

COVID Evaluation of Risk for Emergency Departments (COVERED) Project
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1.0 Background

Rapidly spreading infectious diseases with community transmission put healthcare personnel at risk because patients at the early stage of illness may be difficult to identify, personal protective equipment may not be readily available, and specific modes of transmission may not be well understood. On March 11, 2020, the World Health Organization (WHO) declared COVID-19 a worldwide pandemic, involving at least 114 countries resulting in more than 4,000 deaths. Within 1 month, the worldwide death toll had surpassed 108,000.

In health systems affected early in the pandemic, healthcare personnel (HCPs) were a particularly high-risk group for acquiring the disease, presumably due to workplace exposure. Over one-third of those infected in a COVID-19 case-series in Wuhan, China and 9% of the total cases in Italy were HCP.^{1,2} These findings parallel data from the 2003 SARS-1 and MERS outbreaks, both of which documented HCP transmission.^{3,4}

SARS-CoV-2, the causative agent in COVID-19 infection, is thought to spread primarily through close personal contact and respiratory droplets. In the setting of emergency department (ED) care, additional transmission risk exists due to lack of knowledge of which patients are COVID-infected, unexpected arrival of critically ill patients, and the need to regularly perform life-saving procedures such as endotracheal intubation. Endotracheal intubation was associated with substantially increased risk for infection of HCW during the SARS epidemic, presumably due to aerosolization of virus, and is considered a high-risk event for transmission of COVID-19. Intubation alternatives such as noninvasive positive pressure ventilation and high-flow nasal cannula have also raised safety concerns. As the COVID-19 pandemic spreads throughout the U.S., EDs have been stretched to capacity, and the number of COVID-19 patients with acute respiratory failure requiring endotracheal intubation has been increasing exponentially.

Emergency providers are critically needed to respond to the COVID-19 pandemic, so it is essential to maintain their health and ability to work. The goals of the **COVERED** project are to assess the burden and associated risk factors among HCP for COVID-19 acquisition and identify means to prevent transmission to HCPs in emergency care, with the overall objective to inform response activities for maintaining the emergency care community during the COVID-19 and future pandemics.

2.0 Objectives

The purposes of this project are to:

- 2.1. Estimate the attributable risk of occupational acquisition of COVID-19 infection during emergency care for SARS-CoV-2-positive patients;
 - 2.1.1. Among physicians who perform endotracheal intubation in the ED and other aerosol-generating procedures,
 - 2.1.2. Among physicians performing non-intubation care in the ED,
 - 2.1.3. Among emergency department nurses (stratified by involvement in aerosol-generating procedures), and

- 2.1.4. Among family members of emergency department HCPs (relative to population prevalence);
- 2.2. Identify patient-, provider-, facility- and procedure-based risk factors associated with SARS-CoV-2 transmission during endotracheal intubation;
- 2.3. Estimate the overall burden of COVID-19 infections occurring among ED HCPs in a cohort of EDs (measured from facility-level data in infections-per-hour of patient care stratified by physician, nurse, and non-clinical staff);
- 2.4. Determine the prevalence of asymptomatic and symptomatic COVID-19 illness and viral shedding in ED HCPs; and
- 2.5. Describe current strategies of airway management and personal protective equipment (PPE) use in COVID-19 patients during the 2020 pandemic.
- 2.6. Describe return to work practices among HCPs with COVID-19 infection or seroconversion during the study period.

3.0 Project Design

This project is a multicenter observational enrolled-cohort surveillance conducted in high-volume centers treating COVID-19 patients over a 12-week period. Sites will be recruited from the following two national ED-based research networks and additional high-volume sites with appropriate infrastructure:

- 1) **EMERGENCY IDNet** – This CDC-funded 12-site ED-based emerging infectious disease network was created for surveillance and research of emerging infectious diseases (PI: David Talan, MD); and
- 2) **National Emergency Airway Registry (NEAR)** – This 26-site network is the largest ED-based research network focused on a multicenter observational airway management studies (PI: Calvin Brown, MD).

Participating sites will enroll a population of HCPs (physicians, nurses, and non-clinical staff) working in EDs likely to care for patients with COVID-19. Providers will participate in voluntary surveillance activities with prospectively collected data on endotracheal intubations and other aerosol-generating procedures (patient- and procedure-level data), other unprotected high-risk exposure events, SARS-CoV-2 serology tests, and viral PCR from self-administered nasal swabs. Non-clinical staff will serve as the control group to capture the risk of community transmission and transmission between HCPs (separate from patient exposure) in the work environment. These HCPs will be followed for an estimated 3 months during the study period to evaluate serologic and PCR evidence of SARS-CoV-2 exposure and/or clinical symptoms of COVID-19 infection.

4.1 Inclusion Criteria

Three groups of ED HCPs will be recruited:

- 1) physicians
- 2) nurses
- 3) non-clinical ED staff who have no clinical patient contact with COVID-19 patients.

For the purposes of calculating attributable risk, four cohorts will be defined:

- 1) **Aerosol-Exposed Physician Cohort** – Emergency physicians will be included in the cohort if they have intubated COVID-19 patients (defined as a confirmed positive SARS-CoV-2 PCR test either

within the 14 days before or 2 days after intubation) during the study period. Aerosol-exposed physicians typically are senior residents and attending emergency physicians;

- 2) **Non-aerosol-Exposed Physician Cohort** – Emergency physicians who have not intubated COVID-19 patients either because they did not intubate or because none of their patients were found to be COVID-infected during the study period. For the purpose of analysis, physicians may cross over between groups based on the patients that they treat during the surveillance period. This group would typically include junior residents and some attending emergency physicians.
- 3) **Nurse Cohort** – Emergency department nurses who are treating patients in the ED will be included in this cohort. Specific information on exposures (participating in intubation, management of critically ill COVID patients) will be collected to measure risk.
- 4) **Non-Clinical Exposure Cohort** - Surveillance site ED employees who do not participate in endotracheal intubation procedures or direct patient care will be included. Non-clinical exposure patients include unit clerks, social workers, scribes, and case managers.

All cohorts are at risk of COVID-19 acquisition from other HCPs and community contacts.

4.2 Exclusion Criteria

- 1) HCPs unable to complete surveillance follow-up visits (e.g., temporary HCPs);
- 2) HCPs who have previously been infected with COVID-19; and
- 3) HCPs who decline to provide informed consent.

HCPs should follow their local institutional guidance on the use of PPE for COVID-19 protection.

4.3. Time of Enrollment

Participants will be enrolled from each site at the beginning of the surveillance period. All HCPs will provide electronic informed consent. Surveillance procedures will start immediately. The 12-week surveillance period will be divided into 12 one-week periods, and participant surveys will be completed weekly. Serology will be measured every 2 weeks, and seroconversion will be assumed to be affected by events in the preceding two 1-week periods (since seroconversion is anticipated to occur within 7 days after exposure). Sites will collect data for 14 weeks to account for staggered initial enrollment and to ensure complete data for the entire 12 weeks for each project participant.

For each surveillance period, physicians will be classified as aerosol-exposed or non-aerosol exposed, and aerosol-exposed physicians will record a count of aerosol-generating procedures for dose-response analysis. All participating nurses will be included, and weekly data on their exposure to aerosol-generating procedures will be collected as an exposure. Data from all participants will be used in the final analysis, and data will accrue through the entire epidemic period.

4.4. Informed Consent

Participation in the surveillance is strictly voluntary. All HCPs who are eligible for participation will provide electronic informed consent to participate. This activity is consistent with non-research public health surveillance (by determination of the CDC and institutional review boards at the University of Iowa and Olive View-UCLA).

All participant and patient protected health information will be maintained in a confidential, password-protected secure electronic form. The risks to participant HCPs are minimal and include 1) the time required to complete surveys, 2) pain and discomfort associated with needlesticks and self-administered nasal swabs for serial COVID-19 serology testing and screening for viral shedding, and 3) inadvertent release of protected health care information, which will be kept secure and will only be reported in aggregate.

The surveillance will require project coordinators to collect surveys from participants (electronically) and phlebotomists to collect blood samples. The surveillance poses no more than minimal risk of COVID-19 exposure, because all surveys will be conducted remotely, and blood will only be drawn from patients who are asymptomatic by trained phlebotomists. Any participant diagnosed with active COVID-19 infection will not have any more in-person visits with project staff or blood or nasal specimen collection (although ongoing data collection will occur electronically).

4.5. Project Procedures

All participants will complete the following study procedures:

1. At enrollment – Baseline survey with serology (IgG) and self-collected nasal swab will be obtained.
2. Every week – A survey (PPE use, symptom log) will be collected.
3. Every 2 weeks – Serology (IgG) and nasal swab will be obtained.
4. Intubation – For every intubation or other aerosol-generating procedure (CPR, etc.) performed by the provider, a case report form will be completed (within 24 hours) to collect patient-specific and procedure-specific data elements. Data on cardiac arrest patients will also be captured on the same form (even if patients are intubated prior to ED arrival).
5. Site weekly survey – The total number of HCPs working in an ED who have been diagnosed with COVID-19, along with total COVID-19 patient volume will be reported from local hospital epidemiology records weekly. Also, total hours worked will be collected in each of the employee groups to calculate a rate of infections/1000 hours worked. Additional facility-level variables (PPE supplies, etc.) will be collected in this survey.
6. COVID-19 infection – Participants who contract COVID-19 during the study period will continue to complete weekly surveys but will not continue with blood draws and nasal swabs.

Surveys - The baseline survey will collect information about participant past COVID-19 exposures, COVID-19 testing and diagnosis (to verify inclusion), recent symptoms, comorbidities, and provider experience, usual PPE practices, and intubation approach. Follow-up surveys will collect new symptoms and COVID-19 testing, and will also collect information about household COVID-19 infections. Project coordinators will complete weekly surveys to record changes in ED infection control practices, number of ED cases, and stratified counts of HCP infections at the surveillance site. Project coordinators will monitor all intubations and cardiac arrests and will survey HCPs within 24 hours of these events for specific patient or event-related data. Study assistants will also review medical records of all intubated patients to confirm COVID infection status.

All surveys can be completed outside clinical service, so study participation should not interfere with clinical care.

Serology and nasal swab testing - Testing for serum IgG and self-administered nasal swabs for PCR will be done serially to determine baseline and subsequent COVID-19 infection status. Seroconversion with negative to positive serology will define a new infection (participants positive at the beginning of the surveillance period will be excluded). Combined with information collected by the participant surveys and self-administered nasal swab PCR testing, the rate of asymptomatic infection will be determined. All samples will be stored at sites and mailed to the central laboratory labeled with the participant ID, the date collected, and the sample number.

Blood draws will be performed by phlebotomists at local sites and will be sent to the central study laboratory using standard shipping practices up to twice weekly (in most cases, once weekly will suffice). Self-administered nasal swabs will be collected at the time of each blood draw for PCR testing. Laboratory specimens will be deidentified prior to shipping and will be accompanied by standard documentation and labeling. Serology results will be reported in 1-5 days from receipt of specimens back to the Data Coordinating Center, who will distribute test results to all participants.

Any participant who is found to seroconvert or has a positive nasal swab PCR will be notified immediately by an appointed site team member and advised to get evaluation by local employee health and public health authorities for screening and return to work determination according to current public health guidelines.

COVID-19 testing - Consistent with standard care and institutional policies, if a participant develops fever, respiratory or other symptoms suggestive of COVID-19 infection, they will be referred for COVID-19 evaluation and testing. Participant surveys will capture newly diagnosed COVID-19 infection, and all test results will be collected.

Any patient with COVID-19 symptoms or with known active infection will not have any study visits during the period of symptoms. Any participant who seroconverts or has a positive nasal swab PCR test will not have any subsequent testing performed.

Week	0	1	2	3	4	5	6	7	8	9	10	11	12
Baseline Survey ¹	X												
Serology (Blood) and Nasal Swab	X		X		X		X		X		X		X
Weekly Survey ¹		X	X	X	X	X	X	X	X	X	X	X	X
Facility-level Data and Cases ²	X	X	X	X	X	X	X	X	X	X	X	X	X
Intubations and Cardiac arrests	Event-Level Form												

Table 1. Timeline of Study Procedures. ¹Completed by participant, ²Completed by project coordinator

The results of all collected serology and nasal swab PCR data will be shared with the participant through a personalized REDCap portal. Project staff will communicate with participants by e-mail, text message, and telephone as required.

All participants will be reimbursed for participation including completing multiple surveys and laboratory blood draws and nasal swabs. Shortly after enrollment, participants will receive a Visa debit card by mail. The Data Coordinating Center will manage reimbursements to participants for each activity (e.g., for each blood draw, nasal swab, survey) completed by loading additional value on the debit card weekly.

4.0 Site Selection

Sites will be selected from the *EMERGENCY* IDNet sites, NEAR sites, and other high-volume centers with active local COVID-19 activity. Local activity will be monitored using standard public health reporting (from reporting collated by CDC Science Office) and facility-specific admissions (collected from weekly surveys at all sites). Sites may change throughout the project to capture activity in a large cohort of HCPs, even as the epidemic moves through U.S. hospitals, and start and stop dates may be flexible to reflect local COVID-19 activity.

5.0 Human Subjects

This project has been determined by the Centers for Disease Control and Prevention (CDC), the University of Iowa IRB, and the Olive View-UCLA IRB not to be human subjects research because it constitutes public health surveillance activities. All participant data will be kept confidential using password-protected research servers accessible only to the study team. No testing results or survey data will be shared with employers or public health authorities. Data from individual sites will not be identified, and all data will be reported in aggregate. Each site IRB will make an independent determination about whether study activities constitute human subjects research, and data use agreements will be executed with the Data Coordinating Center as required by individual sites.

6.0 Data Management

All forms will be completed electronically using a REDCap case report form developed and managed centrally at the Data Coordinating Center (University of Iowa). Informed consent documents will be completed electronically and maintained within the REDCap database. Surveys links for participants will be sent via email and/or text message (weekly and after qualifying events). Each site PI and coordinator will have access to site-specific data and will conduct site-level completion monitoring and data validation. Patient-level data will be abstracted by the project coordinator.

7.0 Statistical Analysis Plan

Two strategies of modeling will be used to estimate the effect of endotracheal intubation on seroconversion risk. The **event-level analysis** will use a data set with one record for every COVID-19 intubation, and the outcome will be the seroconversion between 1 and 14 days. The **epoch-level analysis** will use a longitudinal data set with time-dependent covariates with one record for each time epoch, and the exposures for the prior 2 weeks will be independent variables in the model. Epoch-level analysis will include physician, nurse, and non-clinical exposure cohorts. All models will be generated using a hierarchical structure (provider and facility) with Generalized Linear Mixed Model to account for clustering, and analysis for attributable risk will be conducted using survival analysis with time-dependent covariates.

- 6.1.1. **Estimate attributable risk** – Attributable risk is calculated as the difference in disease incidence in the exposed and the unexposed. We will build an extended Cox proportional hazards model (survival analysis) with time-dependent covariates to account for baseline risk, evolving practice over the project period, and provider-level variables. We will include a 3-level categorical variable for provider type (Physician, Nurse, and Non-Clinical Staff), and we will include a separate variable for the count of aerosol-generating procedures (within each 2-week period, for measure of dose-response relationship). The variables of interest

- will be the provider-type variable and the count of aerosol-generating procedures during the lagging 2 weeks, which will provide the hazard ratio for the risk of clinical care vs. non-clinical exposure (reference group) and the risk of endotracheal intubation (and other aerosol-generating procedures) vs. clinical care alone. From this analysis, we will calculate an adjusted attributable risk.
- 6.1.2. **Identify patient-, provider-, and procedure-based risk factors associated with SARS-CoV-2 transmission** – Specific potentially modifiable procedure-related factors associated with SARS-CoV-2 transmission will be identified using the event-level analysis. For each case, the outcome will be whether seroconversion occurred within the subsequent 2 weeks. Patient-, provider-, facility-, and procedure-level factors will be included as predictors in the model to determine the relative contribution of these factors to the probability of seroconversion. We will use a principal components analysis to identify the factors most strongly associated with that risk.
 - 6.1.3. **Identify the extent of subclinical COVID-19 illness in HCPs** – From the weekly symptom surveys, we will identify the proportion of HCPs who developed COVID-19 without symptoms (based on seroconversion without symptoms). This will be reported as a simple prevalence.
 - 6.1.4. **Describe current strategies of airway management and PPE use in COVID-19 patients during the 2020 pandemic** – Report descriptive statistics (means, medians) for how airway management is performed in COVID-19 patients at various institutions during the 2020 epidemic.
 - 6.1.5. **Assess overall risk of HCP acquisition** – Weekly reports of the number of staff (by provider type) who have been newly infected with COVID-19, along with number of hours of coverage by provider type. This will allow an incidence per 100/hours worked to be calculated across all centers. This analysis will not be restricted to the enrolled cohort—it will be across all employees in participating EDs.
 - 6.1.6. **Risk of transmission to HCP family members** – Weekly reports will collect data on COVID-19 infections among family members. We will report descriptive analysis for family members, along with the timing of family member COVID-19 infections (e.g., before or after HCP seroconversion).

6.2. **Sample Size Estimation.** To estimate the power of our surveillance design, we simulated a series of data sets based on the following assumptions:

Baseline population infection risk during study period=1% (estimated at 0.6% based on CDC modeling) Attributable risk of 5% (based on MERS transmission with maximal precautions ⁴) Sites=20 hospitals Physician participants at each hospital=30 Standard deviation for variability in transmission risk between hospitals=3% Standard deviation for variability in transmission risk between individuals within a hospital=3% Probability of intubating COVID-19 patient during 2-week period=20% Alpha=5%

Table 2. Assumptions for power calculation simulation.

These assumptions were built into a simulation replicated 100 times to estimate the power to detect the 5% estimated risk difference. According to data on HCP infections in long-term care facilities, an estimated 20% infection proportion was observed.

Sensitivity analysis was used to measure the impact of changes in the assumption values, and this analysis is reflected in Figure 1.

Separate analysis was conducted by Bill Mower (UCLA) using an explicit estimation of correlation between intubators and by James Baggs (CDC) using survival analysis. Both cohorts estimated similar effect size with slightly more power using survival analysis. Because the simulation uses a clustered analysis with less power than the planned final analysis, we conservatively used these estimates.

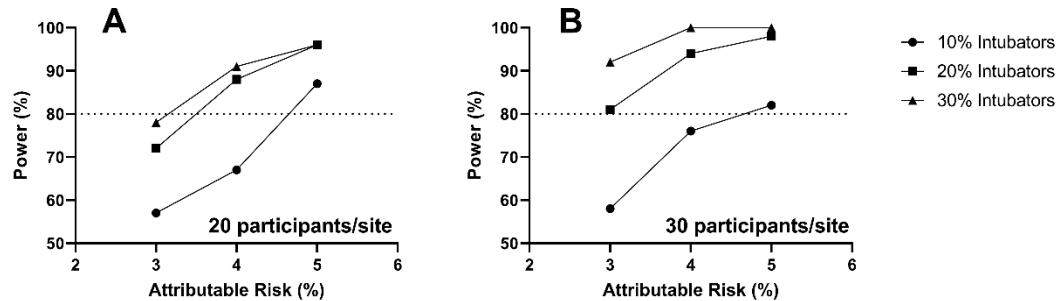


Figure 1. Sensitivity analysis for sample size estimation. Panel A shows the power analysis for 20 physicians/site and Panel B shows the power analysis for 30 physicians/site. The minimum detectable attributable risk is related to power. The 3 lines represent the proportion of total 2-week periods at a site in which a given study participant performs an aerosol-generating procedure.

Assuming 25% loss-to-follow-up, we plan to enroll 40 physicians, 20 nurses, and 20 nonclinical staff at each of 20 sites (1600 participants). All secondary analyses will have similar power. This simulation suggests that our **power is 94%** to detect a difference in COVID-19 acquisition of 4%.

References

1. Wang D, Hu B, Hu C, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus–Infected Pneumonia in Wuhan, China. *JAMA* 2020;323:1061-9.
2. Borghese L, Donato VD, Ruotolo N, Fiegenger J. Nearly 1 in 10 of Italy's infected are health care workers. *CNN* 2020 22 Mar.
3. Ofner-Agostini M, Gravel D, McDonald LC, et al. Cluster of cases of severe acute respiratory syndrome among Toronto healthcare workers after implementation of infection control precautions: a case series. *Infect Control Hosp Epidemiol* 2006;27:473-8.
4. Alraddadi BM, Watson JT, Almarashi A, et al. Risk Factors for Primary Middle East Respiratory Syndrome Coronavirus Illness in Humans, Saudi Arabia, 2014. *Emerg Infect Dis* 2016;22:49-55.