a convalescent sample approximately 4 weeks after illness onset or rRT-PCR detection,
    - If participants receive SARS-CoV-2 vaccine, an additional sample drawn approximately two to four weeks after receipt of each vaccine dose;
- Permission for review of immunization and medical records (as available in EMR sites)

Potential participants who participated in a prior research study at their respective site will have additional language in the consent form specifying consent for study staff to access records and stored sera samples from the prior study in addition to the activities detailed in the general consent form for the main study. This may apply to participants recruited from BSWH and KPNW for the 2018-19 and 2019-20 studies titled "Immunogenicity of egg-based, cell culture-based and recombinant antigen Influenza Vaccines in Healthcare Workers" and the AZ and Florida cohort study titled "Fire Fighter Cancer Cohort Study."

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 optional sub-studies (see Section 9).

5.5 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 in-person interview should participants be unable or become unwilling to access them online. In-person contacts will occur as needed to train participants for respiratory self-swab or mucosal (saliva) specimen collection procedures and for the collection of blood by trained study staff or phlebotomy stations affiliated with the study site. Additional data collection of demographic characteristics, medical history, medical utilization, clinical SARS-CoV-2 and influenza lab testing results and vaccination history will be accessed from medical records with the participant's consent.

5.5.1 Enrollment Activities

5.5.1.1 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;

5.5.1.2 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, based on availability of supplies at each site. Participants will be provided with written and/or visual detailed 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.

5.5.1.3 Enrollment Serum Collection

Participants will be asked to provide a 20ml 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. Depending on availability of resources and restrictions on research personnel at each site, participants may be referred to go directly to phlebotomy stations that are prepared to manage research specimens. Information on each blood sample collection will be documented using the Blood Sample Collection Form (Appendix E: S1 Blood Collection Form).

5.5.2 Medical Records

Among sites with EMR data available, permission will be requested from participants to access medical records. With permission, data will be extracted to supplement self-reported information on health status, influenza and pneumococcal vaccination status and history, and medical care utilization (Appendix F: EMR Extraction Form). Past season influenza vaccination data will include for as many records as are available in the EMR.

Data from the EMR will be extracted to count medical visits for acute illness and chronic medical conditions for the 12 months prior to enrollment and through the end of the study year using (a) International Statistical Classification of Diseases and Related Health Problems (ICD-10) codes for all ambulatory medical encounters, (b) ICD discharge codes for all hospital admissions. Chronic medical conditions will be assessed by self-report for sites without access.

Additionally, for participants with rRT-PCR-confirmed SARS-CoV-2 or influenza infection, all EMR sites will provide information from medical encounters between the date of onset through illness resolution (Appendix G: PCR Positive Encounter Abstraction), including dates of visits, ICD code diagnoses, clinical diagnostic testing for respiratory pathogens (and results of testing if feasible), CPT codes for chest and sinus radiography, ICU admission, and ventilator support. Further information on therapeutic interventions will be extracted, including but not limited to, antivirals, antibiotics, steroids, and other COVID-related therapeutics.

5.5.3 Employee Records

As an optional data collection element, sites may use employee records to supplement self-reported and medical record information on vaccination status and history and employment history. Additionally, for participants with SARS-CoV-2 or influenza detection, sites may document the number of completed workdays and the number of days with an absence associated with illness between the date of onset or detection through illness resolution (Appendix G: PCR Positive Encounter Abstraction).

5.5.4 Active Surveillance for Acute Illness

Active surveillance for acute illness will be conducted throughout the study period in all sites. 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 a text message platform. All text messaging scripts, including for weekly surveillance, specimen collection, and illness assessments, are outlined in Appendix H: Surveillance Messaging Scripts. Site-specific procedures for capturing responses to the weekly surveillance will include SMS response, a link to a response-specific online survey, or in special circumstances, an email

or phone call may be used as well. 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
- Chills
- Cough
- Shortness of breath
- Sore throat
- Diarrhea
- Muscle or body aches
- Change in smell or taste

An acute illness can be identified by responding/selecting "Y" to the weekly text message or by contacting study staff through site-specific procedures as detailed in each site's local context document. At EMR sites, acute illnesses can also be identified by automated reports generated daily that identify a participant had a medical visit for an acute illness. If a participant reports they are not ill, they will be asked 1-4 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 the 2-3 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 messaging 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 (as 0-100%) via text message. Participants will also be prompted to complete the Appendix M: Illness Recovery Survey via web-survey to assess symptoms and additional illness information. Until a participant reports ≥90% recovery progress, the weekly surveillance messaging will continue to ask about recovery progress.

Once a participant reports ≥90% recovery, the weekly messaging will return to the standard questions.

5.5.5 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.

5.5.5.1 Immunization Information Systems

Each site will query their medical record system, the state immunization information system (IIS) or registry, or other vaccine providers to obtain COVID-19, influenza, and pneumococcal vaccination status or history. Administration of COVID vaccines must be documented by public health jurisdictions within 24 hours of administration [21]. Each site will work with IIS personnel to determine the appropriate procedures to document pandemic SARS-CoV-2 vaccination receipt. Monitoring for participant COVID vaccinations should occur daily, if possible.

5.5.5.2 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 in their region (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, if documentation is not available to the site, 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.

Influenza vaccination status (Appendix O1: Influenza Vaccination Update Survey) will be assessed by self-report (including type of vaccine, location, and date of vaccination) on up to 3 occasions starting approximately two months after seasonal influenza vaccine becomes available.

5.5.6 Follow-up Surveys

Brief surveys will be administered over the course of the study for three purposes. First, surveys will allow participants to update information on their occupation and work responsibilities, health status, potential exposures to COVID-19 at work, home, and in the community, and their use of PPE in these settings. Second, surveys will allow participants to report if they were unable to report a qualifying illness and/or submit illness specimens for any reason, and to provide an estimate of when this missed illness event occurred so that their surveillance record can be updated accordingly. Third, surveys will assess participants KAP regarding COVID-19 vaccines, intention to be vaccinated, and then after vaccination, to recall their overall health status on the days following each dose.

- Follow-up Survey 1 (Appendix O: Mid-Year Survey) will ascertain participants' KAP regarding

SARS-CoV-2 vaccine and vaccine intention and supplement the influenza vaccination survey.

- Follow-up Survey 2 (Appendix R: April 2021 Survey) will provide a final opportunity to ascertain influenza vaccination status for the season, supplement the SARS-CoV-2 vaccination survey, and inquire about any illnesses missed during surveillance. This survey will also assess any adverse events following immunization (AEFI) with the SARS-CoV-2 vaccine if vaccinated, or repeated KAP questions as relevant among unvaccinated essential responders.
- Additional follow-up surveys will be administered approximately every 3 months on a rolling basis following Survey 2.

A summary of all interim survey instruments and approximate timing are outlined in the following table:

Instrument	Appendix	Title	Purpose	Timing
Vaccination Survey 1	O1	Influenza Vaccination Update Survey	Self-reported documentation of influenza vaccine receipt	Monthly from November 2020 through January 2021
Vaccination Survey 2	TBD	SARS-CoV-2 Vaccination Update Survey	Self-reported documentation of SARS-CoV-2 receipt and adverse events following immunization (AEFI) survey, or vaccine intent KAP update if unvaccinated	Monthly from vaccine availability (approximately February 2021 through end of study period)
Follow-up Survey 1	O	Mid-Year Survey	Pre-SARS-CoV-2 vaccine intent, KAP, update occupation, exposures, and PPE use	December 2020 (at earliest)
Follow-up Survey2Survey 2Survey2	R	April 2021 Survey	Update occupation, exposures, and PPE use	April 2021
Additional Follow-up Surveys	TBD	Month/Year Survey	Participant Information Update	July 2021, Oct 2021, January 2022, April 2022

5.6 Specimen Collection

5.6.1 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 site teams, Abt, 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 detailed written and/or visual instructions for self-collection of a respiratory specimen. At the start of surveillance, participants will be given a "self-collection kit" that includes written and/or visual 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.

Sites may designate drop-off locations for kits within their facilities, or if permitted 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.

5.6.2 Serum and Blood Specimens

All participants will contribute 20 mL of whole blood at least three times, including at enrollment as described in Section 5.5.1.3, and approximately every 3 months (11-13 week range) for the duration of the study. The timing of each blood collection may be "re-set" by an immune-modifying event, including SARS-CoV-2 infection. In the event of a SARS-CoV-2 or influenza infection, a 20 mL 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 participants receive SARS-CoV-2 vaccine, a post-vaccination 20 mL sample

will be collected approximately two to four weeks after receipt of each vaccine dose, depending on the recommended vaccine regimen for each product. Participants with one of these events will have the subsequent planned collection time shifted to be approximately 3 months after the most recent sample collection. This individual trajectory for blood collection will ensure that collections do not occur unnecessarily close and burdensome for participants.

If the participant is enrolled as part of the convenience sample of HCP or FR with rRT-PCR-confirmed SARS-CoV-2 infection (was not previously recruited under Waves 1 and 2), residual clinical serum collected pre-enrollment, if available, will be obtained with the permission of the participant.

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 -20 degree C or colder freezer and shipped to the central study CDC laboratory for ELISA serologic testing or to CDC-designated laboratories for additional testing (Section 5.7.3). All samples will be logged into REDCap using the Blood Sample Collection Forms (Appendices E, N, P and S).

5.7 Laboratory Assessments

5.7.1 Molecular Assays

The CDC-approved, CLIA-approved reference laboratory will perform a CDC-specified rRT-PCR assay to ascertain infection with SARS-CoV-2. 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.

5.7.2 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. The lab processing participant samples is a CLIA approved CDC-reviewed lab that is applying EUA methods and standard best practices for lab QA/QC to minimize the possibility of reporting false positive results. QA/QC checks are built-in to the process and will not impact the timing of the lab's reporting results to the study sites. All participants will be informed of the results in accordance with site-specific policies as detailed in the Local Context Form. In most instances results will be available in less than 48 hours from sample collection. However, some results may take as long as a week depending on time shipping time, lab volume, etc.

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;
- If we are made aware of a false positive after notifying a participant of their results, we will notify them immediately, as well as any persons/institutions/agencies with whom the positive results were shared;
- 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 essential responders, 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.

5.7.3 Humoral immunity assays

Serologic work will be conducted by the CDC laboratory or a CDC-specified reference laboratory and reported to the CDC investigators who in turn will combine these data with the site data sets to be shared with all investigators. Serum specimens will be tested with CDC-approved serologic assays. Leftover serum will be stored at -20^{o}C or colder for additional testing in the future.

A 0.5 ml serum aliquot from participants at enrollment, post COVID-19 vaccination 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 and post-COVID-19 vaccination samples will be kept for potential future analysis of longitudinal changes in PFAS concentrations and evaluation of the effect of PFAS compounds on COVID-19 vaccine effectiveness including measures of SARS-CoV-2 antibodies and other serological measures assayed.

6. Statistical Considerations

6.1 Sample size

6.1.1 Outcomes and surveillance groups

There are several outcomes of interest. Descriptive analyses will be completed to characterize symptomatic and asymptomatic SARS-CoV-2 infections and re-infections as confirmed by molecular and/or serologic diagnostics.

6.1.2 Power calculations for incidence objective at each network site

The full cohort provides the sample needs for the SARS-CoV-2 detection objectives for all outcomes except for incidence estimation, which will exclude sites unable to establish the source population.

We determined the minimum study size using the cumulative incidence within the cohort to be 400 at each site. Table 2 presents the half-width of a 95% confidence interval centered at various cumulative incidences and at various study sizes. If the cumulative incidence is *p* and the study size is *n,* then we use a normal distribution with mean *pn* and variance *pn* to compute the half-widths in Table 2.

Smaller cumulative incidence estimates are expected for final categories of symptomatic by asymptomatic outcomes using both molecular and serologic diagnosis.

6.1.3 Incidence among naive at each network site

We expect the cumulative incidence of symptomatic rRT-PCR-positive infection to be 10% among those with no documented rRT-PCR-confirmed SARS-CoV-2 before enrollment. To achieve minimal sufficient precision around our estimate of cumulative incidence, we need a study size of at least 250 enrolled per study site.

Table 2: The half-width of a 95% confidence interval for combinations of cumulative incidence and study size.

Cumulative Incidence	Study Size											
	50	100	200	250	300	350	400	450	500	550	600	2000
1%	2.77	1.96	1.39	1.24	1.13	1.05	0.98	0.92	0.88	0.84	0.80	0.44
5%	6.20	4.38	3.10	2.77	2.53	2.34	2.19	2.07	1.96	1.87	1.79	0.98
10%	8.77	6.20	4.38	3.92	3.58	3.31	3.10	2.92	2.77	2.64	2.53	1.39
15%	10.74	7.59	5.37	4.80	4.38	4.06	3.80	3.58	3.39	3.24	3.10	1.70
20%	12.40	8.77	6.20	5.54	5.06	4.69	4.38	4.13	3.92	3.74	3.58	1.96
40%	17.53	12.40	8.77	7.84	7.16	6.63	6.20	5.84	5.54	5.29	5.06	2.77
80%	24.79	17.53	12.40	11.09	10.12	9.37	8.77	8.26	7.84	7.48	7.16	3.92

6.1.4 Incidence estimates of symptomatic and asymptomatic outcomes across network sites

Study objectives focused on looking at both symptomatic and asymptomatic infections as determined by molecular and serologic outcomes will likely require examining observations across study sites. Similar

to previous studies of this kind, the cumulative outcomes of participants could be divided into six mutually exclusive categories; as listed here with one possible distribution of outcomes:

- Symptomatic
    - rRT-PCR-positive 4%
    - Serology-only 4%
- Asymptomatic
    - rRT-PCR-positive 8%
    - Serology-only 8%
- Other
    - Indeterminate 12%
    - Not infected 64%

To statistically power at 80% power (alpha = .05) to detect a true percentage of 4% would require a sample of 853. Power is higher for more common outcomes and combinations. Given a common protocol, surveillance, and laboratory methods across study sites, this may be achievable considering observations across two or more sites. Certainly, the expected cumulative incidence of re-infection will be much lower, and the study is unlikely to be powered to precisely estimate re-infections; nonetheless, describing the frequency of these events within our network will inform hypothesis-generation and future study planning regarding the potential for SARS-CoV-2 re-infection.

6.1.5 Power calculations for VE Objective

In a prospective cohort design, the statistical precision of an estimate of VE depends on the amount of observed person-time at-risk for infection in both the vaccinated and unvaccinated groups, the SARS-CoV-2 incidence rate (the 'background' rate of infection), and the true underlying effect (vaccine effectiveness) size. Vaccine will not be readily available at the start of the study but will be distributed to the cohort gradually. Subjects may change their vaccination status (i.e., vaccinated during follow-up) from unvaccinated to vaccinated, and contribute both unvaccinated and vaccinated person-time at risk. Thus, vaccination status is time-varying. Calculating statistical power with closed-form expression when exposure is time-varying is challenging. Instead, Monte Carlo simulation will be used to estimate the statistical power to detect a vaccine effectiveness of interest. Given the vaccine coverage, SARS-CoV-2 incidence rate, and underlying effect size, survival time will be generated from the equation proposed by Austin PC[22] and a frailty/marginal model will be fitted to estimate vaccine effectiveness. Based on the simulations, the sampling distribution will be constructed, and power can be calculated by the percent of vaccine effectiveness that does not exceed the null value.

6.2 Statistical Analysis

6.2.1 Primary Objectives

The frequency of infection among essential responders will be measured using the cumulative incidence, the proportion of new cases among those enrolled in the study with no evidence of previous infection. Point estimates of cumulative incidence and exact 95% confidence intervals will be presented for both symptomatic COVID-19 illness with laboratory confirmed SARS-CoV-2 infections and asymptomatic laboratory confirmed SARS-CoV-2 infections. Similarly, the frequency of reinfection among essential responders with evidence of infection before enrolling in the study will be measured using the cumulative incidence and presented with point estimates and exact 95% confidence intervals.

6.2.2 Secondary Objectives

To assess the cumulative incidence of primary laboratory-confirmed SARS-CoV-2 infections in the source population, the study's complex survey design was taken into account. The study design incorporated a stratified random sampling approach where random samples were obtained from mutually exclusive strata within the source population (stratified by site, sex, age, and occupation). In order to produce an unbiased cumulative incidence of all essential responders at the study hospitals, survey sample weights that reflect the proportion of the population in each stratum will be applied to each participant's data and the Taylor series approximation method will be used to compute variance estimates.

A mixed-effects Cox proportional hazards model, also known as a frailty model, will be used to examine the predictors of infection. Time to infection will be regressed on study site, individual level predictors, occupational level predictors, and environmental level predictors. Study site will be incorporated as a random effect. Factors in the final model will include those associated with the outcome at a significance level of $p<0.10$. Results will be summarized with hazards ratios and 95% confidence intervals.

Summary statistics of clinical characteristics and outcomes among cases of COVID-19 will be tabulated, as proportions or means, and presented with 95% confidence intervals. To examine associations with prolonged illness, Kaplan-Meier curves of time to recovery among COVID-19 cases by study site, by socio-demographics, and by health characteristics will be compared using the log rank test. Bivariate analysis of severity of illness with socio-demographic and health characteristics will be presented in tabular format with proportions and 95% confidence intervals. The hypothesis of no association between the severity of illness with these factors will be tested using Fisher's exact test or Pearson's chi-squared test.

The impact of COVID-19 on indicators of functioning, such as whether missed work, among COVID-19 cases will be tabulated, as proportions or means, and presented with 95% confidence intervals. The proportion of COVID-19 illness that were medically attended will be presented with an exact 95% confidence interval. Bivariate analysis of seeking medical care and treatment with other factors will be presented in a tabular format with proportions and 95% confidence intervals. The hypothesis of no association between seeking medical care and treatment with these factors will be tested using Fisher's exact test or Pearson's chi-squared test.

To compare illness characteristics and duration among essential responders with primary versus re-infection with SARS-CoV-2, a mixed-effects logistic regression model will be used with bivariate outcome being primary infection and re-infection. Site will be incorporated as a random effect. Covariates of

interest will include individual level predictors, occupational level predictors, and environmental predictors.

6.2.3 Vaccine and VE Objectives

COVID-19 VE will be estimated using Cox regression; calculated as:

$$VE = (1- HR)*100$$

Our primary analysis will consider all participants across occupation groups, since all participants have increased occupational exposure. If vaccine is not available to certain occupation groups within study communities, these participants can be removed from eligible person time accordingly.

The effect of the following covariates on VE estimates will be considered for all outcomes: site, socio-demographic characteristics, occupational exposure, and underlying health status. VE will be calculated by age group, full vs. partial vaccination, and vaccine type if multiple products are in use.

If any statistical method is found to be unsuitable during analysis due to unexpected recruitment or seasonal effects (e.g., inadequate sample size, low participation in surveillance), alternate methods will be used. Any changes in methodology will be documented.

7. Data Entry and Management

Each participating study site will maintain study databases 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. Signed informed consent forms and 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, the text messaging interface, and/or the mobile application. 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. The online, mobile application, text message, and REDCap 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 or through the study coordinating center, 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 by Abt Associates using the Specimen ID. Sites will have access to site-specific data only.

Upon execution of an appropriate data use agreement (DUA), data extracted from the electronic medical record will be loaded into the REDCap database following the specifications of the study

codebook and data dictionary.

8. Human Subjects Issues

8.1 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 institutional review board (IRB) overseeing each site's study activities. Subsequently, all protocols must be re-reviewed at least annually. All protocol amendments must be approved by the IRB prior to implementation. The study sites and coordinating center are responsible for preparation and submission of all documents and periodic reports as required by their respective local 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).

IRB of Record	**Relying Sites**
Baylor Scott and White Health	Baylor Scott and White Health
Kaiser Permanente Northwest	Kaiser Permanente Northwest, Abt Associates, CDC
St. Luke's Hospital IRB	St. Luke's Hospital
University of Miami	University of Arizona, University of Miami
University of Utah	University of Utah

8.2 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, but will only be accessible by local study staff.

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 local databases must 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 access limited to local study staff. 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.

8.3 Benefits

Essential responders 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 essential responders 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.

8.4 Remuneration

Sites may determine the remuneration of study participants as small gifts or incentives to compensate for the time and effort involved in this study. Payments to reimburse participants for the costs of text messaging, cellular data usage, and phone calls is recommended. Further payments for compliance and milestones are recommended based on what is customary for that site, such as per respiratory sample per week during the surveillance period, per blood sample, and at the completion of milestone surveys. Sites may choose not to provide reimbursements for participation.

8.5 Risks

Study investigators and institutions 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 when the study is done. 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. The researchers in this study will be looking at personal health information but will not disclose personally identifying information about individual participants to others.

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.

Participants are at some risk regarding the confidentiality of their medical records. However, as noted above, no personal medical record information will be stored with any participant identifying information. Study staff responsible for collecting medical record information are all employees or contract workers of the local organization, which is providing healthcare to the participants.

Participants may be required to notify their employer if they test positive for SARS-CoV-2 and may be required to stay home from work as a result. Study sites will follow local policies for employer notification as outlined in the local context form.

8.6 Communicable Disease Reporting Requirements

State or local health department regulations may require reporting of results from SARS-CoV-2 testing. 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.

8.7 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**). Sites will report deviations to their local IRBs according to site-specific reporting requirements and consult with Abt and CDC to adjudicate.

9. Optional Sub-Studies

9.1 Serial Serology Sub-Study

Background: The virus SARS CoV-2 is understood to be transmitted from person-to-person by respiratory droplets. Infection is defined as a positive test by rRT-PCR confirming the presence of viral genetic material from an accepted source. Non-respiratory symptoms have been described in association with COVID including discoloration in the fingers or toes, GI symptoms, or neurologic symptoms, though it is not clear if seroconversion can take place after a non-respiratory syndrome, or in the absence of a positive nares swab. Serologic conversion (the development of antibodies) is believed to take place within 1-3 weeks after diagnosis of infection, however there is evidence of variability and it is not clear if everyone with a positive nares swab goes on to develop detectable antibody levels. Finally, the durability of seropositivity is not known. The objectives of this sub-study would be to:

1) Determine time to seroconversion from the time of a positive nares swab, in 14-day increments.
2) Determine whether enrollees can seroconvert without a positive nares swab, and if alternative illness syndromes can precipitate seroconversion with or without a positive nares swab.
3) Define the duration of seropositivity in those who seroconvert, in 14-day increments.

Methods: The RECOVER trial will enroll essential responders and collect nares swabs weekly for the duration of the study with serology performed at the beginning, middle, and end of the study year. This

sub-study would offer increased frequency of serologic testing for the duration of the study, without duplicating serology performed as a part of the RECOVER trial. For serology specimens collected for this sub-study, 7 mL of blood will be collected to produce at least 0.5 mL of serum to be sent to the centralized lab at the CDC for antibody testing or a CDC-designated laboratory.

Enrollees who agree to participate in this sub-study will be asked to complete serology testing every 4 weeks unless they either 1) have a positive COVID-19 nares swab or 2) seroconvert with or without a positive nares swab. When either of those events happens, they will be asked to have serology performed 1 week after the positive swab was obtained or the serology was collected, and every 2 weeks after that for the remainder of the study. If they do not have a positive nares swab or blood test, blood testing will continue every 4 weeks for the duration of the study. If a blood test is performed less than 2 or 4 weeks, respectively, before the scheduled blood test for the main study, the 2 or 4 week increments will resume 2 or 4 weeks after the blood test for the main study.

Objective 1: The RECOVER trial will test serology at the beginning, middle, and end of the study year, allowing us to determine approximately the percent of people with a positive nares swab who will go on to seroconvert, however it does not provide information on how long it takes to do so. If seropositivity is found to be protective against future infection, information regarding the time it takes to seroconvert may be important to guide population recommendations.

Objective 2: At present, the gold standard for diagnosing infection is a positive nares swab. It is not known if seroconversion can be achieved in the absence of a positive nares swab. The RECOVER trial would broadly consider that question by performing serology before, during, and after the trial. However, by surveying serology routinely alternative illness manifestations could be defined (rash, GI illness, headache or neurologic symptoms) with or without respiratory symptoms or positive nares swabs, to establish whether clinically significant non-respiratory COVID-19 syndromes exist, and if seroconversion can take place in the absence of all symptoms with or without positive swabs.

Objective 3: The durability of seropositivity is unknown and could be clinically meaningful if it is protective. By monitoring routinely, we can define not only the time to seroconversion, but the durability of seroconversion within 14-day increments. The RECOVER study will identify serostatus at the beginning, middle, and end of the study year (and possibly one additional time point if there is a confirmed infection after the middle time point). However, if seropositivity doesn't persist through the conclusion of the study, it will be valuable to determine how long it lasted, and what factors played a role in the duration of seropositivity. This may become a point of particular interest if an effective vaccine is developed.

9.2 Serial sampling to assess viral shedding and infectivity

Background: The duration and infectivity of SARS-CoV-2 is not well understood.

Methods: Among essential responders with rRT-PCR-confirmed SARS-CoV-2 infection detected through surveillance within 4 days of illness onset, study staff will ask participants to provide a self-collected respiratory or mucosal sample (as defined in section 5.6.1) every day. This activity will require additional informed consent documented on the main consent form and is offered only to the small subset of

participants who will qualify. The daily samples will be sent to the reference laboratory for rRT-PCR and advanced virology testing (such as sgRNA) necessary to complement rRT-PCR findings. Participants will be asked to continue daily collection until 3 consecutive samples test negative or the participant has reached 28 days post symptom onset.

Objective 1: Describe the viral shedding kinetics following SARS-CoV-2 infection and compare the sociodemographic, health, and occupation characteristics of those with versus without prolonged shedding.

9.3 PBMC/plasma/sera and nasal swab collection to assess cell-mediated immune responses

Background: More information is needed on the cell mediated immune (CMI) response to SARS-CoV-2 infection. Among the knowledge gaps are the extent to which the magnitude and quality of humoral immune response to infection is associated with the breadth of CMI response and the extent to which both humoral and CMI are associated with the duration and severity of COVID-19 illness.

Objective: Examine CMI responses of B, CD4 and CD8 T-cells to SARS-CoV-2, nasal microbiome/virome diversity/composition, and metabolome.

Methods: Enrollees will be invited to contribute additional blood and self-collect a dry mid-turbinate nasal swab (1) at enrollment, and (2) about 28 days following PCR-confirmed SARS-CoV-2 infection or COVID-19 vaccination. This additional 30mL of blood at each collection will be processed to provide supplemental serum and extract PBMCs for use in CMI assays at a CDC-designated laboratory. Nasal swabs collected will be subjected to metagenomic characterization of microbiome and/or virome associated pre- and post-SARS-CoV-2 infection. A detailed description of participant inclusion criteria and sub-study methods is provided for participating sites in Appendix Y: CMI Assessment Sub-Study Protocol.

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11. Appendices

- Appendix A: Recruitment Screening Log
- Appendix B: Screening Survey
- Appendix B1: Contact and Scheduling Form
- Appendix C: Consent Form
- Appendix D: Enrollment Survey
- Appendix D1: Active Surveillance Set Up Form
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- Appendix E: S1 Blood Collection Form
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- Appendix H3: Specimen Reminder Message
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- Appendix L: Illness Update Survey
- Appendix M: Illness Recovery Survey
- Appendix N: S2 Convalescent Blood Collection Form
- Appendix O: Mid-Year Survey (Follow-Up 1 Survey)
- Appendix O1: Influenza Vaccination Update Survey
- Appendix O2: SARS-CoV-2 Vaccination Update Survey
- Appendix P: S2 Mid-Study Blood Collection Form
- Appendix Q: EMR Surveillance Form
- Appendix R: Follow-Up 2 (April 2021) Survey
- Appendix S: S3 Blood Collection Form
- Appendix T: Status Change Form
- Appendix V: Positive Test Result Outside of Study
- Appendix W: Vaccine Verification Form
- Appendix X: Protocol Deviation Log

- Appendix Y: CMI Assessment Sub-Study Protocol
- Appendix Y1: PBMC Blood Collection and Processing Form
- Appendix Z: Documentation of HCP Vaccine Trial (VIT) Participation