Protocol

This trial protocol has been provided by the authors to give readers additional information about their work.

Protocol for: Son MBF, Murray N, Friedman K, et al. Multisystem inflammatory syndrome in children — initial therapy and outcomes. N Engl J Med. DOI: 10.1056/NEJMoa2102605

This supplement contains the following items:

1. Original protocol, final protocol, summary of changes.
2. Original statistical analysis plan, final statistical analysis plan, summary of changes.

OVERCOMING COVID-19

PUBLIC HEALTH SURVEILLANCE REGISTRY PROTOCOL

This protocol is designed to facilitate tracking of severe acute COVID-19 complications in infants, children, adolescents and young adults including multisystem inflammatory syndrome in children (MIS-C)

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- Original pandemic preparedness protocol IRB approval date 9/9/2013
- Protocol implemented 4/2/2020 for COVID-19 pandemic at the request of the CDC
- Protocol last updated 7/22/2020

CONTENTS

I. PREFACE AND PROTOCOL HISTORY

This protocol was designed in July 2013, when the Pediatric Acute Lung Injury and Sepsis Investigator's (PALISI) Pediatric Intensive Care Influenza and Emerging Pathogens (PICFLU-EP) Subgroup (http://picflu.org), comprised of investigators at 38 pediatric sites, was funded by the CDC to be prepared to conduct real-time surveillance in the event of a pandemic. The original (and IRB) protocol is titled "Influenza and Other Emerging Respiratory Pathogens Surveillance Registry" with the single IRB established at Boston Children's Hospital. The protocol was designed to cover a broad range of potential pathogens, and required a public health authority to declare an emergency before it data collection could be initiated.

In April 2020, the U.S. Centers for Disease Control and Prevention requested that the protocol be implemented to track hospitalizations in children and young adults caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) related disease coronavirus disease 2019 (COVID-19). The *Overcoming COVID-19 Investigators* included the original 38 PICFLU-EP pandemic preparedness sites, and additional sites were recruited based on regional representation and disease burden (https://overcomecovid.org). On May 5, 2020 *Overcoming COVID-19* surveillance site clinician investigators were told to report cases of MIS-C meeting a preliminary case definition provided by the CDC.

HISTORY OF PROTOCOL MODIFICATIONS

- Original Protocol IRB Approval Date: 9/9/2013
- Revision 4/2/2020: no longer need IRB approval to make case report form changes
- Revision 4/21/2020: expand data collection to all hospitalized patients (from ICU and high acuity unit patients only) and update case definition to SARS-CoV-2 as the pathogen of focus and COVID-19-related complications as the disease
- Revision 6/8/2020: Clarification of MIS-C criteria for data capture before and after June 1, 2020 as SARS-CoV-2 PCR and antibody testing was not widely available May 31st, 2020 and earlier. Alignment with CDC criteria. Updated length of follow up to 90 days post hospital admission with capture of outpatient data including hospital and clinic visits and diagnostic studies.
- Revision 7/22/2020: 1) Addition of outpatient controls for MIS-C that test SARS-CoV-2 positive via PCR and meet criteria for age category matching a hospitalized MIS-C case; 2) Collection of additional types of data including data available from the laboratory related to the patient's clinical test (e.g. cycle threshold values from PCR testing) and results of all clinical tests or samples sent for clinical or research analyses, data from clinical surveys, and deidentified clinical images (e.g. MRI, echocardiogram); and 3) Collection of deidentified respiratory sera or plasma samples that are leftover from clinical testing.

II. BACKGROUND AND RATIONALE

The ease of international travel and the rapidly growing human population increase the risk that novel strains of microbes will be transmitted globally and lead to widespread pandemics. Between 2002 and 2003, Severe Acute Respiratory Syndrome coronavirus (SARS-CoV) infected 8,096 individuals and caused 774 deaths worldwide.[1] Quarantining and preventing air travel of infected individuals was paramount in stopping the spread of SARS-CoV. A successful national surveillance program might have alerted the index country earlier when the first SARS-CoV cluster of cases occurred in late 2002.[2] Expansion of the usual pathogen reporting of healthcare institutions to local and regional public health agencies is unlikely to provide an accurate picture of an outbreak for many reasons. Provision of consistent high-quality real-time data that can inform decision-making at a national level requires creation of an infrastructure that includes 1) use of highly structured case report forms designed to answer specific clinical and resource-related questions; 2) staff trained in case ascertainment, data abstraction and data entry; 3) a data-management system that includes a web-based data portal linked to a back-end system that can provide real-time data analysis and reporting; and 4) evaluation of how representative the sites contributing data are of the underlying population and region of interest. The infrastructure for such a real-time surveillance registry requires time and preparation to develop[3], which are in short supply during a rapidly spreading outbreak of influenza or other pathogens causing severe respiratory disease.

A recent example supporting the need for having a surveillance registry arose in 2009 when a novel strain of influenza A (2009 H1N1) was identified. First detected as causing severe illness in April of that year, 2009 H1N1 quickly spread worldwide, leading the World Health Organization (WHO) to raise the influenza alert to pandemic level by June of that year.[4] Although countries scrambled to collect, analyze and report data, it took months for many to create a data collection infrastructure which resulted in much of the case ascertainment and data collection being retrospective. The pattern of incidence, morbidity, and mortality for 2009 H1N1 differed from the usual pattern for seasonal influenza, with younger individuals disproportionately affected by 2009 H1N1. Unfortunately, identification of the effect of viral outbreaks on infants, children, and adolescents is complicated by healthcare referral patterns that differ distinctly from those for adult patients. Much of what was learned about the effect of 2009 H1N1 in children was not reported until after the pandemic had ended. Countries

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[1] Summary of probable SARS cases with onset of illness from 1 November 2002 to 31 July 2003. Global Alert and Response, WHO. Available at: http://www.who.int/csr/sars/country/table2004_04_21/en/index.html Accessed July 1, 2013

[2] Heymann DL & Rodier G. Global Surveillance, National Surveillance, and SARS. Emerg Infect Dis. 2004 February; 10(2): 173–175.

[3] Fowler RA, Webb SA, Rowan KM, Sprung CL, Thompson BT, Randolph AG, Jouvet P, Lapinsky S, Rubinson L, Rello J, Cobb JP, Rice TW, Uyeki T, Marshall JC. Early observational research and registries during the 2009-2010 influenza A pandemic. *Crit Care Med*. 2010; 38:e120-e132.

[4] Centers for Disease Control and Prevention. H1N1 Flu Questions and Answers: Novel H1N1 Flu (Swine Flu and You). Available at: http://www.cdc.gov/h1n1/qa.com. Accessed August 27, 2009.

reported different mortality rates and different predictors of mortality in pediatric and adult populations.

It is well-known that children play an important role in the dissemination of influenza virus,[5,6,7] through contact with other children in settings such as school and daycare. Furthermore, seasonal influenza causes considerable illness in children, especially those less than 2 years of age.[8] Despite vaccination efforts, influenza infection is still the most common cause of pediatric outpatient visits and inpatient hospitalizations during the winter months.[9] To assess the burden of influenza infection among children and estimate the protective benefit of vaccination, it is important to consider the role of co-circulating non-influenza pathogens as an additional source of acute respiratory illness and as a source of complications due to co-infection. The potential effect of bacterial co-infection among severely ill patients with influenza is of particular interest and has risen dramatically in the past five years.[10] Indeed, U.S. children with influenza-bacterial co-infection have a significantly higher case fatality rate, especially when co-infected with *Staphylococcus aureus*.[11] It is essential to accurately track co-circulating pathogens during any epidemic so that healthcare professionals can tailor antimicrobial recommendations aimed at preventing morbidity and mortality.

Ongoing microbial threats are the novel influenza A H7N9 virus and Middle East Respiratory Syndrome Coronavirus (MERS-CoV). Prior to 2013, transmission of influenza A viruses with the H7 subtype was considered rare in mammals and transmission of N9 viruses in humans had not been documented.[12] However, genetic reassortment led to this novel influenza strain that infected 132 people, and led to 32 known deaths by May 29, 2013.[13] Though it is unlikely that all mild cases were reported, this fatality rate of 24% in identified cases is very concerning. A global pandemic of influenza with a high fatality rate like H7N9 would be devastating. As a result of the 2009 H1N1 pandemic, influenza vaccine development and methods for rapidly assessing vaccine efficacy have improved. Investigational intravenous influenza antiviral medication is available for treating severe

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[5] Koliou, M, Soteriades, ES, Toumasi, MM, et al. Epidemiological and clinical characteristics of Influenza A (H1N1)v infection in children: the first 45 cases in Cyprus, June-August 2009. *Eurosurveillance* 2009; 14(33):pii=19312.

[6] Fox JP, et al. *Am J Epidemiol*. 1982 Aug;116(2):228-42. PubMed PMID: 7114034.

[7] Monto AS, et al. *Am J Epidemiol*. 1975 Dec;102(6):553-63. PubMed PMID: 1202957.

[8] Centers for Disease Control and Prevention. H1N1 Flu: Interim Guide for Clinicians on the Prevention and Treatment of Novel Influenza A (H1N1) Influenza Virus Infection in Infants and Children. Available at: http://www.cdc.gov/h1n1/childrentreatment.htm. Accessed September 3, 2009.

[9] Poehling, KA, Edwards, KM, Weinberg, GA, et al. The Underrecognized Burden of Influenza in Young Children. *N Engl J Med* 2006; 355:31-40.

[10] Finelli L, Fiore A, Dhara R, Brammer L, Shay DK, Kamimoto L, Fry A, Hageman J, Gorwitz R, Bresee J, Uyeki T. Influenza-associated pediatric mortality in the United States: increase of Staphylococcus aureus coinfection. *Pediatrics.* 2008 Oct;122(4):805-11..

[11] Reed C, Kallen AJ, Patton M, Arnold KE, Farley MM, Hageman J, Finelli L. Infection with community-onset Staphylococcus aureus and influenza virus in hospitalized children. *Pediatr Infect Dis J*. 2009 Jul;28(7):572-6.

[12] Gao R, Cao B, Hu Y, et al. Human infection with a novel avian-origin influenza A (H7N9) virus. *N Engl J Med*. 2013;368(20):1888-1897.

[13] Overview of the emergence and characteristics of the avian influenza A(H7N9) virus. WHO. May 31, 2013. Available at: http://www.who.int/influenza/human_animal_interface/influenza_h7n9/WHO_H7N9_review_31May13.pdf Accessed July 1, 2013.

cases in which there is concern for malabsorption of enteral medications, or for whom antiviral resistance is suspected. Similarly, novel medications are currently under study for treatment of a potential pandemic influenza virus strain that may be resistant to conventional antiviral medications. A surveillance registry would be able to not only track cases and clinical outcomes from infections, but could produce data on use and effectiveness of vaccines and antivirals.

The Centers for Disease Control and Prevention (CDC) has established programs for identifying and monitoring infectious disease outbreaks in the community. These programs are designed to understand the overall burden of disease and focus to a large extent on outpatients and prevention. While a mandatory national reporting system for deaths from influenza in children has been available since 2004[14], pediatric deaths from other infections are not intensively monitored, nor are the details of the clinical course and resource utilization of fatal cases.

In 2009, the National Institutes of Health, Department of Health and Human Services and the CDC asked the Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network to establish a surveillance registry to track the 2009 H1N1 influenza. The PALISI Network is a consortium of clinical investigators across pediatric intensive care units in the United States and Canada with voluntary membership that includes the majority of the large pediatric-focused institutions in the U.S and Canada. The PALISI Network has studied acute lung injury and sepsis in infants and children since its inception in 2002 and has an extensive repository of data collection tools and methods to facilitate multicenter studies in children who are the most severely ill. In collaboration with the National Heart Lung and Blood Institute (NHLBI) and ARDS Clinical Trials Network (ARDSNet) which tracked adult cases[15], the PALISI Pediatric Intensive Care Influenza (PICFLU) group effectively developed a surveillance registry for the 2009 H1N1 pandemic which captured approximately 25% of the pediatric deaths reported to the CDC.[16] This real-time reporting system provided data to the U.S. DHHS National Disaster Medical System and Office of the Assistant Secretary for Preparedness, so that they could more accurately determine the national impact of the pandemic, and assess whether resources such as antivirals, ICU beds, and mechanical ventilators were sufficient and appropriately allocated. Analysis of the final dataset revealed, surprisingly, that co-infection with *methicillin-resistant S. aureus* (MRSA) was the only independent factor identified to be predictive of mortality in previously healthy U.S. children.

[14] Overview of Influenza Surveillance in the United States. Centers for Disease Control and Prevention. Available at: http://www.cdc.gov/flu/pdf/weekly/overview.pdf Accessed July 18,2013

[15] Rice TW, Rubinson L, Uyeki TM, Vaughn FL, John BB, Miller III RR, Higgs E, Randolph AG, Smoot BE, Thompson BT for the NHLBI ARDSNet. Critical illness from 2009 pandemic influenza A (H1N1) and bacterial co-infection in the United States. *Crit Care Med*. 2012; 40:1487-1498.

[16] Randolph AG, Vaughn F, Sullivan R, et al. Critically ill children during the 2009-2010 influenza pandemic in the United States. *Pediatrics*. 2011;128;e1450.

In early 2020, the CDC asked the PALISI Network to provide real-time surveillance in hospitalized children of a new pathogen that emerged and caused a pandemic called severe acute respiratory syndrome virus caused by a novel coronavirus (SARS-CoV-2) with the disease it caused called coronavirus disease 2019 (COVID-19)[17]. Acute COVID-19 is associated with high mortality in hospitalized adults causing profound hypoxia and acute respiratory distress syndrome; survivors have prolonged recovery.[18] In contrast, the majority of children infected in China, where the outbreak first began, had a mild clinical course or were asymptomatic.[19] To better assess life-threatening disease in children, the CDC funded the PALISI Pediatric Intensive Care Influenza and Emerging Pathogens Network (PICFLU-EP, http://picflu.org) in April of 2020, which expanded to recruit additional representative sites across the U.S. to become the Overcoming COVID-19 Network (https://overcomecovid.org).

In the UK and Europe, reports of a life-threatening syndrome in children associated with inflammation and multisystem involvement began to emerge, with many children having cardiac involvement and features of Kawasaki Disease or toxic shock syndrome.[20] After cases. were reported in the U.S., the Centers for Disease Control and Prevention defined the syndrome as Multisystem Inflammatory Syndrome in Children or MIS-C. It became clear that the pattern of COVID-19 illness was different in children and older adults. Rapid deployment of this registry allowed us to capture data on 213 U.S. cases of MIS-C across 53 centers in 26 states.[21] As the COVID-19 pandemic progressed, the study of MIS-C became a major goal of Overcoming COVID-19, including diagnostic criteria, risk factors, treatments and health outcomes.

Influenza and other respiratory pathogens are constantly changing, yet surveillance persists as one of the most important tools for containing and dealing with an outbreak. National and international surveillance by the CDC and WHO perform vital functions in obtaining data on the spread of infections. The PALISI Network's established infrastructure and regional diversity enables it to efficiently and effectively identify novel cases and track disease spread, assess severity, resource burden, and report clinical outcomes. This protocol was initially established in 2013 for the development of a registry to track the incidence and spread of influenza and other emerging respiratory pathogens. The tools and infrastructure created for use in the 2009 H1N1 pandemic were modified to create this surveillance registry that can be rapidly deployed in the event of a public health emergency and modified as needed for the viral pathogen and its spread.

[17] Guan WJ, Ni ZY, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med 2020.
[18] Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020;395:1054-62.
[19] Castagnoli R, Votto M, Licari A, et al. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection in Children and Adolescents: A Systematic Review. JAMA Pediatr 2020.
[20] Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic. Lancet 2020
[21] Feldstein LR, Rose EB, Horwitz SM, et al. Multisystem inflammatory syndrome in U.S. children and adolescents. N Engl J Med 2020, published online June 29th.

III. MAJOR OBJECTIVES (MASTER PROTOCOL)

The purpose of this surveillance registry is to characterize the demographics, clinical features, outcomes, and resource utilization of children requiring hospitalization during a novel epidemic or pandemic, and it is expected that this master protocol will be broad, flexible with a goal of long-term use for multiple pathogens. This purpose will be accomplished through the following five specific aims:

1. To describe in detail the demographics and clinical characteristics, including clinical course and treatment, of infected children who require hospitalization in PALISI hospitals and medical centers.
    a. If the pathogen of interest is a virus, we will evaluate antiviral effectiveness in preventing severe outcomes in patients admitted to the hospital.
2. To describe the incidence of acute respiratory failure in infected children admitted to participating hospitals. Specifically:
    a. To describe the ventilator needs during the hospital stay of infected patients cared for in PALISI Network hospitals and medical centers including use of non-invasive ventilation modalities.
    b. To describe the frequency that rescue therapies are used, including alternative modes of ventilation (high frequency ventilation, extra-corporeal gas exchange, and prone ventilation), inhaled pulmonary vasodilators, corticosteroids, and neuromuscular blockers used in children with severe respiratory failure from the respiratory pathogen of interest.
3. To determine the incidence and timing of non-respiratory complications and organ failures, such as encephalitis, myocarditis, renal failure and use of dialysis, cardiovascular collapse and use of vasopressors, coagulopathies and hepatic failure, and bone marrow suppression and hematologic failure, in infected children requiring hospitalization in PALISI Network hospitals and medical centers.
4. To report outcomes and estimate resource utilization by assessing 28-day, 90-day, and hospital mortality, cause of death, duration of mechanical ventilation, length of dialysis, and intensive care unit and hospital lengths of stay in infected children at PALISI Network hospitals and medical centers.
5. To compare the endpoints outlined in aims 1-4 for children infected with the pathogen of interest who require hospitalization in PALISI Network hospitals and medical centers to those not infected with the pathogen who require hospitalization in PALISI Network hospitals and medical centers.
6. To provide U.S. disease surveillance by expanding the network to add hospitals and medical centers as needed once data capture is triggered by the public health authority requesting implementation of this protocol.

IV. REGISTRY PROCEDURES

A. USE OF CENTRAL INSTITUTIONAL REVIEW BOARD (IRB)

Assurance of patient privacy and protection of human subjects requires approval of a registry protocol at institutional review boards (IRBs) at multiple clinical centers. Although necessary, the burden of submitting and maintaining an IRB protocol can lead to inconsistent initiation of data collection across sites, different protocol versions, and difficulty updating protocols consistently across sites when updates are needed. Use of a central IRB has been suggested to minimize this burden and its associated delays.[22] To ensure accuracy and efficiency, we propose to use the Boston Children's Hospital IRB as the central IRB for this surveillance registry. Serving as the central IRB for other PALISI Network studies and national pediatric registries, the Boston Children's Hospital IRB has the experience and reputation to provide this support for other pediatric IRBs. As the central IRB, Boston Children's Hospital IRB must review and approval the protocol first. After approval, Boston Children's Hospital with distribute a packet that includes a questionnaire on local practices, a reliance agreement, an investigator agreement, among other standard materials, to all participating sites for review and execution.

If PALISI Network sites are unable to utilize a central IRB, they will be required to obtain approval from their local IRB and submit approval documents to Boston Children's Hospital.

B. PATIENT IDENTIFICATION

There will be no randomization in this surveillance registry. All patients who meet the inclusion criteria and not the exclusion criteria will be enrolled by participating site study personnel. All identified patients who meet criteria will be given an ID number comprised of a site number and patient number.

C. PATIENT INCLUSION/EXCLUSION CRITERIA (OVERCOMING COVID-19)

Patients admitted to the hospital on or before May 31, 2020:

Inclusion Criteria

- Hospitalized at a participating site
- ≦ 25 years old
- Disease is suspected of being related to SARS-CoV-2:
    - SARS-CoV-2 positive PCR AND/OR
    - SARS-CoV-2 positive antibody test AND/OR
    - Meets Multisystem Inflammatory Syndrome in Children (MIS-C) criteria (see below) and hospitalized March 15, 2020 – May 31, 2020*
      *Additional data are collected related to COVID-19 exposure history

[22] Flynn KE, Hahn CL, Kramer JM, Check DK, Dombeck CB, et al. Using Central IRBs for Multicenter Clinical Trials in the United States. *PLoS ONE*, 2013; 8(1): e54999. doi:10.1371/journal.pone.0054999

Exclusion Criteria

- Not hospitalized OR >25 years old OR no suspected association with SARS-CoV-2

Multisystem Inflammatory Syndrome in Children (MIS-C) Criteria:

Inclusion Criteria

- Fever ≥38 ^{o}C (100.4 ^{o}F) for ≥ 24 hours, or report of subjective fever lasting ≥ 24 hours, **AND**

- Laboratory markers of inflammation (including but not limited to one or more of the following: e.g. elevated C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), fibrinogen, procalcitonin, d-dimer, ferritin, lactic acid dehydrogenase (LDH), or interleukin 6 (IL-6), elevated neutrophils, reduced lymphocytes and low albumin), **AND**

- Clinical evidence of severe hospitalized illness including multi-organ (≥2) involvement based on clinical judgement from record review, discharge diagnosis, laboratory or diagnostic tests:
    - Cardiac (e.g. shock, elevated troponin, BNP, abnormal echocardiogram, arrhythmia)
    - Respiratory (e.g. pneumonia, ARDS, pulmonary embolism)
    - Renal (e.g. acute kidney injury or renal failure)
    - Gastrointestinal (e.g. elevated bilirubin or elevated liver enzymes)
    - Neurologic, (e.g. CVA, aseptic meningitis, encephalopathy)
    - Hematologic (e.g. elevated D-dimers, thrombophilia, or thrombocytopenia)
    - Dermatologic (e.g. rash, erythema, peeling)
    - Fulfill full or partial criteria for typical or atypical Kawasaki disease
    - Other (specify):_____

Exclusion Criteria: Other likely microbial or other cause, including bacterial sepsis, staphylococcal or streptococcal shock syndrome

Patients admitted to the hospital on or after June 1, 2020:

Inclusion Criteria:

- Hospitalization at a participating site
- ≤ 21 years old
- SARS-CoV-2 positive PCR or SARS-CoV-2 positive antibody test
- Symptoms of COVID-19 or MIS-C that prompted test (not done as a screening test for an elective procedure or visit)

Exclusion Criteria:

- Negative (PCR and antibody) or no testing for SARS-CoV-2 (COVID-19)

Outpatients from March 1st, 2020 onwards as controls for hospitalized MIS-C patients:
Inclusion Criteria:

- Evaluated in the outpatient setting (e.g. emergency department, affiliated clinics, preoperative, etc.) at a participating site
- ≤ 21 years old
- SARS-CoV-2 positive PCR test during that visit
- Meets criteria for matching for a hospitalized MIS-C case (age bracket, study site)

Exclusion Criteria:

- Negative (PCR) or no testing for SARS-CoV-2 (COVID-19)
- Non-elective (unplanned) admission to the hospital within 4 weeks of the positive SARS-CoV-2 test (COVID-19) based upon site chart review

D. PATIENT LOCATION AND REGISTRY SITES

We will enroll patients from the population of children admitted to PALISI Network hospitals and medical centers and will add additional non-PALISI member sites as needed. We have contacted over 60 individual PALISI Network sites identified as willing and able to participate in this surveillance registry.

V. DATA AND IMAGE COLLECTION

All procedures for this surveillance registry pose minimal risk and are for public health surveillance. The case report form will be used to enter all information collected from the child's medical records into a secure electronic database, Research Electronic Data Capture (REDCap). Certain questions in the modular case report form and REDCap database will need to be updated depending on the specific pathogen being studied, while other modules are less likely to need further revision (e.g. patient demographics and prior medical history). Modules that will require refinement include the inclusion/exclusion criteria, case definition, the clinical prodrome and case presentation, vaccination history, viral and bacterial testing, antiviral therapies, antibacterial and antifungal therapies, and the clinical course and outcome.

All identified patients who meet criteria will be given an ID number comprised of a site number, patient number, and may include a random three-digit code. As the clinical coordinating center, Boston Children's Hospital will verify collected data by completing double data entry using REDCap when feasible.

For patients who meet criteria, PALISI Network site study staff will collect comprehensive clinical information via medical chart abstraction and from other available clinical sources. Information collected will include patient demographics, medical history including the presence of chronic medical conditions, clinical status on day of admission, respiratory illness severity, vaccination status, bacterial and viral test results on presentation, and

course of illness and treatment in the intensive care unit and hospital. Results of clinical testing that was performed will be collected. Additional data that is available from the laboratory related to the patient's clinical test such as unreported but available results of clinical tests or samples sent for public health related analyses that can be used for further interpretation may be collected (e.g. flow cytometry analysis details, SARS-CoV-2 viral testing details such as cycle threshold values, deidentified patient codes to link samples sent for viral sequencing to CDC affiliated sequencing sites or results of SARS-CoV-2 sequencing). Data available from clinical surveys (symptom screening, exposures, etc.) may also be collected.

Sites may also send deidentified clinical images (i.e. CT, MRI, echocardiogram, chest radiograph, other radiographic images) for secondary interpretation. Deidentification of all images will occur at the site or through a deidentification computer algorithm through a portal prior to reaching Boston Children's Hospital. We may also receive deidentified clinical pictures of dermatologic (rashes, lesions, peeling, etc.), ophthalmologic (conjunctivitis, etc.) and extremity manifestations (swelling, and other), to better characterize the presenting signs of MIS-C and other complications.

Most patients will be enrolled prospectively; however, there may be a need to retrospectively capture cases due to staff unavailability and other reasons. The retrospective timeframe can be defined more accurately when the study is initiated, based on the onset of the public health emergency and the status of IRB approval(s).

Weekly or bi-weekly summary reports will be disseminated to the CDC to ensure real-time tracking of the epidemic. Reports will also be made available upon request. These reports will include the number of patients that met the registry criteria by location, baseline demographics, comorbid conditions, clinical presentation, baseline lab results, intensive care unit admission status, hospital course, antimicrobial therapy, intensive care unit outcomes, and mortality outcomes. Actual dates may also be included to aid in real-time decision making.

VI. DISCARDED CLINICAL SAMPLE COLLECTION

During a pandemic, there is an urgent need for samples from infected patients to better understand the pathogen itself and the host immune response to the pathogen. This information is essential for development of accurate diagnostic tests, for tracking mutations in the pathogen's genetic code that could influence disease severity, and for development of vaccines. With site approval, respiratory and sera or plasma samples that are leftover from clinical testing may be collected and sent from the site to Boston Children's Hospital. These samples may come directly from the clinical laboratories or may be stored in a site biorepository. If samples are accessed through a biorepository the mechanisms used to request those discarded samples will follow those outlined by the site biorepository and will not be made directly from this protocol to the clinical laboratories (e.g. at Boston Children's Hospital the Taking on COVID-19 Together Biobank

secondary use request to the IRB). A copy of the sites biorepository protocol will be obtained for our records.

- Samples may be used for assays such as antibody evaluation and evaluation of other immunity or can be focused on the virus such as viral sequencing or viral load.
- Samples can be shared with public health authorities (e.g. Centers for Disease Control and Prevention or the National Institutes of Health) for public health surveillance, or for creation of vaccines or diagnostic tests or other urgent needs for public health.
- Samples may not be used for genomics or genetics studies, to develop cell lines or for use that may identify the subject.
- Samples may not be used for commercialization.

The samples will be stored at Boston Children's Hospital in a biobank in the laboratory of Dr. Adrienne Randolph.

VII. STATISTICAL CONSIDERATIONS

All patients meeting inclusion criteria at a participating institution will be included in this surveillance registry. The exact sample size remains unknown due to uncertainty about the number of people who will be infected and the percentage of those that will require hospitalization.

VIII. HUMAN SUBJECTS ISSUES

A. WAIVER OF CONSENT AND HIPAA AUTHORIZATION

We propose to conduct this surveillance registry with both a waiver of the requirement for informed consent and HIPAA authorization for both retrospective and prospective data and sample collection. Waiver of consent is appropriate because the procedures pose minimal risk to study participants. For the surveillance registry to be useful, data are needed from every patient who meets inclusion and exclusion criteria at every site. Legal guardians/parents may be ill with the pathogen of interest or encouraged not to come to the hospital due to the risks of exposure to themselves and others. Moreover, due to sedation and delirium, many patients will not be able to provide informed consent or assent for themselves. Since there is also an inevitable shortage of health care workers due to illness and absenteeism related to novel epidemics, it is anticipated that many research personnel will be involved in patient care activities. The time required to contact legal guardians/parents poses an undue burden on these healthcare personnel. Thus, conduct of this study would not be practicable without a waiver of consent.

Assuming spread of infection can occur from person-to-person via droplets of respiratory secretions, limiting exposure will be an integral part of limiting the spread of disease. As such, the number of people exposed to these patients should be limited to as few as possible, including both family members and surveillance registry personnel who are not

involved in direct care of these patients. Mandating consent would increase exposure and possibly worsen the spread of the infection.

The surveillance registry procedures are minimal risk in that all data being collected is available in the medical record as part of routine care or as part of sample analysis for clinical or disease surveillance purposes. Any lab test, value, or piece of data that is not available through approved mechanisms will be left as missing in the database. No tests or data will be required solely for this surveillance registry. Samples are taken after they are discarded after clinical use. A waiver of authorization under HIPAA is needed as the data cannot be fully de-identified due to the need to include dates and the first four digits of the patients' zip code. Dates are needed to fully and accurately track the epidemic and thus serve the national interest and the first four digits of the patients' zip code are needed to appropriately estimate incidence by mapping back to the source population. The data will be held on a server at the clinical coordinating center, Boston Children's Hospital. A subcontract containing data and sample use language with Boston Children's Hospital will be required from all sites. We anticipate that all sites will participate in data collection, but not all sites will be able to participate in discarded sample collection.

B. CONFIDENTIALITY AND PRIVACY

Data will be entered into REDCap, an electronic web-based database. REDCap, housed on servers located at Boston Children's Hospital, is a secure, web-based application designed to support data capture for research studies and registries. REDCap provides: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources. Data will be automatically sequestered by site so individuals at any institution may see their own site's data, but not data collected at other sites. Primary study coordinators will have access to case report form views and access to an export module designed to enable export of all site data.

All study data will be stored separately from study records that contain names or other personal identifiers. All local databases must be secured with password protected access systems. Forms, lists, logbooks, and any other listings that link participant ID numbers to other identifying information must be stored in a separate, locked file in an area with limited access. If participant names and corresponding participant IDs are entered into a computer database, this database must be password protected and must be maintained in a directory separate from any study specific data.

Samples will be sent to external laboratories for processing deidentified with the study ID only. External investigators performing assays will sign an agreement to make no attempts to further identify the samples.

C. RISKS

The only procedures for this surveillance registry are collection and transmission of existing clinical data that will be collected solely for non-research purposes. This surveillance registry represents minimal risk as defined by the federal regulation 45 CFR 46.110 (F)(5) for expedited IRB review. Loss of confidentiality represents the main risk, and this is minimized through the use of the secure electronic REDCap database.

Only de-identified data will be included in the database, with the exception of dates and the first four digits of the zip code. Because the REDCap database is housed on the servers at Boston Children's Hospital, hospital staff will have access to the actual dates in the database. Due to their access to dates and the fact that dates represent identifiable Private Health Information (PHI), a subcontract containing data use language with Boston Children's Hospital will be required from all sites.

Weekly reports will be prepared for the CDC and other government agencies for real-time tracking and decision-making. Data will be released as outlined in the data use agreement between the clinical sites and Boston Children's Hospital.

D. ADVERSE EVENTS OR UNANTICIPATED PROBLEMS

The main potential adverse event is loss of confidentiality via breach of private health information. Any disclosure of identified health information to unauthorized parties will be reported to the Boston Children's Hospital Institutional Review Board within 5 days of discovery. In addition, the breach will also be evaluated to determine if it also needs to be reported to the local, state, or federal authorities according to respective regulations.

E. RECORD RETENTION

Patients will only be followed to the earlier of 90 days post hospital discharge, death, or until the end of the surveillance period. For the purposes of government comparisons, de-identified data will be indefinitely stored for research purposes. The final dataset will not contain site identification numbers and date and age shifting will be used. Residual samples will be completely deidentified and retained indefinitely at Boston Children's Hospital in Dr. Adrienne Randolph's laboratory for use as determined by the CDC.

STATISTICAL ANALYSIS PLAN FOR OVERCOMING COVID19

SUBSTUDY EVALUATING MIS-C TREATMENTS

A. ORIGINAL ANALYTIC PLAN

Substudy Proposal Approved by CDC August 29th, 2020
Immunomodulatory Treatment of Multisystem Inflammatory Syndrome in Children (MIS-C)

Variables

Exposures

- IVIG at index (index, defined as day 0)
- IVIG + glucocorticoid at index

Note: both groups can have adjunctive treatments (glucocorticoid, IVIG dose 2, or biologics) on day 1 or greater after index.

Outcomes

- Primary: cardiovascular dysfunction (vasopressor requirement or left ventricular (LV) ejection fraction<55%) on ≥Day 2
- Secondary
    - Individual components of composite outcome:
        - vasopressor requirement on ≥Day 2
        - left ventricular (LV) ejection fraction<55%) on ≥Day 2
    - adjunctive treatment on ≥Day 1
    - fever on ≥ Day 2
    - CRP > 20 mg/dL on ≥ Day 2

Covariates (all collected on day of admission)

- Age
- Sex
- Race and ethnic group
- Previously healthy
- Kawasaki disease signs without cardiorespiratory involvement
- Pulmonary infiltrates on chest x-ray
- Intensive care unit admission
- Vasopressor use
- Mechanical ventilation
- Neutrophil to lymphocyte ratio (NLR)
- Absolute neutrophil count (ANC)

- Absolute lymphocyte count (ALC)
- C-reactive protein (CRP)
- D-dimer
- Erythrocyte sedimentation rate (ESR)
- Ferritin
- Platelet Count

Exclusions

- Missing treatment dates
- Glucocorticoid or biologic therapy alone or combine on index day due to small sample size
- Underlying cardiac conditions

Statistical Analysis Plan

- For each outcome of interest, patients in the two treatment groups will be matched using variables that may affect both the treatment decision and the outcome.
- We will use greedy nearest neighbor matching without replacement and a caliper width of 0.2 standard deviation to match patients.
- We will analyze the effect of the treatment on any of the primary or secondary outcomes using logistic regression on the matched data.
- Sensitivity analyses of inverse probability of treatment weighting will be used to confirm matching results.

B. FINAL ANALYTIC PLAN

Last Updated March 5th, 2021

Variables

Exposures

- IVIG at index (index, defined as day 0)
- IVIG + glucocorticoid at index

Note: both groups can have adjunctive treatments (glucocorticoid, IVIG dose 2, or biologics) on day 1 or greater after index.

Outcomes

- Primary: cardiovascular dysfunction (vasopressor requirement or left ventricular (LV) ejection fraction<55%) on ≥Day 2
- Secondary
    - Individual components of composite outcome:
        - vasopressor requirement on ≥Day 2
        - left ventricular (LV) ejection fraction<55%) on ≥Day 2
    - Adjunctive treatment (a second dose of IVIG, glucocorticoid or biologic) treatment ≥Day 1 from index treatment
    - Persistent/recurrent fever >38˚C ≥Day 2 from index treatment

*Covariates used for matching**

- Age
- Sex
- Race and ethnic group
- Previously healthy
- Kawasaki disease signs without cardiorespiratory involvement
- Pulmonary infiltrates on chest x-ray
- Intensive care unit admission
- Vasopressor use
- Mechanical ventilation
- Neutrophil to lymphocyte ratio (NLR)
- C-reactive protein > 30 mg/dL
- Platelet Count

**All covariates collected at admission*

Statistical Analysis Plan

- For each outcome of interest, patients in the two treatment groups will be matched using variables that may affect both the treatment decision and the outcome.

- We will use greedy nearest neighbor matching without replacement and a caliper width of 0.2 standard deviation to match patients.
- We will analyze the effect of the treatment on any of the primary or secondary outcomes using log-binomial regression on the matched data.
- Sensitivity analyses of inverse probability of treatment weighting will be used to confirm matching results.
- Sensitivity analysis to evaluate the strength (measure the evidence of causality by calculating E-value) required of a potential unmeasured confounder to change the association of treatments with the primary and secondary outcomes.

Summary of Changes

- Covariates changed to final list of covariates used based on review of paired correlations, success of balancing distributions of treatment groups, and reducing missingness.
- Secondary outcome of CRP dropped due to high missingness of data and unclear clinical definition of "high" CRP in MIS-C patients
- Binarized CRP admission variable
- Analyzed matched data with log-binomial regression instead of logistic regression to report risk ratios instead of odds ratios
- Calculation of E-values for the primary and secondary outcomes to assess the potential of unmeasured confounders to influence results.