SARS-CoV-2 Infection in Healthcare Personnel and Their Household Contacts at a Tertiary Academic Medical Center: Protocol for a Longitudinal Cohort Study

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Abstract

Background: Healthcare personnel are at high risk for exposure to the SARS-CoV-2 virus. While personal protective equipment may mitigate this risk, prospective data collection on its use and other risk factors for seroconversion in this population is needed.

Objective: The primary objectives of this study are to (1) determine the incidence of and risk factors for SARS-CoV-2 infection among healthcare personnel at a tertiary medical center and (2) actively monitor personal protective equipment use, interactions between study participants via electronic sensors, secondary cases in households, and participant mental health and well-being.

Methods: To achieve these objectives, we designed a prospective, observational study of SARS-CoV-2 infection among healthcare personnel and their household contacts at an academic tertiary care medical center. Enrolled healthcare personnel completed frequent surveys on symptoms and work activities and provided serum and nasal samples for SARS-CoV-2 testing every two weeks. Additionally, interactions between participants and their movement within the clinical environment were captured with a smartphone app and Bluetooth sensors. Finally, a subset of participants' households was randomly selected every two weeks for further investigation, and enrolled households provided serum and nasal samples via at-home collection kits.

Results: As of September 30, 2020, 164 healthcare personnel and 33 household participants have been enrolled. Recruitment and follow-up are ongoing and expected to continue until March 2021.

Conclusions: Much remains to be learned regarding risk of SARS-CoV-2 infection among healthcare personnel and their household contacts. Through use of a multi-faceted study design enrolling a well-characterized cohort, we will collect critical

information regarding SARS-CoV-2 transmission in the healthcare setting and its linkage to the community.

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SARS-CoV-2 Infection in Healthcare Personnel and Their Household Contacts at a Tertiary Academic Medical Center: Protocol for a Longitudinal Cohort Study

ABSTRACT

Background: Healthcare personnel are at high risk for exposure to the SARS-CoV-2 virus. While personal protective equipment may mitigate this risk, prospective data collection on its use and other risk factors for seroconversion in this population is needed.

Objective: The primary objectives of this study are to (1) determine the incidence of and risk factors for SARS-CoV-2 infection among healthcare personnel at a tertiary medical center and (2) actively monitor personal protective equipment use, interactions between study participants via electronic sensors, secondary cases in households, and participant mental health and well-being.

Methods: To achieve these objectives, we designed a prospective, observational study of SARS-CoV-2 infection among healthcare personnel and their household contacts at an academic tertiary care medical center in North Carolina. Enrolled healthcare personnel completed frequent surveys on symptoms and work activities and provided serum and nasal samples for SARS-CoV-2 testing every two weeks. Additionally, interactions between participants and their movement within the clinical environment were captured with a smartphone app and Bluetooth sensors. Finally, a subset of participants' households was randomly selected every two weeks for further investigation and enrolled households provided serum and nasal samples via at-home collection kits.

Results: As of December 31, 2020, 211 healthcare personnel and 53 household participants have been enrolled. Recruitment and follow-up are ongoing and expected to continue through March 2021.

Conclusions: Much remains to be learned regarding the risk of SARS-CoV-2 infection among healthcare personnel and their household contacts. Through the use of a multi-faceted prospective study design and a well-characterized cohort, we will collect critical information regarding SARS-CoV-2 transmission risks in the healthcare setting and its linkage to the community.

Keywords: SARS-CoV-2; Health Personnel; Cohort Studies; Bluetooth contact tracking; Survey-based research; Occupational Health; Seroprevalence

INTRODUCTION

Background

As of October 2020, the global COVID-19 pandemic accounts for more than 43 million confirmed infections and 1.1 million deaths, along with unprecedented disruption to social networks and economic systems[1]. The etiologic agent, the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) betacoronavirus, is primarily spread from person-to-person via inhalation or direct contact with aerosolized droplets. Frontline healthcare personnel (HCP) have been shown to be at increased risk of infection due to frequent exposure to, and close contact with, infected patients and contaminated surfaces.[2–4] Shortages of critical personal protective equipment (PPE) during the pandemic have further exacerbated risks to HCP. A review of the epidemiological data from the site of the initial SARS-CoV-2 outbreak in Wuhan, China showed that 63% (1,080 of 1,716) of HCP were infected with SARS-CoV-2, 14.8% (247 of 1,668) of whom developed severe disease.[5] The seroprevalence of SARS-CoV-2 among HCP in the United States (US) and Europe appears to be far lower, ranging from 1.9-12.6%, with 0.0-1.7% of those infected being hospitalized due to severe disease.[6] Data from two nosocomial outbreaks of SARS-CoV-2 in the US demonstrate that the risk of virus transmission to HCP is highest during episodes of close patient contact without adequate PPE.[7]

Infected HCP may also contribute to disease transmission, both in the hospital setting and in the community. When infection results in overt clinical symptoms, identifying and isolating infected HCP is relatively straightforward. However, many SARS-CoV-2 infected individuals are asymptomatic or develop only mild symptoms.[8–10] In the absence of regular screening, asymptomatic individuals are unlikely to isolate or seek care. Yet, even asymptomatic or pre-symptomatic individuals can harbor high viral loads in respiratory secretions and may account for high numbers of secondary infections.[9,11,12] Outside of the hospital, little is known about the role HCP play in the transmission of SARS-CoV-2, particularly among household members and close contacts. However, numerous studies have demonstrated that the household is an important venue for SARS-CoV-2 transmission.[13] Potential transmission from HCP to family members and other close contacts is a source of considerable stress that may adversely impact mental health and job performance[14]

Most studies of SARS-CoV-2 seroprevalence among HCP have been cross-sectional or case series analyses.[15] Although basic longitudinal analyses of SARS-CoV-2 incidence among HCP in the US have also been conducted, none have included household contacts and none have digitally tracked HCP interactions and movement in the healthcare setting to identify potential points of risk and transmission.[16] Therefore, there is a need to better study the prospective risk factors for SARS-CoV-2 infection among HCP, track their interactions in the workplace, and quantify infection risks among their household contacts.

Study Objectives

The overarching goal of the study was to quantify and describe the risk of SARS-CoV-2 infection among frontline healthcare personnel, ancillary support staff, and their household contacts amidst the ongoing SARS-CoV-2 pandemic. To accomplish this goal, we designed a layered prospective cohort study of HCP and their household contacts. We enrolled frontline HCP including physicians, nurses, and ancillary staff providing and supporting emergency room, respiratory diagnostic center, and inpatient care at a large, academic, tertiary medical center. We collected survey data and venous blood samples and a nasal swab for detection of SARS-CoV-2 every two weeks for three months and then monthly thereafter for a period of up to six months. We also tracked individuals' interactions using Bluetooth sensors that were linked to a smart phone app for each participant and also attached to various locations within their workplace. Our central hypothesis was that preventive behaviors outside of work, interactions in the workplace, and use of protective equipment would predict the risk of infection in HCP and their household contacts.

METHODS

Study Design Overview

We conducted a prospective, observational study of SARS-CoV-2 among HCP and their household contacts during a global pandemic at a large regional southern medical center. The setting was a tertiary care facility with over 900 beds. The SARS-CoV-2 response at the medical center involved the cohorting of suspected and infected patients on particular floors (Figure 1) and localization of care by specific teams of providers. Within the hospital, this included a team in the intensive care unit and on a medical floor, staffed by a subset of medical providers (physicians, advanced practice providers, respiratory therapists, and nurses) as well as ancillary staff (environmental services, food services, and rehabilitation therapists). Both the medical providers and ancillary staff at times also worked on other floors in the hospital. The Emergency Department (ED) was responsible for evaluating and admitting the most severe infections. Together, these providers were at the highest risk for SARS-CoV-2 exposure. Outside the hospital, the medical center was operating a drive-through testing center to allow for the diagnosis of SARS-CoV-2 in ambulatory patients away from the main hospital. Providers and support personnel at the drive-through site routinely interacted with patients before knowing the individual's infection status.

Based on sample size calculations (see Data Analysis section), we sought to enroll 300 HCP providing care and services in inpatient, ED, and testing center settings during the SARS-CoV-2 pandemic. Of note, HCP were not routinely screened for SARS-CoV-2 infection at this institution. Eligibility criteria for HCP included: (1) provided patient care or support services at the University of North Carolina Medical Center (UNCMC) or the Respiratory Diagnostic Center (RDC) during the SARS-CoV-2 pandemic, (2) planned to remain employed by UNC for the duration of the study, (3) willing and able to provide informed consent/assent, and (4) had access to stable internet, email, and a computer at home. The only exclusion criterion was an inability to provide informed consent. As described in detail below, HCP and ancillary staff were surveyed regarding potential occupational exposures and patient care activities. Venous blood, nasal swabs, and nasal epithelial lining fluid were collected every two weeks. HCP participants who developed clinical symptoms at any point during the study and were not self-identified as SARS-CoV-2 positive were referred to occupational health for evaluation. Additionally, proximity contacts between individual HCP participants and between HCP participants and high-risk locations in the hospital were collected via a mobile application using Bluetooth technology.

Finally, we enrolled a subset of the household members of HCP participants to assess transmission dynamics outside of the hospital environment. For household members to be considered eligible, they had to (1) cohabitate for an average of at least 40 hours/week with an HCP participant, (2) have the ability to use a collection device for serum collection on one's own or with assistance from another household member, and (3) be willing and able to provide informed consent/assent or parental consent. Those younger than 18 months of age and those who were unable to provide informed consent (or parental consent if under 18 years of age) were excluded from the household study. This study was approved by the Institutional Review Board of the University of North Carolina at Chapel Hill (20-0942).

Recruitment and Consent Process

Healthcare Personnel

To recruit HCP, study leaders met with administrative leadership for divisions within the Department of Medicine (Infectious Diseases, Pulmonary and Critical Care, Hospital Medicine, etc.) and other departments within the School of Medicine (Pediatrics, Emergency Department, etc.), nursing leadership for hospital units, respiratory therapy administrators, and leadership for ancillary and support services (e.g., environmental health, patient transport, food services, etc.) to present and discuss the study. Various additional approaches for recruitment were used as well, including 1) direct communication to personnel through email or face-to-face encounters, 2)

presentation/discussion about the study at virtual or in-person staff meetings, 3) flyers, posters, or other public displays, and 4) small gifts on which the study logo was printed such as miniature hand sanitizer bottles, pens, and stress balls. Interested individuals were referred to a study-specific website where they were able to learn more about the study, ask questions through a study-specific email address, and submit an online pre-screening survey to communicate their interest to the study team. The study team then scheduled a time to discuss the study with participants by phone and complete an electronic consent, a copy of which was emailed to the participant. HCP participants were able to opt-out of electronic contact tracking and collection of nasal epithelial lining fluid samples on the consent form but still participate in the other study procedures. Once enrolled, a unique participant ID was generated for linkage of data sources. HCP recruitment and enrollment began in July 2020 and is ongoing as of January 2021.

Households

Due to logistical and financial constraints, we could not include all households of participating HCP in the study. Therefore, to recruit household members of HCP participants, we selected a random sample of high- and low-risk HCP participants for household investigation every two weeks. HCP were considered high risk if any of the following occurred:

1. HCP self-reported contact with suspected or confirmed patient with SARS-CoV-2 infection without proper PPE (defined as N95 respiratory, gown, gloves, and eye protection)
2. HCP self-reported errors and/or malfunction of PPE during patient encounters
3. Positive SARS-CoV-2 rapid serology test result (either IgM or IgG)
4. Suspected or confirmed SARS-CoV-2 infection

If none of the above criteria applied, the HCP was considered low risk. Once participants were stratified into high- and low-risk categories, a third-party biostatistician performed probability-based sampling to select 6-10 households for investigation (3-5 per risk category). Study staff were masked to the assigned risk categories for the selected households. The HCP were approached to provide emails and ages for all household contacts. If the HCP participant agreed to the household investigation, the study team contacted their household members about study participation by phone. The study team reviewed the study documents, electronic consent form, and the process for at-home sample collection. If the household member agreed to participate, they signed the consent form electronically. Each household member was provided a handout about when to seek care for potential SARS-CoV-2 infection and when to contact the study staff by email. Household member recruitment began in July 2020 and is ongoing as of January 2021.

Study Procedures (Figure 2)

Healthcare Personnel

Questionnaires (see Supplementary Materials: Appendices 1-4)

Baseline: At baseline, HCP participants received an electronic questionnaire regarding demographics, occupational duties, current symptoms, known exposures to SARS-CoV-2-infected persons, and PPE usage. This initial questionnaire also gathered data about the participant's household (e.g., number of people, occupations, etc.) and included basic mental health assessments for depression, anxiety, and post-traumatic stress disorder.

Daily: Once the first in-person study visit was completed (see Study Visits and Sample Collection below), daily electronic surveys were sent to participants for the first 12 weeks of study participation via an automated email reminder. Questions included a clinical symptom assessment (with self-recorded temperature if symptomatic), hours worked at the medical center, number of contacts with patients with suspected or confirmed SARS-CoV-2, and occupational activities performed during interactions with patients.

Every two weeks: The participant received a longer electronic survey by email every two weeks containing questions concerning current symptoms, known exposures to SARS-CoV-2-infected

individuals, PPE availability and usage since they last completed the two-week questionnaire, and pandemic-related stress.

Throughout the study, if a participant indicated symptoms consistent with SARS-CoV-2 infection, they were referred to the medical center's Occupational Health department for evaluation and testing. Additionally, if a participant indicated that they were having thoughts of self-harm more than half of the days in the last two weeks, they were sent an email referral to an institutional mental health hotline that was developed to address the mental health support of all healthcare personnel as well as other local and national mental health support resources.

Study Visits and Sample Collection

Baseline: After completion of the baseline questionnaire, a research assistant met the participant at one of three designated sites in or near the medical center for the baseline study visit during which the following study procedures took place:

1. Venous blood was collected in an EDTA tube by trained phlebotomists for SARS-CoV-2 IgM/IgG rapid diagnostic testing and preparation of dried blood spots for storage. Venous blood was also collected in two 8mL cell separator tubes for peripheral blood mononuclear cell isolation and storage (BD Vacutainer Mononuclear Cell Preparation Tube (CPT) - Sodium Citrate, BD Biosciences, San Jose, CA). Plasma was isolated from the CPT tubes for SARS-CoV-2 antibody testing by ELISA.
2. We asked a subset of participating HCP (100 individuals) to have blood drawn for SARS-CoV-2 antibody testing by ELISA using the Tasso serum self-collection kit (Tasso, Inc., Seattle, WA) in parallel with venous phlebotomy as part of a sub-study. Tasso devices were used per the manufacturer's instructions. Briefly, individuals washed their hands and prepped their skin by rubbing until warm and wiping with alcohol to sterilize. The device was then adhered to the skin for 5 minutes to collect the sample and removed.
3. Participants self-collected a mid-turbinate nasal swab (MTNS) using the protocol described in previous studies.[12,14] We employed MTNS as opposed to nasopharyngeal swabs as this method of collection has demonstrated comparable performance for the identification of respiratory pathogens,[12] while involving less risk to both the subject and study staff. The swab was placed in a collection tube filled with DNA/RNA Shield (Zymo Research, Irvine, CA) for SARS-CoV-2 polymerase chain reaction (PCR) testing.
4. Participants self-collected nasal epithelial lining fluid (NELF) using absorbent strips inserted into the nose (if they opted into this part of the study) as described previously (Multimedia Appendix 5).[17] Briefly, participants moistened the nasal passage using a metered spray bottle and normal saline. They then inserted absorbent strips, cut to fit into the nasal passages, into each nare. Participants then clamped the strips in place with a padded nasal clamp, to ensure maximal contact with the nasal mucosa, for two minutes. Participants then removed the strips from the nose and placed them into provided storage tubes.
5. Each individual was given a digital thermometer to track and report their temperature at home.
6. Participants who opted into downloading an app to track their interactions in the workplace were given a Bluetooth Low Energy (BLE) beacon for contact tracking to attach to their hospital-issued ID badge or lanyard. They were also instructed on how to download and set-up the Ethica smartphone application (Ethica Data, Toronto, Canada; see Network Data Collection section).

Follow-up Study Visits: Every two weeks for the first 12 weeks and then monthly for the remainder of the study, participants again presented to one of three designated sites for an in-person, follow-up study visit (Figure 3). Venous blood, MTNS, and NELF strip (if opted in) samples were collected at each visit as above. To minimize potential exposure to study staff, if a participant was due for their biweekly visit but was experiencing symptoms consistent with SARS-CoV-2 infection or had recently tested positive by PCR and was within the quarantine period recommended by Occupational Health, they were not seen in person by the study staff and instead were sent a home collection kit

containing a Tasso serum self-collection kit and nasal swab.

Households

Questionnaires (see Supplemental Materials: Appendices 6-8).

Baseline: At the time of enrollment, each household member received a survey regarding demographics, relationship to the HCP participant, occupation, medical history, and any recent clinical symptoms, SARS-CoV-2 exposures, or past SARS-CoV-2 testing.

Weekly: Enrolled household members completed weekly questionnaires about possible symptoms of SARS-CoV-2 infection and any testing since the previous survey.

Day 21: At the end of their study participation, 21 days after their first sample collection, household members completed a final questionnaire asking about any changes in occupation since the baseline survey, and any SARS-CoV-2 symptoms, exposures, and/or testing since the previous weekly survey.

Throughout their participation in the study, if a household member reported fever and either cough or shortness of breath, they were referred to the testing center or their primary care provider's office for testing.

Sample Collection

Baseline and Day 21: Within three days of enrollment, the study team mailed a kit for at-home baseline sample collection to each consented household member that included the following:

1. *Tasso at-home serum collection kit for SARS-CoV-2 antibody testing by ELISA.* The Tasso device was provided in a box labeled with the date and patient identifier that contained written instructions and a link to the website that demonstrates use of the collection device (https://www.tassoinc.com/tassom20-ifu). Once collected, the participant placed the device in a sealable biohazard bag and then into the Tasso kit's box.
2. *Nasal swab and DNA/RNA Shield Tube for MTNS collection for SARS-CoV-2 PCR testing*. The nasal swab was provided with an instruction sheet and link to an online video with instructions for nasal swab specimen collection. After specimen collection, the participants placed the sealed tubes containing the swabs in sealable biohazard bags.

Completed at-home collection kits were then packaged in a pre-addressed, pre-posted box and mailed back to the laboratory to minimize face-to-face contact between the study team and household members. The same at-home sample collection process was then repeated at 21 days after baseline sample collection.

Other Study Procedures

Network Data Collection

HCP participant-participant and HCP participant-environment interactions were collected electronically via Bluetooth Low Energy (BLE) with the Ethica (Ethica Data, Toronto, Canada) smartphone application (Figure 4). We followed a similar protocol previously described in our earlier work.[18,19] The Ethica application functions with the use of two devices: the participant's cell phone, and a BLE beacon. While the participant has the Ethica application open on their phone and Bluetooth is active, the application passively collects and records incoming Bluetooth signals with a universally unique identifier (UUID) that corresponds to the study. Due to phone manufacturer constraints, scanning for Bluetooth signals is done at a resolution of approximately five minutes. Information recorded for valid UUID are the Ethica-assigned ID for the participant, time of the incoming signal, strength of the incoming signal as measured by the received signal strength indicator (RSSI), and identifiers corresponding to the incoming valid beacon signals. Data is stored locally on the participant's smartphone until uploaded to the Ethica secure servers through a wireless connection (Wi-Fi or cell signal).

BLE beacons are devices used to broadcast a set of identifiers at a predetermined rate. For our application, BLE beacons were programmed with a unique combination of UUID, major values, and minor values as assigned by the Ethica system. While other devices can see the broadcast beacon identifiers, the beacon identifiers are not linked to the other participants' information or data sources aside from a linkage within REDCap, the electronic data management system used for the study. [20] BLE beacons can be further designated as participant-owned or environmental. Therefore, proximity to both other participants carrying beacons and beacons placed in the environment can be recorded. For our implementation, Gimbal Series 10 (Los Angeles, California) beacons were used. BLE beacons were configured using the iBeacon configuration. Environmental beacons were set at a power level of -8 dBm, which corresponds to an approximate capture distance of 20 feet in internal testing. Participant beacons were set at a power level of -18 dBm, corresponding to nine feet. To increase the likelihood a beacon was recorded during the time window of collection by the phone, the beacon transmission was set to 1 Hz. In summary, the BLE beacon broadcasts the participant's identifier and the participant's smartphone collects incoming Bluetooth signals from nearby environmental and participant BLE beacons.

During the consent process, HCP had the option to opt-in to the proximity contact data collection. HCP who consented to use the Ethica application were given instructions on installing the application on their smartphone. Environmental BLE beacons were placed at locations within the Emergency Department, RDC, Medical Intensive Care Unit (MICU), Pediatric intensive care units, elevators, and floor COVID-19 units for adults and children (Figure 1). BLE proximity data were downloaded weekly by study staff from the Ethica web portal and monitored.

PPE Observations

To document trends in the use of PPE, members of the research team were stationed in the areas in which care for patients with suspected or confirmed SARS-CoV-2 infection most often took place. At least one team member observed each of the following areas once weekly for 2-3 hours each time: the Emergency Department bay where patients suspected of having SARS-CoV-2 infection were cohorted, the inpatient ward for SARS-CoV-2-infected patients, and the MICU. The observations were collected on an electronic form, including unit-level PPE use and availability and individual HCP-patient interactions, specifically appropriateness of hand hygiene and PPE use and procedures performed by the provider. This observational data collection will supplement the self-reported daily PPE usage information by the HCP.

Sample Processing and Testing Procedures

The collection, processing, and storage of samples followed national and international guidelines, and all processes will be approved by Environmental Health Services at UNC.[21] Please see Supplemental Materials - Appendix 9 for full laboratory protocol.

Venous Blood

SARS-CoV-2 IgM/IgG Rapid Diagnostic Test (RDT). The RDT followed the manufacturer's guidelines (Elabscience, Houston, TX).[22] Briefly, 20 ul of whole blood was applied to the sample well using an enclosed micropipette. Three drops of reagent were added to the sample well. The RDT was read after 10 minutes.

Dried blood spot (DBS) processing: Approximately 200ul of blood were used to make four dried blood spots per patient time-point. Blood was spotted on appropriately labeled Whatman 904 cards. The card was dried for 15 minutes, or until completely dried, before packaging in individual ziplock bags with desiccant. Blood spots were stored at -80 ºC for future research.

ELISA for SARS-CoV-2 Antibody: Using both the plasma collected from HCP participants during their in-person study visits and the household participant self-collected serum samples, we

performed an ELISA using the recombinant spike protein antigen to detect total SARS-CoV-2 immunoglobulin (Ig) in plasma.[23] The cut-off to differentiate positive versus negative for the ELISA assay was chosen to ensure the test had 99.5% specificity per CDC recommendations for COVID-19 serology testing.[24]

Peripheral Blood Mononuclear Cell (PBMC) Isolation: Cell preparation tubes were processed and PBMCs isolated as previously described and as detailed in the Supplemental Materials - Appendix 9.[25] PBMCs were stored in aliquots of 3-6 million cells/uL at -80 ^{o}C for future research.

Mid-turbinate nasal swabs (MTNS)

SARS-CoV-2 PCR Testing: The DNA/RNA Shield medium in which the swabs were collected inactivates all viral particles. RNA was extracted from 200ul of DNA/RNA shield using a Qiagen HT system. Samples were screened for SARS-CoV-2 infection using the Thermo COVID multiplex real-time PCR assay including the MS2 phage spike during extraction. All samples positive by this initial test underwent confirmation testing with the CDC assay and viral copies quantified.[26] PCRs were batched and assayed retrospectively. For clinical diagnosis of symptomatic individuals, participants were referred to occupational health for standard PCR testing at a rapid diagnostic testing center.

Nasal Epithelial Lining Fluid

Absorbent strips for capturing the nasal epithelium were frozen at -80°C for storage and batched for processing. One strip was utilized for protein analysis via multiplex ELISA for cytokines and chemokines, and the second strip was utilized for viral PCR testing. Samples were inactivated prior to analysis via approved protocols which included heat and chemical treatment. Processing for protein analysis and PCR analysis occurred as described previously.[17] The remaining nasal epithelial lining fluid was stored for other future characterization of the respiratory epithelial immune response and gene expression analysis.

Data Analysis

All data were stored in a HIPAA-compliant database using REDCap.[20]

Sample Size

Given the rapid emergence and evolving situation regarding the SARS-CoV-2 pandemic, limited data were available at the time of study design on which to base sample size estimates. Preliminary data from northern Italy suggested an infection rate approaching 20+%,[27,28] but this prevalence estimate exceeded what was expected in the southeastern US in Spring 2020 with the implementation of social distancing restrictions and stay-at-home orders. Therefore, a goal sample size of 300 HCP participants and an additional 250 household members was chosen as a logistically feasible enrollment target based on power calculations. The sample size choice was further informed by recent work regarding epidemic spread in dynamic networks as measured via Bluetooth devices, with the selected target sample size exceeding the largest previous such study. [18,29]

Exposures

Our primary exposure of interest was employment in a department or unit involved in frontline healthcare of confirmed or suspected SARS-CoV-2-infected patients. Results from this group will be compared to a group of healthcare personnel and ancillary staff employed in a department or unit that is not involved in care of patients infected with SARS-CoV-2. Secondary variables of interest also include other occupational factors (e.g., type of PPE used, specific occupation, etc.) and preventative behaviors outside of work (e.g., mask use, handwashing, etc.).

Outcomes

Our primary outcome of interest was the incidence of SARS-CoV-2 infection defined as either development of SARS-CoV-2 specific antibodies as determined by ELISA (i.e. seroconversion) or clinical infection with SARS-CoV-2 confirmed by PCR testing. Secondary outcomes of interest

included: (1) demographic, clinical, and occupational factors associated with SARS-CoV-2 infection; (2) proportion of confirmed infections that are sub-clinical and/or asymptomatic; (3) risk of secondary transmission and serial interval within household contacts; (4) analysis of the Bluetooth contact networks to assess the efficacy of community mitigation policies; and (5) agreement between serological testing results obtained from venous blood collection, DBS, and Tasso device. Exploratory outcomes included the characterization of the immune response in the nasal epithelium at various points during SARS-CoV-2 infection and genotypic analyses of the SARS-CoV-2 viral isolates.

Confounders

To account for common causes of department employment and SARS-CoV-2 infection, information on demographics (age, race, ethnicity, gender, household context), occupational factors (PPE use, PPE availability, occupational characteristics), behaviors outside of work (mask use, hand hygiene), and mental health (symptom screeners for anxiety, depression, and PTSD; stress level assessments) were collected. Since risk of infection is affected by the characteristics and behaviors of others, we also collected information on locations worked (unit, time spent on the unit) and proximity contacts as measured through the Bluetooth beacons.

Proposed Statistical Analyses

Demographic, clinical (i.e. baseline medical conditions) and occupational characteristics of the HCP and household member cohorts will be described using standard summary statistics. The risk ratio and risk difference of SARS-CoV-2 infection among HCP participants working in COVID-19 areas versus non-COVID-19 areas while accounting for identified confounders will be estimated using Bayesian Additive Regression Trees.[30] 95% credible intervals will be calculated from the posterior. Furthermore, we will explore potential heterogeneity in outcomes as a function of demographic and occupational characteristics. We will analyze household data following methods applied to influenza transmission studies.[31,32] Loss-to-follow-up has been actively monitored and participants who discontinue the study are asked the reasoning for their discontinued participation. Data managers periodically audit survey responses and participant engagement with the study and reach out directly to those participants who are not submitting data regularly. In addition, we are corroborating SARS-CoV-2 testing information using the medical record. Depending on the extent of missing data and the pattern, we will use multiple imputation or weighting informed by this data. For sensitivity analyses, we plan on evaluating the nonparametric bounds for missing data and other systematic biases.[33]

We will determine the test performance (e.g., sensitivity and specificity) of the SARS-CoV-2 IgM/IgG RDT using the ELISA antibody test as the reference assay. To validate serological results obtained using the Tasso at-home collection device, we will also assess for concordance between ELISA antibody testing results from samples collected by the Tasso self-collection kit as compared to venous phlebotomy, which is considered the standard specimen-collection procedure, through calculation of Cohen's kappa coefficient.

NELF samples will be analyzed using multiplex ELISAs to quantify 1) the expression of cytokines and chemokines important in the upper respiratory tract antiviral immune response and 2) quantitative SARS-CoV-2 viral load. In conjunction with NELF collected in cohorts of patients with SARS-CoV-2 infection from other ongoing research studies, we will evaluate the association of the measured inflammatory mediators and COVID-19 disease severity as defined by the World Health Organization.[34] We will also evaluate the association between epidemiologically-observed risk factors for severe COVID-19 disease[35–38] and mediators of antiviral defense.

The information collected from the Bluetooth beacons will be summarized and visualized using network analysis tools, providing insight into the patterns of movement of study participants within the hospital. Because BLE signals can travel through objects (e.g. walls, doors, etc.), proximity

contacts will be filtered by RSSI values determined by internal assessments of the beacons when used in conjunction with the Ethica application. Furthermore, individual-level likelihood-based methods will be used to study the dynamics of epidemic spread as it relates to the network of individual contacts and potential explanatory variables.[29]

RESULTS

Recruitment for this study is currently ongoing and has occurred in phases. When the study began, the types of HCP interacting with patients known to be positive for SARS-CoV-2 were limited per hospital policy, so the groups that were providing direct in-person care were targeted for recruitment first (i.e. physicians, nurses, nursing assistants, respiratory therapists, etc.). As the pandemic continued, hospital policies shifted, and ancillary staff (i.e. interpreters, food services, environmental services, patient transporters, etc.) were again entering patient rooms, so our recruitment efforts also shifted to include these groups. Specifically, we used the same recruitment strategies described above but targeted them to the support staff employee groups. In addition, we performed additional outreach to the environmental services group, attending shift huddles and rounding with management multiple times in person.

As of December 31st, 2020, we have enrolled a total of 211 HCP participants. Of these, 65 are male and 146 are female. We have also enrolled 53 household participants from 37 households. Of those 53 household participants, 16 are under 18 years old. Many types of HCP have enrolled in the study (Table 1), with the majority being physicians and registered nurses.

Table 1. Demographics of HCP participants enrolled in the study as of December 31, 2020 (n=211). [a]CRNA - Certified Registered Nurse Anesthetists; [b]CST - Certified Surgical Technician; [c]LPN - Licensed Practical Nurse; [d]CNA - Certified Nursing Assistant.

Demographic	n (%)
Sex	
Male	65 (30.8)
Female	146 (69.2)
Role at UNCMC	
Case Management	1 (0.5)
Child Life Specialist	3 (1.4)
Clinical Dietitian	2 (0.9)
CRNA[a]	5 (2.4)
CST I or CST II[b]	4 (1.9)
ECMO Specialist	1 (0.5)
Environmental Services	2 (0.9)
Food Services	1 (0.5)
Front Desk Coordinator	1 (0.5)
Health Unit Coordinator	1 (0.5)
Interpreter	3 (1.4)
LPN[c]	2 (0.9)
Midwife	2 (0.9)
Nurse Aide/CNA[d]	5 (2.4)
Nurse Practitioner	4 (1.9)
Patient Transporter	3 (1.4)
Physical/Occupational Therapist	10 (4.7)
Physician	84 (39.8)
Physician Assistant	4 (1.9)
Radiology Technologist	3 (1.4)
RDC Swabber	1 (0.5)
Registered Nurse	56 (26.5)
Respiratory Therapist	10 (4.7)
Speech Therapist	1 (0.5)
Ultrasound Technologist	2 (0.9)

A larger proportion of women as compared to men have enrolled. 86% (182 of 211) of participants have opted into the Bluetooth contact tracking, while 90% (190 of 211) of participants have opted into the NELF sample collection sub-study. Thus far, forty-five participants have withdrawn prior to

12 weeks of participation due to schedule constraints.

DISCUSSION

In this article, we describe the protocol for a multi-faceted, longitudinal, observational cohort study to obtain crucial information about the risk of SARS-CoV-2 infection among healthcare personnel and their household contacts. There are several novel aspects to the study design that will maximize its impact. First, the cohort of HCP will be very well-characterized because of (1) frequent sampling, especially during the first 12 weeks, to assess for infection and/or seroconversion and (2) the depth and breadth of information collected through electronic questionnaires regarding clinical symptoms, potential exposures to SARS-CoV-2, occupational activities, PPE access and use, perceptions of the epidemic, and mental health. As we intentionally designed to the study to include many different types of healthcare personnel to maximize the generalizability of our results, we have applied careful measurement where we can to identify occupational roles and activities so these can be accounted for in our analyses.

Second, the use of Bluetooth beacon contact tracking is a robust methodology that will complement the self-reported exposure data. Finally, our study is unique in that it is enrolling both HCP and a randomly selected subset of linked households.

There are a few potential limitations to our study. First, this study design employs frequent in-person study visits and electronic contact throughout of the study period. We designed the study this way intentionally, seeking to obtain highly granular and detailed information about risks and exposures among our study participants. There is a chance that this level of participation may limit our ability to reach our recruitment goal of 300 individuals. To offset this burden, after the first 12 weeks of the study, participants transition to having only monthly study visits and one survey every two weeks. Second, it is possible that the people who chose to enroll in this type of longitudinal study may be more attune to the COVID pandemic and therefore, more focused on preventative measures. This could induce selection bias. We plan to compare characteristics of our study population to those that are available for our target population (all HCP at UNCMC) and consider weighting if appropriate based on that evaluation.

Through this study, we will generate important data about the incidence of SARS-CoV-2 infection among frontline HCP, their workplace contact network, transmission to their household members, and trends in incidence over time. We will also evaluate the accuracy and feasibility of using a minimally invasive, point-of-care rapid test to assess for seroconversion. Together, this information will be invaluable in determining the effectiveness of active surveillance programs to reduce nosocomial transmission and the need for additional non-pharmaceutical interventions to protect HCP and their families.

ACKNOWLEDGEMENTS
We thank the participants for their willingness to contribute to advancing our understanding of the SARS-CoV-2 epidemic and its impact on healthcare personnel, especially during the early and uncertain months of the pandemic. We also acknowledge Elise Hickman for the development of the NELF sampling schematic, which was created with BioRender.com. Finally, we greatly appreciate the contribution of Dr. Premkumar Lakshmanane who spearheaded development of the ELISA assay.

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Authors' Contributions and Funding Information
EJC designed and supervised the study, composed and revised the paper, and helped to secure study funding. She is supported by the National Heart, Lung, and Blood Institute [5T32HL007106-43].
PNZ led the design and implementation of the Bluetooth beacon network part of the study and composed and revised the paper.
EKL contributed to study design and assisted with composition and revision of the paper. He is supported by the Population Research Training Grant [T32HD007168] awarded by the Eunice Kennedy Shriver National Institute of Child Health and Human Development and the Biostatistics for Research in Environmental Health Training Grant [T32ES007018] awarded by the National Institute of Environmental Health Sciences.
DZ contributed to study design, paper revision, and composition of supplemental materials.
EL contributed to study design, paper revision, and composition of supplemental materials.
JLT implemented the study, composed the results section, and created Table 1 and Figure 3.
CC implemented the study, contributed to results section composition and revised the manuscript.
JX assisted with design of and data analysis plan for the Bluetooth beacon network part of the study.
AV assisted with design of and data analysis plan for the Bluetooth beacon network part of the study.
CB designed the study and revised the manuscript
HA conducted the laboratory testing, composed Appendix 9 and revised the manuscript
EK conducted the laboratory testing, composed Appendix 9 and revised the manuscript
HEG conducted the laboratory testing, composed Appendix 9 and revised the manuscript
AJM developed the ELISA assay, trained laboratory staff, and revised appendix 9 and the full manuscript
MER designed the nasal epithelial lining fluid sub-study and composed the corresponding sections of the paper.
SS designed and supervised the nasal epithelial lining fluid sub-study and revised the corresponding sections of the paper.
DJW assisted with study design and revised the paper.
RR assisted with study design, co-led study recruitment, and revised the paper.

NA assisted with study design, co-led study recruitment, and revised the paper.
JJJ designed and supervised the laboratory testing component of the study and revised the manuscript.
RMB conceptualized the study, designed and supervised the study, revised the paper, and helped to secure study funding. He is supported by the National Institute of Allergy and Infectious Diseases through grant number [5K23AI141764-03].
AEA conceptualized the study, designed and supervised the study, revised the paper, and helped to secure study funding.

Conflicts of Interest
None declared.

Multimedia Appendices:

- **Multimedia Appendix 1**: Baseline survey for HCP
- **Multimedia Appendix 2**: Daily survey for HCP
- **Multimedia Appendix 3**: Biweekly survey for HCP
- **Multimedia Appendix 4**: Week 12, 24, and 36 survey for HCP
- **Multimedia Appendix 5:** Instructions for participant self-collection of nasal epithelial lining fluid (NELF) samples.
- **Multimedia Appendix 6:** Baseline survey for Household Participants
- **Multimedia Appendix 7**: Weekly survey for Household Participants
- **Multimedia Appendix 8:** Day 21 survey for Household Participants
- **Multimedia Appendix 9**: Standard Operating Procedure for Laboratory Sample Processing

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Figure 1. Schematic representation of hospital units in which patients with COVID-19 disease are cohorted with locations of environmental Bluetooth beacons.

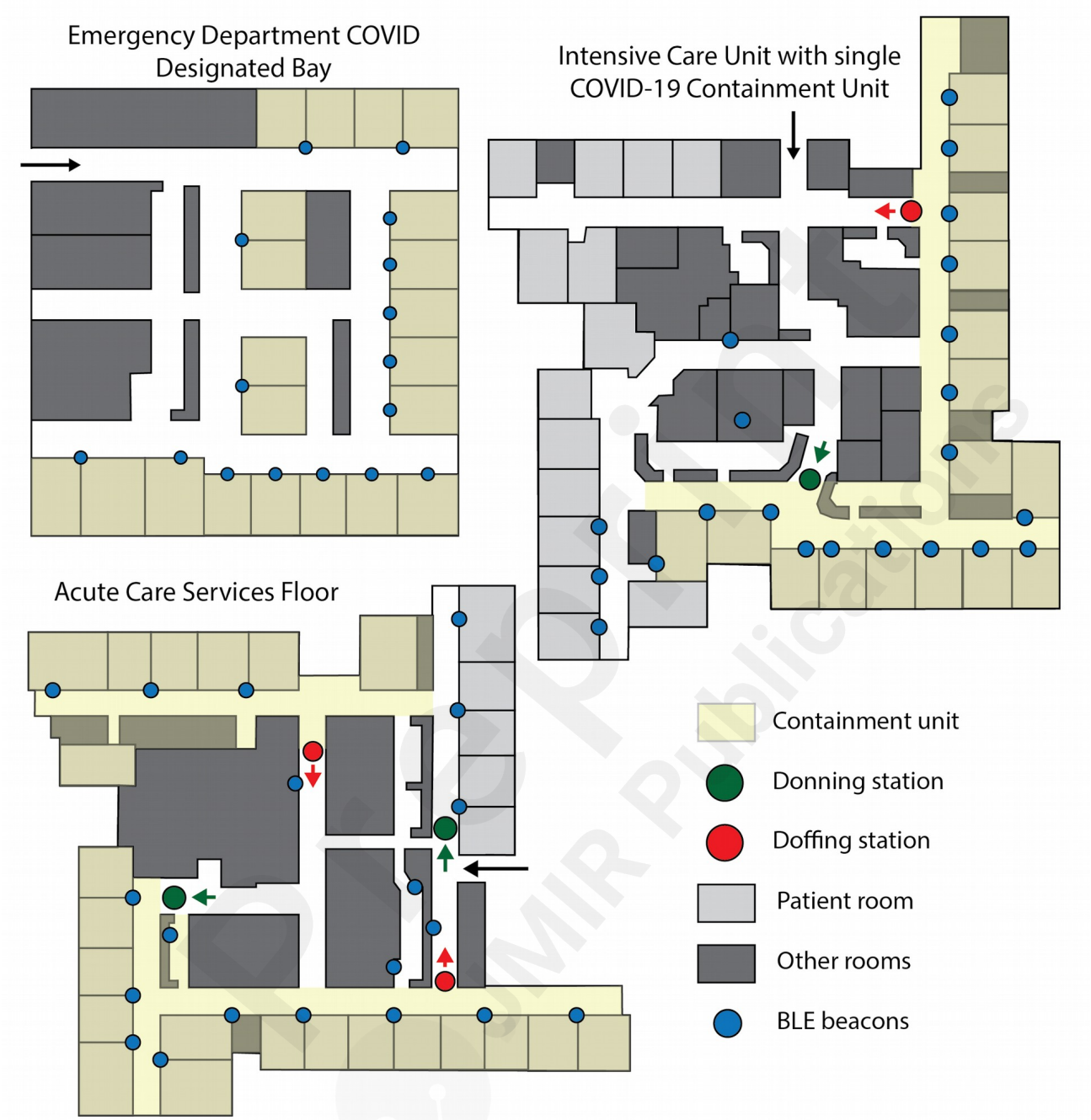


Figure 2. Overview of study design including HCP participant visits and household selection process.

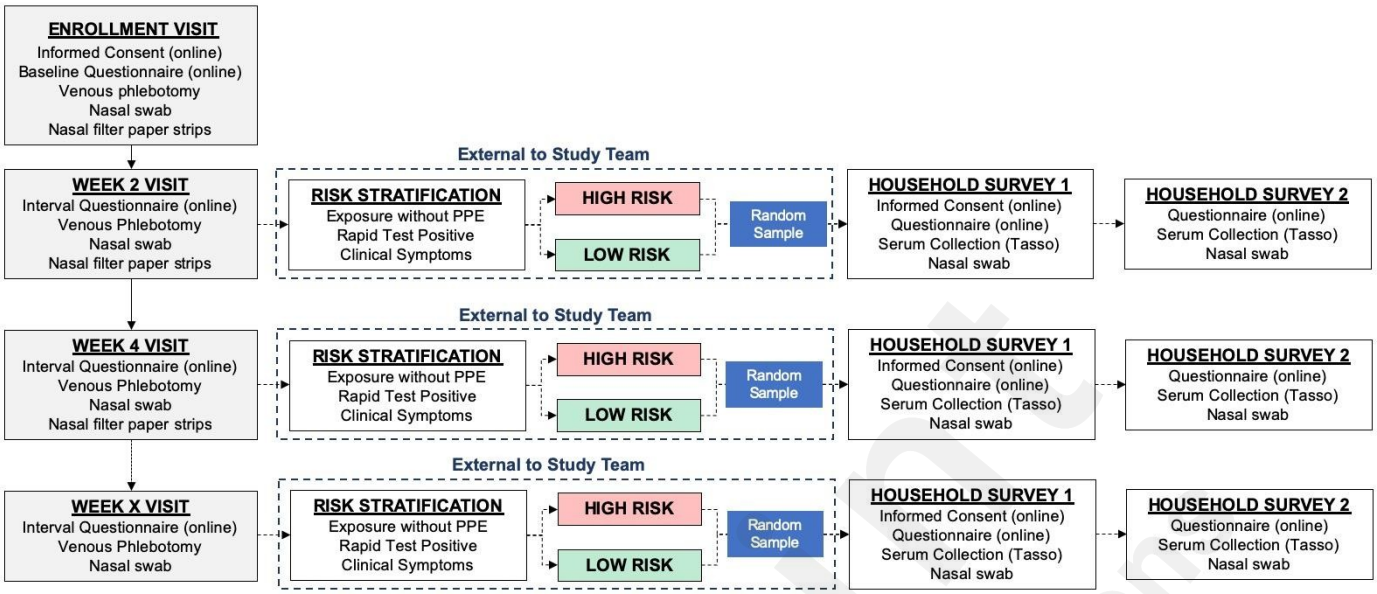


Figure 3. Enrollment and in-person study procedures for HCP participants.

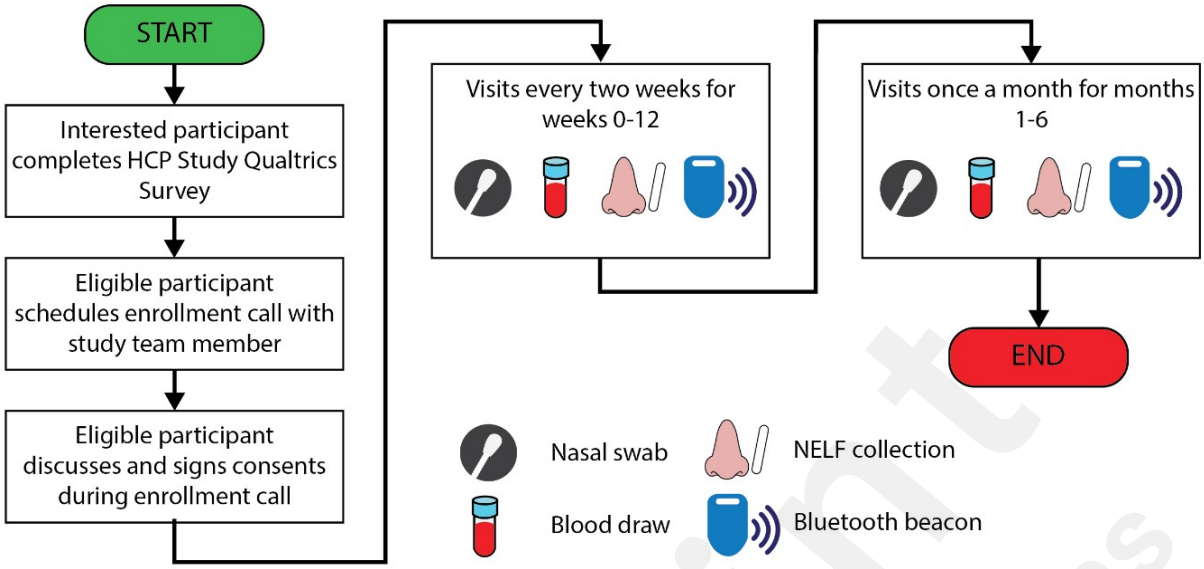
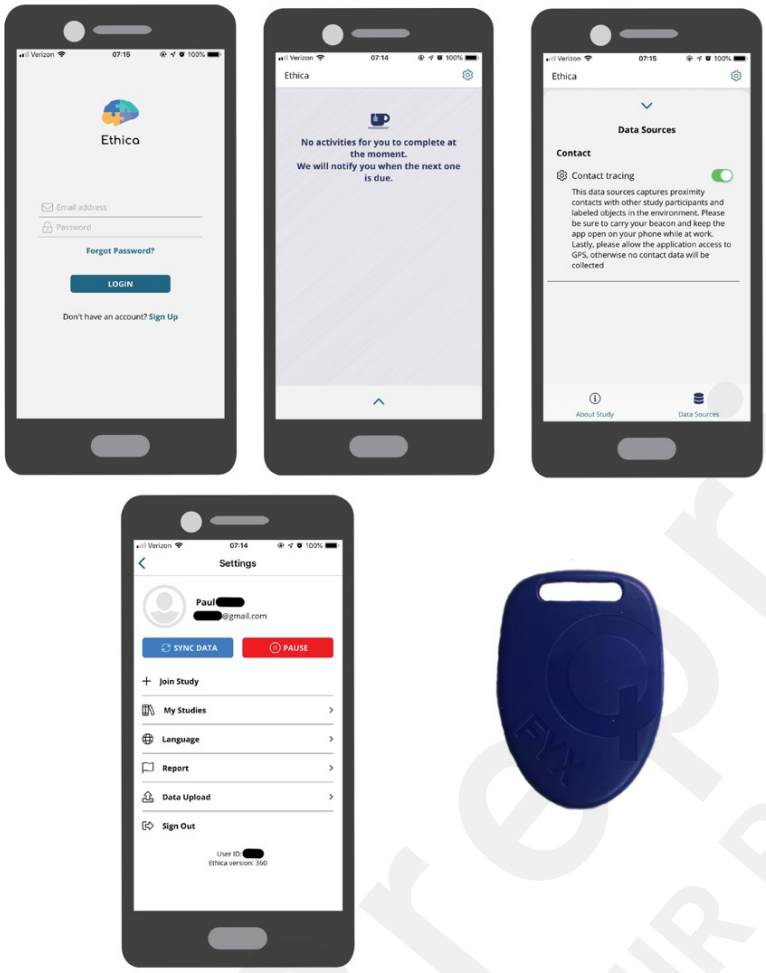


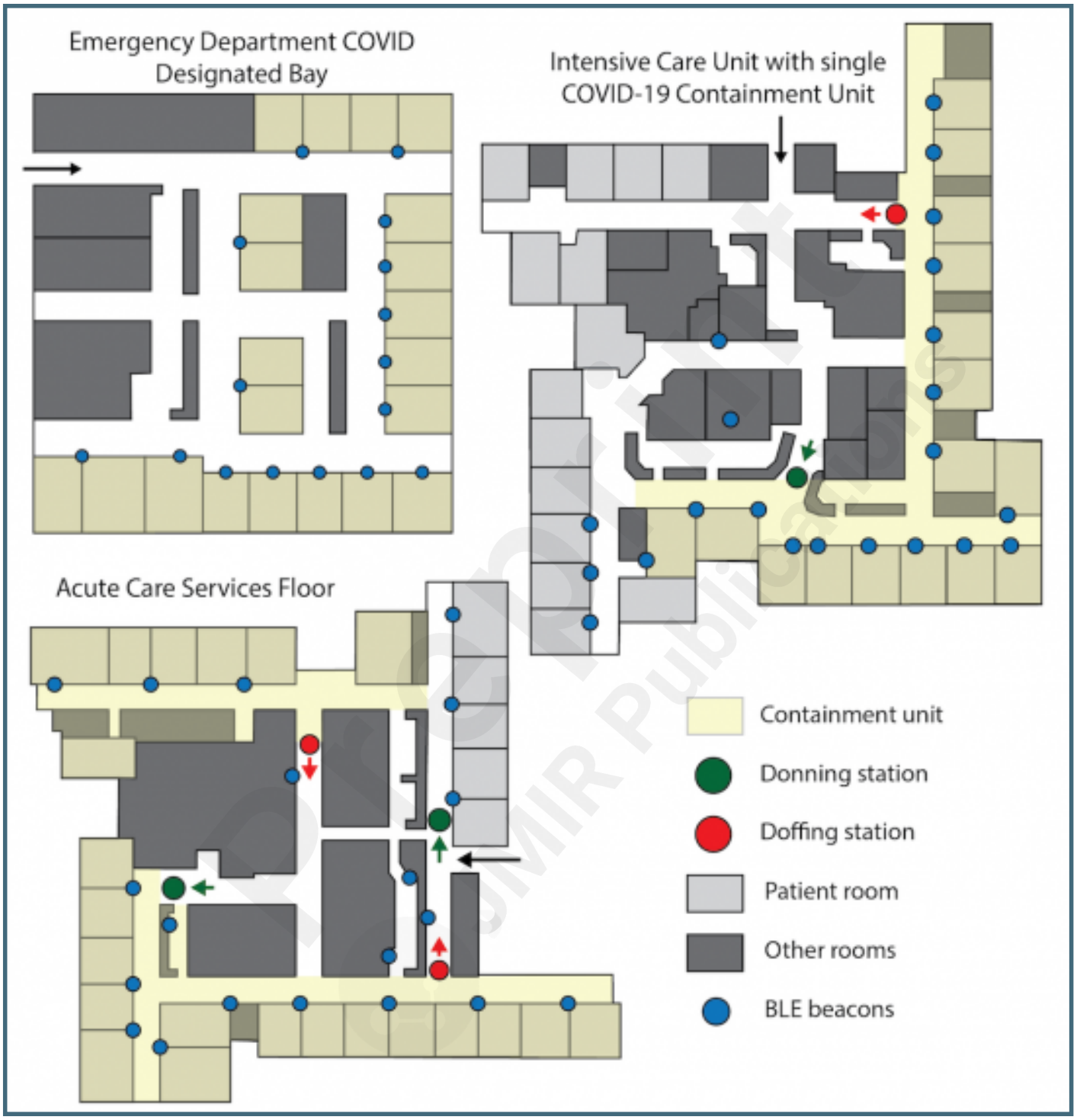
Figure 4: Participant-facing Ethica smartphone application and Bluetooth beacon for collection of proximity contacts. Ethica smartphone application from left to right: log-in page, home page for the study, data sources collected and option to pause participation, and settings page. Beacon dimensions are 1.6 inches (length) by 1.1 inches (width) by 0.2 inches (height).



Supplementary Files

Figures

Schematic representation of hospital units in which patients with COVID-19 disease are cohorted with locations of environmental Bluetooth beacons.



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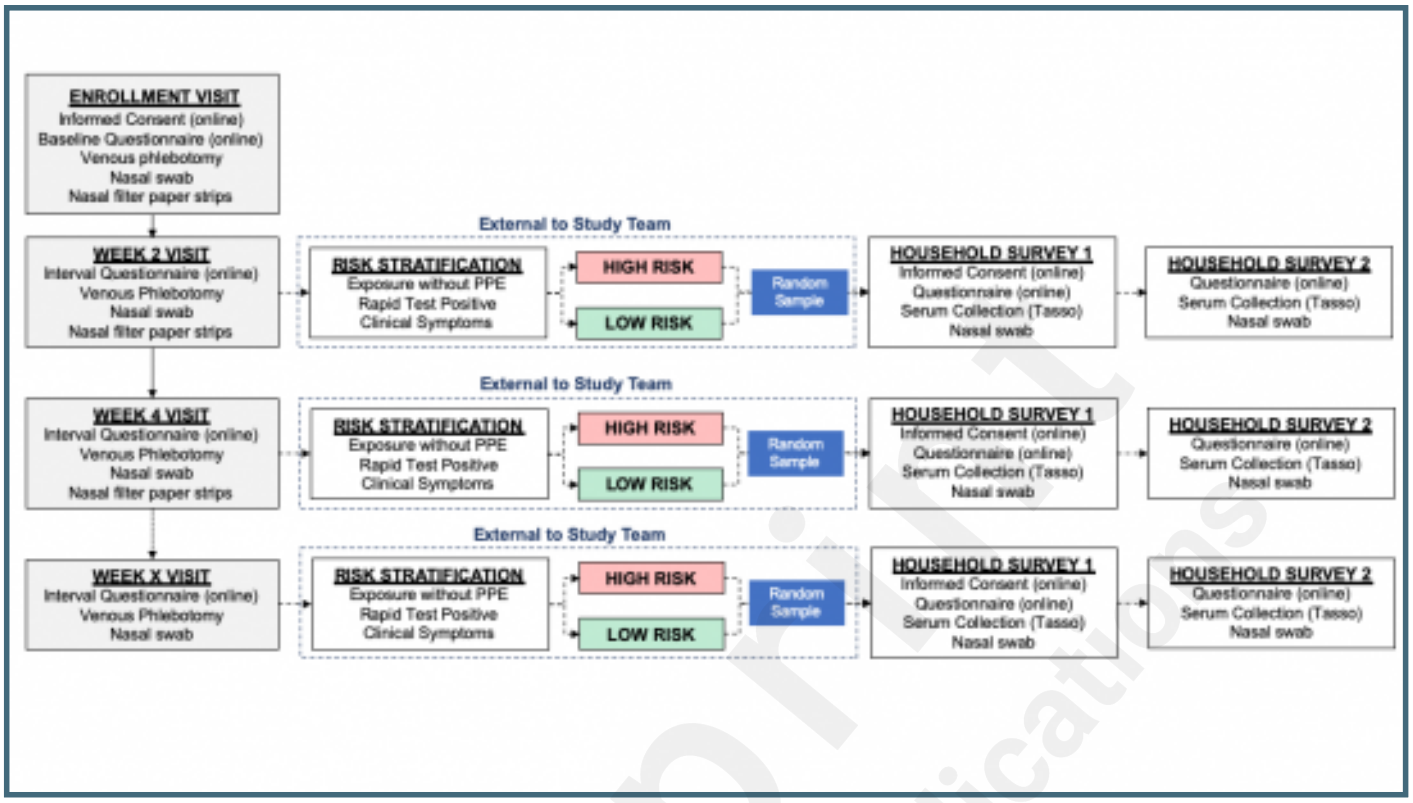

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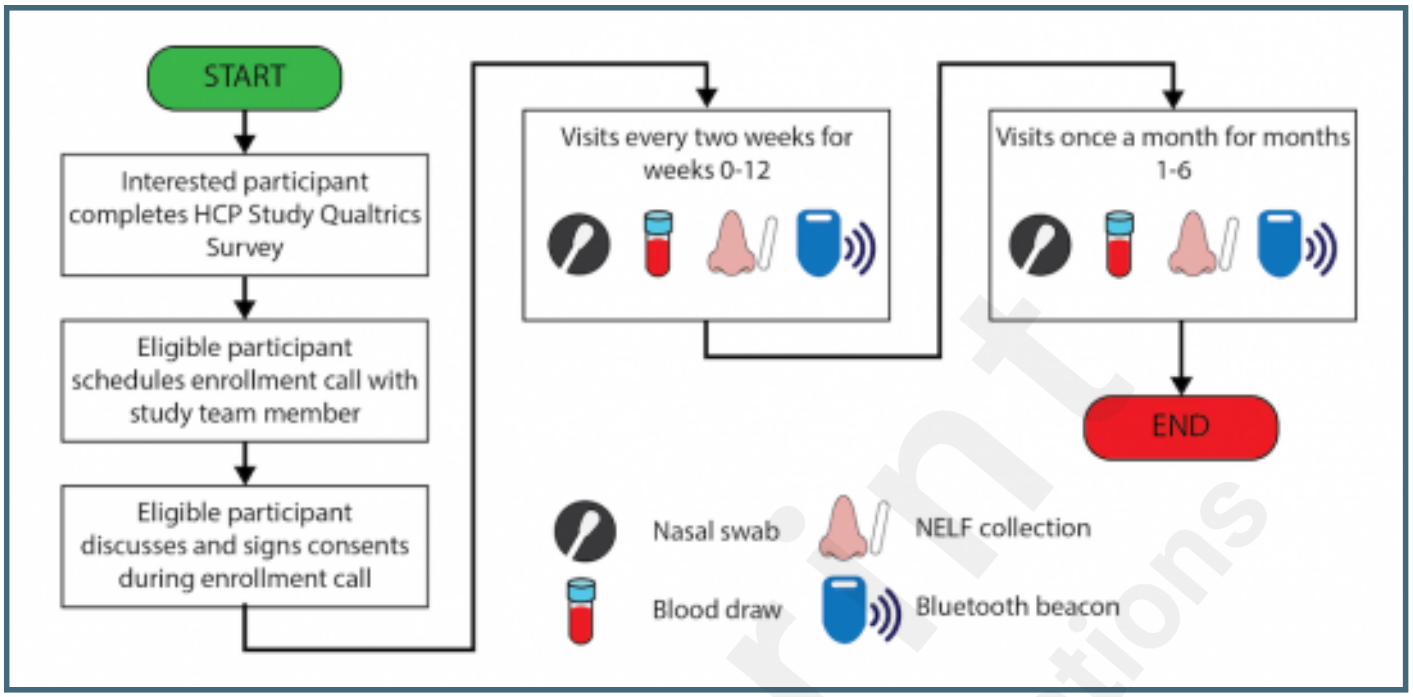

Participant-facing Ethica smartphone application and Bluetooth beacon for collection of proximity contacts. Ethica smartphone application from left to right: log-in page, home page for the study, data sources collected and option to pause participation, and settings page. Beacon dimensions are 1.6 inches (length) by 1.1 inches (width) by 0.2 inches (height).

Multimedia Appendixes

Baseline survey for healthcare personnel.
URL: http://asset.jmir.pub/assets/3ea75c50e447185418e55d19cf5035c7.pdf

Daily survey for healthcare personnel.
URL: http://asset.jmir.pub/assets/3dbf7bf17ed33da6715ae009b83c2606.pdf

Biweekly survey for healthcare personnel.
URL: http://asset.jmir.pub/assets/f352cc87572a27b5ad4e86d372018308.pdf

Biweekly survey for healthcare personnel (weeks 12, 24, and 36 only).
URL: http://asset.jmir.pub/assets/f21761aac5e8a224ed8a9583350a611d.pdf

Instructions for participant self-collection of nasal epithelial lining fluid (NELF) samples.
URL: http://asset.jmir.pub/assets/795161e744893dc95d9fc0c174554460.png

Baseline survey for household participants.
URL: http://asset.jmir.pub/assets/3cc6134ff83eee7bb267216f41dfba32.pdf

Weekly survey for household participants.
URL: http://asset.jmir.pub/assets/bf54f2438b1c354265d4e5586cb86d3d.pdf

Day 21 survey for household participants.
URL: http://asset.jmir.pub/assets/c2db7cfd0f3fd30c138ed6842527aa54.pdf

COVID HCP Study Laboratory Protocol.
URL: http://asset.jmir.pub/assets/c9df50e680a1c69762b30222ccc102cc.pdf