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STUDY PROTOCOL

Louisville Coronavirus Surveillance Program

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Abstract

An important feature of COVID-19, the disease produced by the new coronavirus SARS-CoV-2, is the high number of health care workers (HCWs) that acquire the disease. In an initial report of 138 patients hospitalized with COVID-19 pneumonia in China, 40 patients (29%) were HCWs. One reason why HCWs are at higher risk of acquiring COVID-19 is that some patients with COVID-19 are admitted to the hospital without the classical presentation and are therefore not tested for the disease early during hospitalization. Presently in the US, it is recommended to test for COVID-19 when physicians suspect the disease. This subjective approach may allow hospital transmission of COVID-19 from patients without the classical clinical presentation. The primary objective of this study is to establish a surveillance system for early identification of patients hospitalized with COVID-19 to allow for early implementation of infection control interventions in an attempt to prevent transmission of COVID-19 to HCWs and other hospitalized patients. We are proposing to test all patients who present to the emergency departments and/or are hospitalized with signs and symptoms of respiratory infection or gastrointestinal infection for SARS-CoV-2, regardless of clinical suspicion of COVID-19. Biological samples obtained from all patients having symptoms of respiratory or gastrointestinal infection will be tested using real-time reverse transcriptase-polymerase chain reaction (RT-PCR) for detection of SARS-CoV-2. Using a robotic instrument, the CMP laboratory will be able to test more than 500 samples a day. Data will be reported in real-time to participating hospitals for rapid implementation of infection control measures.

Introduction and Rationale

The reliability of the healthcare system is a critical component in the fight against new pandemics. To have an effective healthcare infrastructure, it is critical to have a healthy healthcare workforce. The healthcare workforce encompasses a wide range of professions and occupations who provide any type of healthcare service, such as physicians, nurses, surgeons, dentists, physical and behavior therapists, as well as allied health professionals such as respiratory therapists, phlebotomists, medical laboratory scientists, dieticians, and social workers.

An important feature of COVID-19, the disease produced by the new coronavirus SARS-CoV-2, is the high number of health care workers (HCWs) that acquire the disease. In an initial report of 138 patients hospitalized with COVID-19 pneumonia in China, 40 patients (29%) were HCWs.[1] One reason why HCWs are at higher risk of acquiring COVID-19 is because some patients with COVID-19 are admitted to the hospital without the classical presentation, and are therefore not tested for the disease early during hospitalization. Wang *et al*. reported one patient admitted to the surgical ward complaining of fever, abdominal pain, and diarrhea. This patient infected 10 HCWs from the surgical department.[1] The concern with the current surveillance system is that patients are tested only when clinicians suspect the disease. Patients are suspected to have COVID-19 when they present with a syndrome of respiratory infection associated with pneumonia or respiratory failure. Early manifestations of COVID-19 may include a syndrome of upper respiratory tract infection, a flu-like syndrome, or a gastrointestinal syndrome presenting with diarrhea (**Figure 1**).[2]

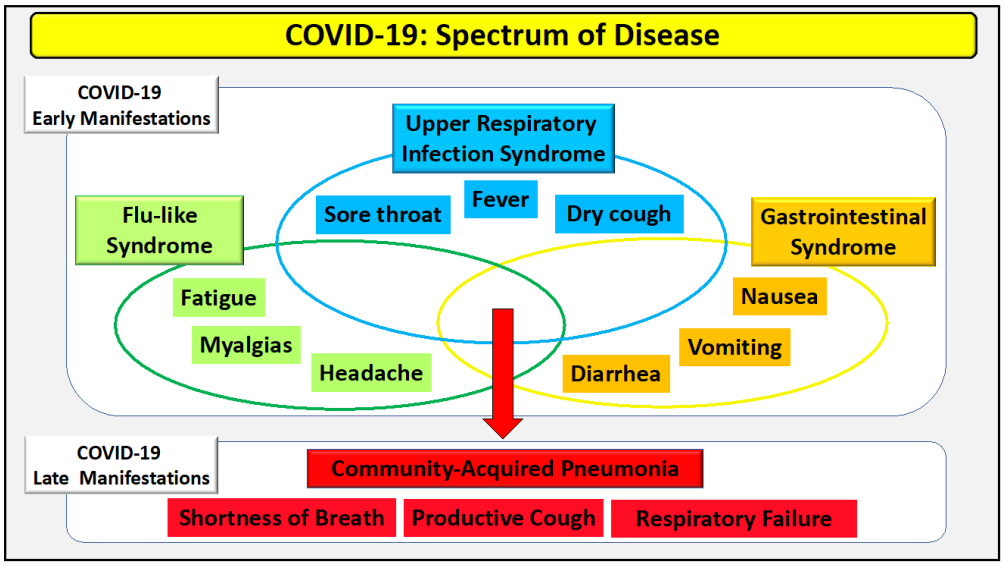

Figure 1. Spectrum of disease of patients with COVID-19 (adapted from reference 2).

In the Louisville Coronavirus Surveillance Program, we are proposing to remove the subjective nature of testing and instead test for SARS-CoV-2 all patients in the emergency department with signs and symptoms of respiratory infection or gastrointestinal infection, regardless of clinical suspicion of COVID-19. Some of these patients will be hospitalized and others will be discharged home. Some patients are hospitalized as a direct admission from ambulatory settings. These patients will be tested in the patient care area after they are hospitalized. We are proposing the implementation of this testing in all hospitals in the city of Louisville as part of a comprehensive SARS-CoV-2 surveillance program.

It is also important to address the concern that HCWs may be afraid to come to work where there is documented hospital transmission of COVID-19. By having an active surveillance system, it is reasonable to assume that this knowledge may serve to make HCWs feel safer than the unknown that is present without this level of comprehensive surveillance. Further, this organized approach may serve to minimize unnecessary use of hospital resources such as personal protective equipment (PPE) as part of incremental testing, as opposed to testing done through a standardized surveillance process.

The information gained through this surveillance system will be used to generate guidelines for real-time hospital and community education and response activities. Additionally, data obtained as part of this surveillance will be used to produce educational components for a wide range of audiences, including daily multimedia announcements that will keep the community up to date on local and reliable COVID-19 information. The lessons learned from this program will be immediately transferred to manuscript for submission to peer-reviewed publications with the goal of rapid dissemination of the knowledge gained from this project. The information will also be shared community-wide through select University of Louisville digital channels.

Objectives

Primary objectives

1. To establish a new surveillance system for early identification of hospitalized patients with COVID-19.
2. To prevent transmission of COVID-19 to health care workers and other hospitalized patients.

Secondary objectives

1. To strengthen existing systems of surveillance for COVID-19.
2. To better inform Public Health authorities of local COVID-19 activity.
3. To define areas of the community where surveillance activities should be increased.
4. To identify cases of COVID-19 from emergency departments among patients who may not be hospitalized.

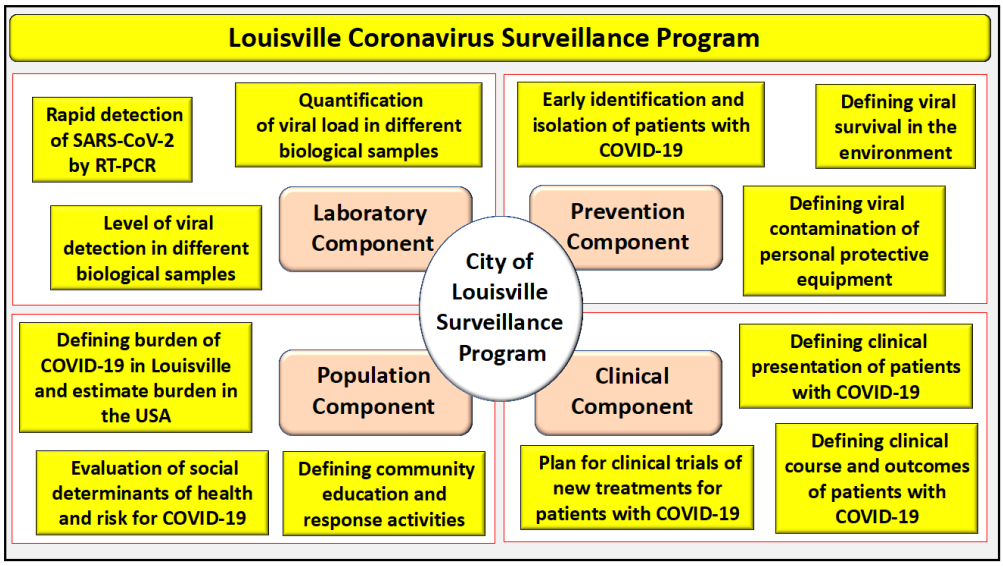

Figure 2. The four components of the program with the primary activities for each component.

5. To generate educational components and guidelines for real-time hospital and community education and response activities.

6. To rapidly disseminate the new knowledge gained by this project.

An overview of the different components of this project with the most relevant activities for each component is depicted in **Figure 2**.

Study Design

Program Overview

This proposal is a collaboration of 1) the Center of Excellence for Research in Infectious Diseases (CERID), University of Louisville, 2) the Center for Predictive Medicine for Biodefense and Emerging Infectious Diseases (CPM), University of Louisville, 3) all hospitals in the city of Louisville, and 4) the Louisville Metro Department of Public Health and Wellness. An overview of the program is depicted in **Figure 3**.

On February 12, 2020 the University of Louisville Regional Biocontainment Laboratory received an isolate of the SARS-CoV-2 from the CDC. Investigators from the CPM cultured the virus and started to work on the development of real-time polymerase chain reaction (RT-PCR).

Patients with signs and symptoms of respiratory or gastrointestinal infection seen in one of the ten emergency departments will be included in the surveillance process. Hospitalized patients directly admitted to the hospital will also be included. Samples will be collected as soon as possible and transferred to the CPM laboratory for testing. Three databases will be developed to store project data. Clinical and epidemiological data will be collected by the surveillance team and maintained in a REDCap database specifically designed for this purpose. Specimen collected will be retained in a biorepository for future testing and a REDCap database will be designed for this purpose. Data from the CPM laboratory will be collected and maintained in a REDCap database specifically designed for this purpose. All three of these REDCap databases will comprise the Comprehensive Surveillance Database for this COVID-19 surveillance program, and will be accessible in real-time with secure passwords to all participating institutions, public health authorities, and other stakeholders.

Program Advisory Board

An advisory board will be established with the following objectives: 1) To maintain open and consistent communication related to the original status of COVID-19 disease; 2) To provide feedback for improvement of the surveillance program; and 3) To support the dissemination of information. In addition to public health and other relevant stakeholders, the advisory board members may include representation from hospital emergency, infection control, nursing, medical staff, and administration departments. Project investigators and members of the advisory board will hold regular meetings to align the course of the project with the COVID-19 epidemic.

Preliminary Studies

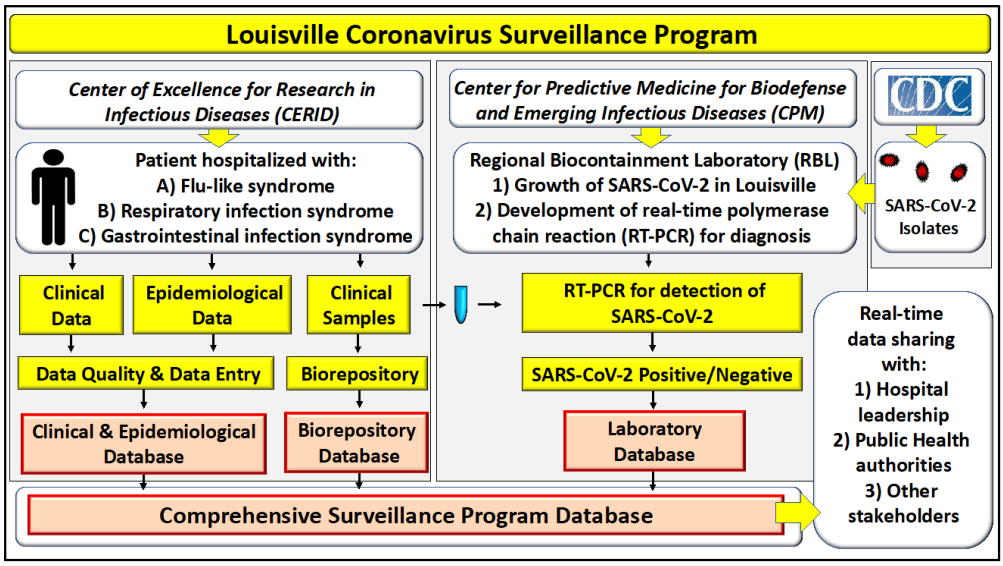

Figure 3. Overview of the Louisville Coronavirus Surveillance Program.

The two principal investigators, Drs. Julio Ramirez and Kenneth Palmer, have vast experience in development and implementation of these types of projects.

Dr. Ramirez is the Chief of the Division of Infectious Diseases and Director of the Center of Excellence for Research in Infectious Diseases (ceridlouisville.org). He has led multiple surveillance programs in the State of Kentucky, including the Severe Influenza Pneumonia Surveillance (SIPS) Project. SIPS was funded by the Department of Homeland Security.[3] He was also funded by the Centers for Disease Control and Prevention to study the role of oseltamivir in hospitalized patients with influenza in the city of Louisville. This was done in collaboration of CERID with all adult hospitals in Louisville.[4] More recently, Pfizer Pharmaceuticals sponsored CERID to perform a population-based study of all hospitalized adult patients in the city of Louisville to define the burden of community-acquired pneumonia. Data from this study was used to estimate burden of pneumonia in the United States.[5] The successes of these studies led to the selection of CERID as the North American Center of Excellence for Vaccine Epidemiology, funded by Pfizer. This is the first such center in the world, and recognizes the unique infrastructure and capabilities of UofL CERID (Center of Excellence announcement).

Dr. Kenneth Palmer is the Director of the Center for Predictive Medicine for Biodefense and Emerging Infectious Diseases (CPM), and Professor of Pharmacology and Toxicology. He was trained as a virologist at the University of Cape Town, and his research program has focused on development of biologic-based antivirals and vaccines. Q-Griffithsin (Q-GRFT) is a broad-spectrum antiviral protein that was discovered and developed in Dr. Palmer's laboratory. Q-GRFT has been formulated for rectal administration and Dr. Palmer leads an NIH-funded translational research program that is testing the product safety in a first-in-humans clinical trial for HIV-1 prevention.[6-8] Dr. Palmer has also worked as part of teams that have demonstrated Q-GRFT activity against a broad array of Coronaviruses, including SARS-CoV and MERS-CoV. Dr. Palmer is leading a team of researchers that are now working on developing in vitro and in vivo systems for assessing SARS-CoV-2/COVID-19 antiviral and vaccine strategies.

The CV of the two principal investigators are included in Appendices 2 and 3.

Laboratory Methods

Since one of the goals of this study is to define if SARS-CoV-2 is present in different biological samples, specimens regularly collected as part of standard of care clinical practice (e.g., respiratory, blood, stool, and urine specimen) will be obtained as they are available. The specimen will be transferred from the local hospital to the CERID Biorepository Laboratory for labeling and cataloging. Each specimen will be labeled with a Patient Sample ID to maintain privacy, while also allowing real-time reporting to a specific hospital. Specimen are transported from the CERID Biorepository Lab to the CPM Laboratory for testing.

The CPM laboratory will use the specimen for RNA extraction. This will involve use of two commercial RNA isolation platforms for performance assessment.

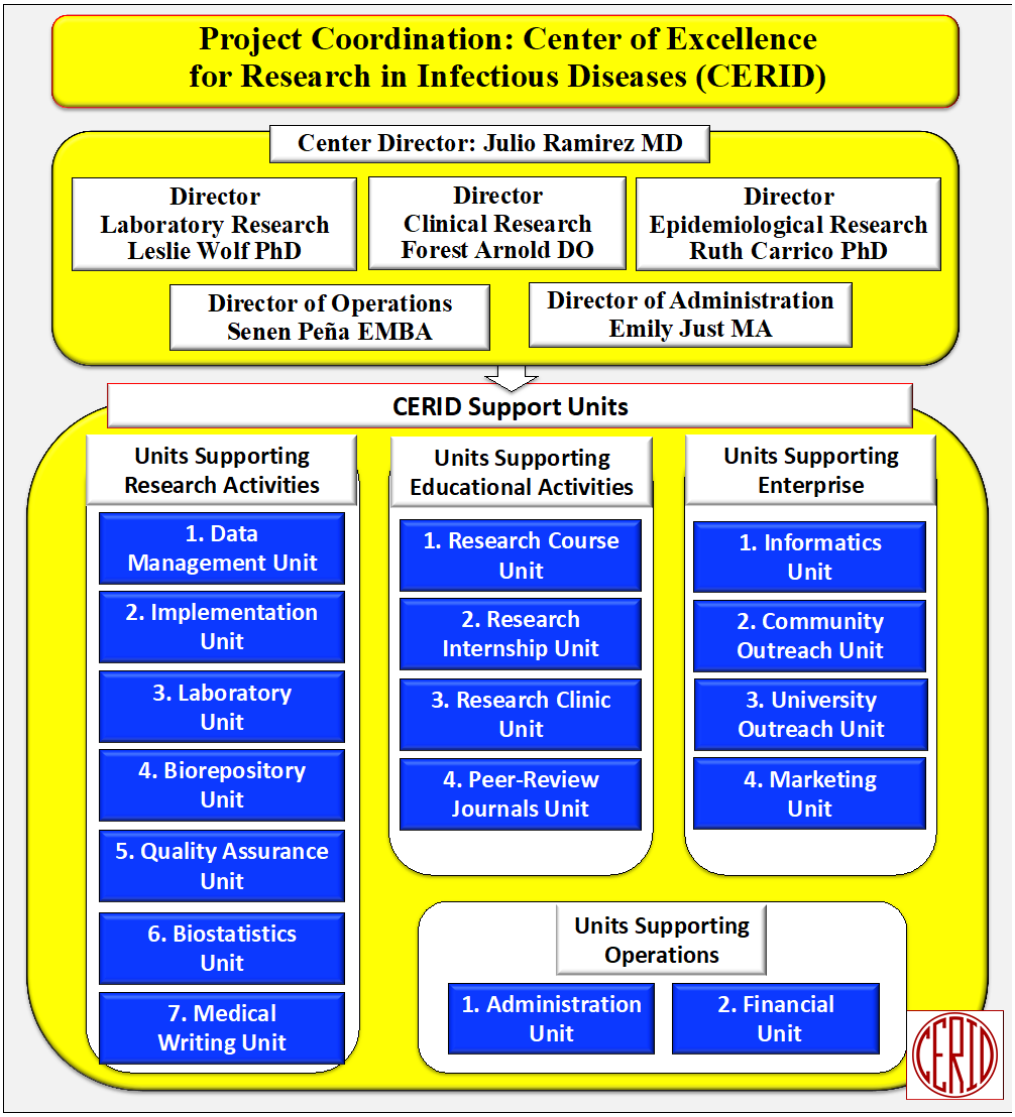

Figure 4. Structure of the project coordinating center.

CPM will also assess two different quantitative reverse transcriptase PCR platforms for SARS-CoV-2 detection. Once CPM has validated the test outcomes with spiked samples, they will chose a single RNA isolation platform and qRT-PCR platform for the surveillance project.

CPM will collect qPCR data, provide an analytical report, and enter the data into the laboratory database.

Program Coordinating Center

The study will be coordinated by Center of Excellence for Research in Infectious Diseases (CERID). The current structure of CERID is depicted in **Figure 4**.

The activities related to this project for each of the CERID units are as follows:

Data Management Unit: generate the data collection form and the three REDCap databases, clinical, epidemiological, and laboratory, for this project.

Implementation Unit: responsible for all surveillance activities, transport of the specimen to the CPM laboratory, data collection, and data entry into the REDCap databases.

Laboratory Unit: catalog all clinical samples and coordinate with the CPM laboratory for testing.

Biorepository Unit: will be responsible for maintaining all specimen for future testing and entering data into the biorepository database.

Quality Assurance Unit: will be responsible for monitoring data quality and ongoing process improvement.

Biostatistics Unit: will be responsible for periodic and real-time analysis of clinical, epidemiological, and laboratory data.

Medical Writing Unit: will support the generation of manuscripts.

Peer-Review Journals Unit will facilitate rapid publication of new knowledge.

Informatics Unit: will interface the three databases and generate real-time reports with de-identified information about local COVID-19 activity.

Community Outreach Unit: will be responsible for maintaining open lines of communication with community leaders and coordinating activities of the Advisory Board.

University Outreach Unit: will be responsible for maintaining open lines of communication with UofL leaders and will work with the Community Outreach Unit to coordinate the activities of the Advisory Board.

Marketing Unit: will collaborate with investigators to develop education and response communications.

Protection of Human Participants

All patient information will be entered into REDCap databases, which are HIPAA-compliant. All surveillance information is considered protected health information and standard data safety processes will be followed.

Letters of Support

Please see Appendix 4.

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Conflict of Interest: All authors declared no conflict of interest in relation to the main objective of this work.

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(11):1061-9. doi: 10.1001/jama.2020.1585. PMID: 32031570.

2. Ramirez JA, Carrico R, Beavin L, et al. Community-acquired pneumonia due to endemic human coronaviruses compared to 2019 novel coronavirus: A review. Univ Louisville J Respir Infect **2020**; 4(1):Article 2. doi: 10.18297/jri/vol4/iss1/3.

3. Wiemken T, Peyrani P, Bryant K, et al. Incidence of respiratory viruses in patients with community-acquired pneumonia admitted to the intensive care unit: Results from the Severe Influenza Pneumonia Surveillance (SIPS) project. Eur J Clin Microbiol Infect Dis **2013**; 32(5):705-10. doi: 10.1007/s10096-012-1802-8. PMID: 23274861.

4. Ramirez J, Peyrani P, Wiemken T, Chaves SS, Fry AM. A randomized study evaluating the effectiveness of oseltamivir initiated at the time of hospital admission in adults hospitalized with influenza-associated lower respiratory tract infections. Clin Infect Dis **2018**; 67(5):736-42. doi: 10.1093/cid/ciy163. PMID: 29659754.

5. Ramirez JA, Wiemken TL, Peyrani P, et al. Adults hospitalized with pneumonia in the United States: Incidence, epidemiology, and mortality. Clin Infect Dis **2017**; 65(11):1806-12. doi: 10.1093/cid/cix647. PMID: 29020164.

6. O'Keefe BR, Vojdani F, Buffa V, et al. Scaleable manufacture of HIV-1 entry inhibitor griffithsin and validation of its safety and efficacy as a topical microbicide component. Proc Natl Acad Sci U S A **2009**; 106(15):6099-104. doi: 10.1073/pnas.0901506106. PMID: 19332801.

7. Férir G, Palmer KE, Schols D. Synergistic activity profile of griffithsin in combination with tenofovir, maraviroc and enfuvirtide against HIV-1 clade C. Virology **2011**; 417(2):253-8. doi: 10.1016/j.virol.2011.07.004. PMID: 21802104.

8. Kouokam JC, Huskens D, Schols D, et al. Investigation of griffithsin's interactions with human cells confirms its outstanding safety and efficacy profile as a microbicide candidate. PLoS One **2011**; 6(8):e22635. doi: 10.1371/journal.pone.0022635. PMID: 21829638.

Appendices

Available upon request.

Appendix 1: List of sub-investigators

Appendix 2: Ramirez CV

Appendix 3: Palmer CV

Appendix 4: Letters of support

Appendix 5: Proposal budget