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Prospective Cohort Study of Children Potentially Infected by SARS-CoV-2 Presenting to Pediatric Emergency Departments: A Pediatric Emergency Research Networks (PERN) Study

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Title: Prospective Cohort Study of Children Potentially Infected by SARS-CoV-2 Presenting to Pediatric Emergency Departments: A Pediatric Emergency Research Networks (PERN) Study

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Abbreviations:

CDC - United States Centers for Disease Control and Prevention

COVID-19 - 2019 novel coronavirus related disease

CRF – case report form

ED – emergency department

PECARN – Pediatric Emergency Care Applied Research Network

PEM – CRC – Pediatric Emergency Medicine Collaborative Research Committee

PERC – Pediatric Emergency Research Canada

PERN – Pediatric Emergency Research Network

PHAC – Public Health Agency of Canada

PREDICT – Pediatric Research in Emergency Departments International Collaborative

REDCap - Research Electronic Data Capture

REPEM – Research in European Pediatric Emergency Medicine

RIDEPLA – Red de Investigacion y Desarollo de la Emergencia Pediatrica Latinoamerica

RISEUP-SPERG - Red de Investigación de la Sociedad Española de Urgencias de Pediatría / Spanish Pediatric Emergency Research Group

SARS-CoV-2 - severe acute respiratory syndrome coronavirus-2

UNICEF – United Nations Children's Fund

WHO – World Health Organization

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Abstract

Introduction: Relatively limited data are available regarding pediatric COVID-19. Although most children appear have mild or asymptomatic infection, infants and those with comorbidities are at increased risk of experiencing more severe illness and requiring hospitalization due to COVID-19. The recent but uncommon association of SARS-CoV-2 infection with development of a multisystem inflammatory syndrome has heightened the importance of understanding pediatric SARS-CoV-2 infection.

Methods and Analysis: The PERN-COVID-19 cohort study is a rapid, global, prospective cohort study enrolling 12,500 children who are tested for acute SARS-CoV-2 infection. 47 emergency departments across 12 countries on four continents will participate. At enrolment, regardless of SARS-CoV-2 test result, all children will have the same information collected, including clinical, epidemiological, laboratory, imaging, and outcome data. Interventions and outcome data will be collected for hospitalized children. For all children, follow-up at 14 and 90 days will collect information on further medical care received, and long-term sequelae, respectively. Statistical models will be designed to identify risk factors for infection and severe outcomes.

Ethics and Dissemination**:** Sites will seek ethical approval locally, and informed consent will be obtained. There is no direct risk or benefit of study participation. Weekly interim analysis will allow for real-time data sharing with regional, national, and international policy makers. Harmonization and sharing of investigation materials with the World Health Organization, will contribute to synergizing global efforts for the clinical

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characterization of pediatric COVID-19. Our findings will enable the implementation of countermeasures to reduce viral transmission and severe COVID-19 outcomes in children.

Registration: NCT04330261

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Article Summary

Strengths and limitations of this study

- This multi-site international research project has the unique ability to create a very large global dataset of children with COVID-19 and other infectious etiologies that will include extensive details on exposures, symptoms, investigations, treatments and outcomes.
- This study builds upon an existing multi-center research network to enable the rapid launch of a global study to address the COVID-19 pandemic.
- By collecting data on both SARS-CoV-2-positive and -negative children, we will be able to conduct comparisons to develop models, using epidemiological and clinical characteristics, to predict pediatric SARS-CoV-2 infection.
- In the context of the quickly evolving COVID-19 pandemic, varying and evolving testing and control strategies are being put in place globally, which may limit ability to combine and generalize findings across different study sites.
- As testing at some sites may overwhelm research capacity, we will be unable to collect data on 100% of SARS-CoV-2 tested children.

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INTRODUCTION

Pediatric 2019 novel coronavirus related disease (COVID-19) following severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection is not yet well characterized, and detailed reports on this topic are sparse.[1-7] Reported infections are less common in persons younger than 18 years compared with older age groups. As of early June 2020, in reports with sample sizes of COVID-19 cases ranging from 4,695 to 149,082, from China, the United States, Italy, and Spain, individuals younger than 18 years have constituted less than 2% of the total study cohort.[3 8-10]

For reasons that remain elusive, children appear to be more likely than adults to present with asymptomatic or mild disease.[1 11] The proportion of children with asymptomatic infection ranges between 4% and 16%.[4 12] However, these reports likely underestimate the frequency of asymptomatic carriage, as symptomatic patients are much more likely to be tested.[13] Moreover, symptoms in children appear to be less typical with only 73% of children with confirmed infection experiencing fever, cough or shortness of breath, which are reported in over 90% of infected adults.[3] Even when symptomatic, children appear to be less likely to develop dyspnea, hypoxemia, acute respiratory distress syndrome and multiorgan system failure.[12-14] Other symptoms, such as vomiting and diarrhea are present in 5 – 15% of children;[3 4] in older children, a loss of the sense of smell (anosmia) has been noted as a possible predictor of infection.[15] Furthermore, there is emerging evidence of a delayed multi-system inflammatory syndrome in children (MIS-C) that is linked to SARS-CoV-2 exposure that has been associated with severe outcomes.[16-19]

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The reported proportion of children with COVID-19 requiring hospitalization, although seemingly lower than that of adults, is variable and not well understood. In the United States and Canada, among children who tested positive for SARS-CoV-2, between 0.9 and 20% have reportedly required hospitalization.[3 20] Children with comorbidities and those aged <1 year appear to be at particularly high risk for hospitalization, intensive care unit admission, and death.[3 4] Although prior to mid-March, 2020, only two deaths had been reported among children worldwide,[1] in a subsequent large case series of 2,572 infected children in the United States, three additional deaths were reported.[3]

Though reports related to pediatric hospitalization and mortality exists, there is a paucity of large-scale, multi-national descriptions of the clinical features and disease course of children with COVID-19. Thus, a detailed examination of the risk factors for infection, clinical characteristics of infected children, predictors of severe outcomes, and treatments provided, is urgently needed for this unique and potentially vulnerable population. As the symptoms of COVID-19 infection are a common reason for pediatric presentation to hospital, the early identification of high-risk children and clinical phenotypes is vital to optimizing care. Moreover, as viral shedding may occur in minimally symptomatic children,[21] an in-depth study of pediatric infection characteristics, both mild and severe, will contribute to a better understanding of transmission risks.[22] It will also be important to characterize and compare COVID-19 disease with other common pediatric respiratory illnesses to contextualize the severity of illness.

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To achieve the aforementioned objectives, our study's primary aim is to fully evaluate clinical characteristics and outcomes of SARS-CoV-2 infected children. Specifically, among children presenting to a participating hospital's ED, we will (1) describe and compare the clinical characteristics of children with *confirmed* (i.e. nucleic acid and/or serological test-positive) and *suspected* (i.e. nucleic acid and/or serological test-negative) infections, and (2) identify factors associated with severe outcomes (i.e. intensive care unit admission, assisted ventilation, vasoactive medication use, MIS-C, death). The secondary aims of this study include (1) describing and comparing health care resource utilization for patient management (e.g. isolation, testing, imaging, supportive care) of both *suspected* and *confirmed* SARS-CoV-2-infected children according to changes in national and regional policies, and (2) describing the effects of changing case screening policies for the detection of *confirmed* SARS-CoV-2 in children.

METHODS AND ANALYSIS

Study Design and Setting

The Pediatric Emergency Research Network (PERN; https://pern-global.com/) represents the largest global pediatric acute care research collaboration, spanning 35 countries in four World Health Organization (WHO) regions representing >200 pediatric hospitals providing care to >5 million children annually.[23] PERN represents a collaboration between seven existing pediatric emergency care medicine research networks –Pediatric Emergency Research Canada (PERC),[24 25] Pediatric Research in Emergency Departments International Collaborative (PREDICT),[26] Pediatric Emergency Medicine Collaborative

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Research Committee (PEM CRC), Pediatric Emergency Care Applied Research Network (PECARN), Research in European Pediatric Emergency Medicine (REPEM), Red de Investigacion y Desarollo de la Emergencia Pediatrica Latinoamerica (RIDEPLA), and Red de Investigación de la Sociedad Española de Urgencias de Pediatría / Spanish Pediatric Emergency Research Group (RISEUP-SPERG).[27]

In early 2019, the network launched the PERN-Pneumonia prospective cohort study to identify clinical predictors of severe outcomes in children diagnosed with community-acquired pneumonia (CAP). This global study includes 70 pediatric ED sites across 13 countries, including the United States, Canada, Spain, Italy, France, Switzerland, Romania, Argentina, Chile, Costa Rica, Paraguay, Australia, New Zealand, and Singapore. The existence of the PERN-Pneumonia study has provided a unique opportunity to expeditiously initiate a prospective cohort study of children potentially infected by SARS-CoV-2. By building on the PERN-Pneumonia study's infrastructure (e.g. ethics approvals, data sharing agreements, electronic database, study teams), we were able to rapidly initiate the PERN-COVID-19 study to fill critical gaps in the understanding of COVID-19 in children.

PERN-COVID-19 is a prospective cohort study of children with suspected acute SARS-CoV-2 infections who present for care in one of 47 participating pediatric EDs located in 12 countries on 4 continents (see Figure 1). Study recruitment began on March 16th, 2020 at the Alberta Children's Hospital in Calgary, Canada. Most other participating sites initiated recruitment between mid-April and mid-May, 2020.

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Participants and Recruitment

Eligible participants are less than 18 years of age who present to a participating ED for care and are tested for acute SARS-CoV-2 infection because of suspected infection (i.e. symptoms, travel history, or exposure history) according to local institutional policy. Participants are excluded if the caregivers and/or children do not provide informed consent and assent, as required, respectively.

This pragmatic observational study does not specify the SARS-CoV-2 testing criteria, the specimen type collected for testing or the SARS-CoV-2 nucleic acid test performed. In some sites, a combination of nucleic acid and serological tests may be performed. Information on *all* SARS-CoV-2 tests performed on study participant specimens will be collected. It is recognized that the standard procedures and criteria for SARS-CoV-2 testing are continuously evolving, often based on access to swabs, reagents and the regional epidemiology of disease. Therefore, detailed information on these policies will be reported weekly by sites. Local practices and illness severity will dictate decisions regarding isolation, investigations, treatments and hospitalization.

Protocol implementation will vary by site to enhance feasibility. Sites may recruit participants in real-time as they present at the ED, or after the ED visit (e.g. via a daily list of all children who presented to the ED and underwent SARS-CoV-2 testing). Contact procedures (e.g. in-person or via telephone) and the consent process (e.g. written or verbal) will adhere to each site's approved ethics agreements. Sensitive to the child's

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clinical condition and isolation policies, a research team member at each institution will contact the guardian to obtain informed consent and assent, as appropriate. The initial contact with hospitalized patients may occur in-person within the hospital or via telephone and will always occur by telephone if the patient has returned home (i.e. not admitted or already discharged).

When the study was launched, testing was limited at most sites and sites were instructed to attempt to recruit all children screened for SARS-CoV-2 infection. However, over time, the number of children screened increased, at which time the protocol was revised to have sites attempt to consecutively recruit the first five children tested each day. In sites located in areas where community prevalence of COVID-19 was very low, we moved to recruit the first two children tested each day. As enrolment may occur prior to SARS-CoV-2 test results becoming available, if none of the enrolled children on a given day are ultimately test-positive (i.e. *confirmed* SARS-CoV-2), then we will attempt to enroll up to two additional test-positive children. This is performed by returning to the list of children tested, and continuing consecutively, attempting to recruit children with known positive test results.

Data Collection

Participant demographic, epidemiological and clinical data will be collected at the time of enrolment in the ED, or shortly after. Clinical data will be collected throughout the period of hospitalization (if relevant). At 14 and 90 days following the index ED visit, information on healthcare revisits and persistent symptoms will be collected,

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respectively. (Figure 2) Follow-up data collection time points were selected based on the presumed natural history of COVID-19 (i.e. symptom progression 7 – 10 days after onset) while accounting for both short- and longer-term potential complications.[28] To complete case report forms (CRFs), study staff will consult hospital medical records and caregivers. A medical record review to verify 14-day outcome data will be performed which will also minimize loss-to-follow-up. We anticipate that children lost to follow-up without a hospital revisit did not experience an adverse outcome as study sites all serve as regional tertiary care centers, and thus it is unlikely that a critically ill child would both be lost to follow-up and would be cared for elsewhere. Follow-up will be performed via telephone, text, or email as per caregiver preference and as feasible based on-site resources and approvals. Our data forms are harmonized with the WHO recommended CRFs for clinical characterization of COVID-19 (https://www.who.int/docs/default-source/coronaviruse/who-ncov-crf.pdf?sfvrsn=84766e69_4).

Baseline data: A study team member will complete the enrolment CRFs using the participants medical records and through a caregiver interview. Data collected will include: calendar date and site of enrolment, epidemiological risk factors (e.g. recent travel, exposures), demographics (e.g. age, sex), health information (e.g. past medical history, vaccination status, comorbidities), onset of current illness (e.g. timing, symptoms), imaging and laboratory investigations performed in the ED and treatments and care received (e.g. intravenous fluids, antivirals, antibiotics).

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Hospitalization data: Enrolment CRFs will further capture management and outcome data related to events occurring during the initial hospitalization, if required. Data collected will include length of hospital stay, level of hospital care required (e.g. intensive care unit), laboratory tests, interventions, and complications.

14-day follow-up: Day 14 follow-up will be conducted through telephone, text, or email survey as per participant preference to determine if any additional healthcare visits or SARS-CoV-2 testing occurred. As appropriate, additional data related to medical care and treatments provided along with complications, will be collected. If, at Day 14, a child has been continuously hospitalized since the time of initial ED presentation, this information will be captured.

Medical record review: To minimize missing data and supplement caregiver reports regarding additional medical care, a medical record review will occur 30 days after enrolment. This review will identify additional healthcare visits occurring up until 14 days following the initial ED visit. If the child was hospitalized during an eligible revisit, all outcome data available until the time of the review will be extracted.

90-day follow-up: Day 90 follow-up will be conducted through telephone, text, or email survey as per participant preference to determine if the participant is experiencing any ongoing symptoms that may be associated with the illness that prompted the initial ED presentation. Study team members will ask specifically about respiratory symptoms, psycho-behavioral concerns, and other general, persistent, new, or worsening health

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problems. If, at Day 90, a child has been continuously hospitalized since the time of initial ED presentation, this information will be captured.

Site testing criteria and regional pandemic control measures: Every week, participating sites will complete a standardized log of their institution's testing policies (e.g. symptoms and other risk factors prompting SARS-CoV-2 testing of children). In addition, they will record regional and national isolation and travel recommendations along with other pandemic control measures. Form completion will rely on institutional official documents, regional and national governmental websites, and other sources, as required.

Data Storage

A Research Electronic Data Capture (REDCap) database that is encrypted, password protected, and de-identified, is serving as the master study database. Due to our desire to launch recruitment as quickly as possible, some study sites initiated data collection using paper CRFs and subsequently back-entered data into the REDCap database once it was made available.

Sample Size

At the time of study development, there were many unknown factors related to the epidemiology of COVID-19 that precluded a robust sample size estimate. Our study design aims to enable the recruitment of more confirmed than suspected cases relative to the prevalence in the general population, creating a cohort whereby 20 – 40% of enrolled participants are confirmed to be SARS-CoV-2 positive. According to preliminary data

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from the United States the proportion of infected children with severe outcomes may be as high as 2%.[3] Among children admitted or with a high likelihood of requiring hospitalization who were tested for SARS-CoV-2 in Spain, approximately 10% needed intensive care.[9] In calculating a sample size we estimated that 2% of SARS-CoV-2 positive cases will experience severe outcomes. This is conservative estimate as the power of our study for assessing discriminative performance depends on the number of the less-frequent outcome level (i.e. severe vs. non-severe COVID-19 outcomes). For the latter outcome, the predictive model will be limited to approximately 10 degrees of freedom. Recruiting 12,500 screened COVID-19 participants (~250 screened children, on average/site) to identify 50 severe outcomes using the most conservative assumptions (12,500 x 20% x 2%) we will have 93.9% power to detect when the predictive model discriminating severe from non-severe outcomes truly (i.e. in the larger population) has a c-statistic of 0.70. These calculations used a variance inflation factor of 2.0 to account for model complexity (as measured by degrees of freedom). Power increases with higher assumed values for the c-statistic and with a higher number of assumed cases, attaining near certainty (>99.9%) to detect c=0.70 for the confirmed vs. suspected outcome. The principal investigators will analyze data and recruitment totals, alongside updated information from other studies on the behavior of COVID-19, weekly, in order to determine the optimal data dissemination plans.

Data Analysis

The following definitions will be used during data analysis:

- Suspected Case/Person Under Investigation - Patient screened (i.e. tested) but with a negative test result for SARS-CoV-2.

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- Probable Case - Suspected case with inconclusive SARS-CoV-2 result.
- Confirmed Case - Suspected case with laboratory confirmed SARS-CoV-2 infection.
- Severe outcomes - Positive pressure ventilation (invasive or noninvasive) OR intensive care unit admission with ventilatory or inotropic support OR multi-system hyper-inflammatory syndrome OR death; other outcomes may be added as the understanding of the epidemic evolves.

Statistical Analysis: The collected epidemiological, demographic, clinical, and laboratory data for all case-status groups will be summarized and compared using one-way analysis of variance, Kruskal-Wallis, or Pearson Chi-square tests, as appropriate. Simple and multiple ordinal logistic regression models will be used to estimate the capacity of the independent variables (e.g. clinical characteristics such as age and sex) to discriminate among the three-level case-status variables (i.e. suspected, probable, confirmed) and to predict severe outcomes of COVID-19. Proportional odds specifications will model two separate dichotomizations of the three-level case-status model, 1) suspected vs. probable/confirmed and 2) suspected/probable vs. confirmed, under the assumption that the multiplicative effects of individual predictors are similar for both dichotomizations, while the partial proportional odds specification allows some predictors to have separate multiplicative effects for the two dichotomizations. Data on health care resource utilization across the three case-statuses will be compared employing similar methods, with alternative specifications of link and distribution functions from the generalized linear model, as appropriate to account for outcome variable distributions. All data will

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be interpreted alongside changes to case screening and testing criteria and regional pandemic control measures.

Patient and Public Involvement

Patients and/or the public were not involved in developing the research questions or designing the study methods. This study currently has no plans to involve patients in the dissemination of study results. However results will be shared via social media and using knowledge translation tools designed to inform the public.

Timeline

As of June 11th, 2020 most (31/47) study sites have obtained regulatory approvals and have initiated recruitment. We plan to continue recruitment for up to 12 months (i.e. from April 2020 to March 2021), however this will depend on the timing and intensity of the pandemic. Allowing for the completion of the 90-day follow-up period and 3 months to complete data analysis, we anticipate that all data will be available for dissemination within 18 months of study initiation.

ETHICS & DISSEMINATION

The start-up, regulatory approvals, eligibility screening, recruitment, consent, data collection, and data entry activities for this study arm will take place locally at each site. The study was first approved in Calgary (Canada); ethics review board number REB18-0107. In the United States, similar to the PERN-Pneumonia study, sites have the option to rely on the Cincinnati Children's Hospital Medical Center Institutional Review Board

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(IRB) to act as the central institutional review board of record for this study. As this study is non-interventional, and collects no biological specimens, the risk to participants is minimal. There are no direct benefits or remuneration offered to children or families who participate in the study.

The greatest challenge to this study is the unpredictable nature of the COVID-19 pandemic and the public health policies that are enacted to control it. In the midst of this public health emergency, our study maximizes feasibility and creates limited additional stress on healthcare systems and reduces the risk of transmission by minimizing direct contact with infected patients. All CRFs can be completed by telephone, e-mail or text messaged survey, and medical record review.

We will share the results of the data collected in real-time as rapidly and as openly as possible. We will run descriptive interim analyses weekly to enable data sharing with key national and international stakeholders, our study partners, and the public. The study team includes individuals representing several leading organizations including the Public Health Agency of Canada (PHAC), the United States Centers for Disease Control and Prevention (CDC), the World Health Organization (WHO), and the United Nations Children's Fund (UNICEF). Through close communication and sharing of data with these stakeholder partners, study results may rapidly lead to evidence-based changes to, or confirmation of, institutional, regional, national, and international COVID-19 pandemic planning, case management policies, and recommendations. As appropriate and relevant, our interim analysis outputs will be made available, via links, on our research network

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organization websites. Findings will be shared in briefings and via social media platforms as appropriate. We will participate actively in relevant academic conferences and will publish all substantial findings in peer-reviewed, open-access journals. All articles will include citations to repositories that host the data underlying the results, together with details of any software used to process results. We will review and adapt our outputs management plan throughout the conduct of our project, as per discussion with all investigators as well as key knowledge users.

Harmonization with the WHO recommended CRFs will enable us to rapidly share raw anonymous source data in keeping with the *joint statement on sharing research data and findings relevant to the novel coronavirus (nCoV) outbreak* (https://wellcome.ac.uk/coronavirus-covid-19/open-data). Anonymized data will be made available upon reasonable request. Furthermore, we will collaborate and share the PERN-COVID-19 study protocol and CRFs openly with other study groups, such as the WHO Clinical Characterization and Management Research Working Group, to support the synergizing of global efforts to study pediatric COVID-19.

This study will assemble a substantial amount of data that will be analyzed to identify predictors of severe COVID-19 in children, and risk factors for pediatric SARS-CoV-2 infection. These advances will allow for the earlier identification of confirmed SARS-CoV-2 infected children, assist with creating testing criteria, and the prioritization of those likely to have severe COVID-19. These advances have the potential to predict the presence of SARS-CoV-2 infection and severe outcomes in SARS-CoV-2 infected

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children. Healthcare resource utilization will be optimized, which will improve resource availability, thereby optimizing the care for those at greatest risk. Finally, this study will establish a global multicenter network poised to rapidly respond to novel infectious pathogens, which can urgently be reactivated for future public health crises.

Author contributions

SF, TF, NK, TK, SD and AF conceptualized the study and formulated the initial study protocol. SD, SM, MS, DT, MN, DP, AP, TK, RM, LA and KK further developed and provided critical feedback on the study protocol. AF and SF wrote the manuscript. All authors edited and approved the final version of the manuscript.

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Competing interests statement.

None of the authors have any conflicts of interest to disclose.

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FIGURES

Figure 1: Locations of 47 participating PERN-COVID-19 study sites (blue dots) against a world map highlighting number of cases reported, by country, over the past 7 days (map *adapted from the WHO Situation Report, June 11th, 2020).*[29]

Figure 2: PERN-COVID-19 study participation timeline with data collection events

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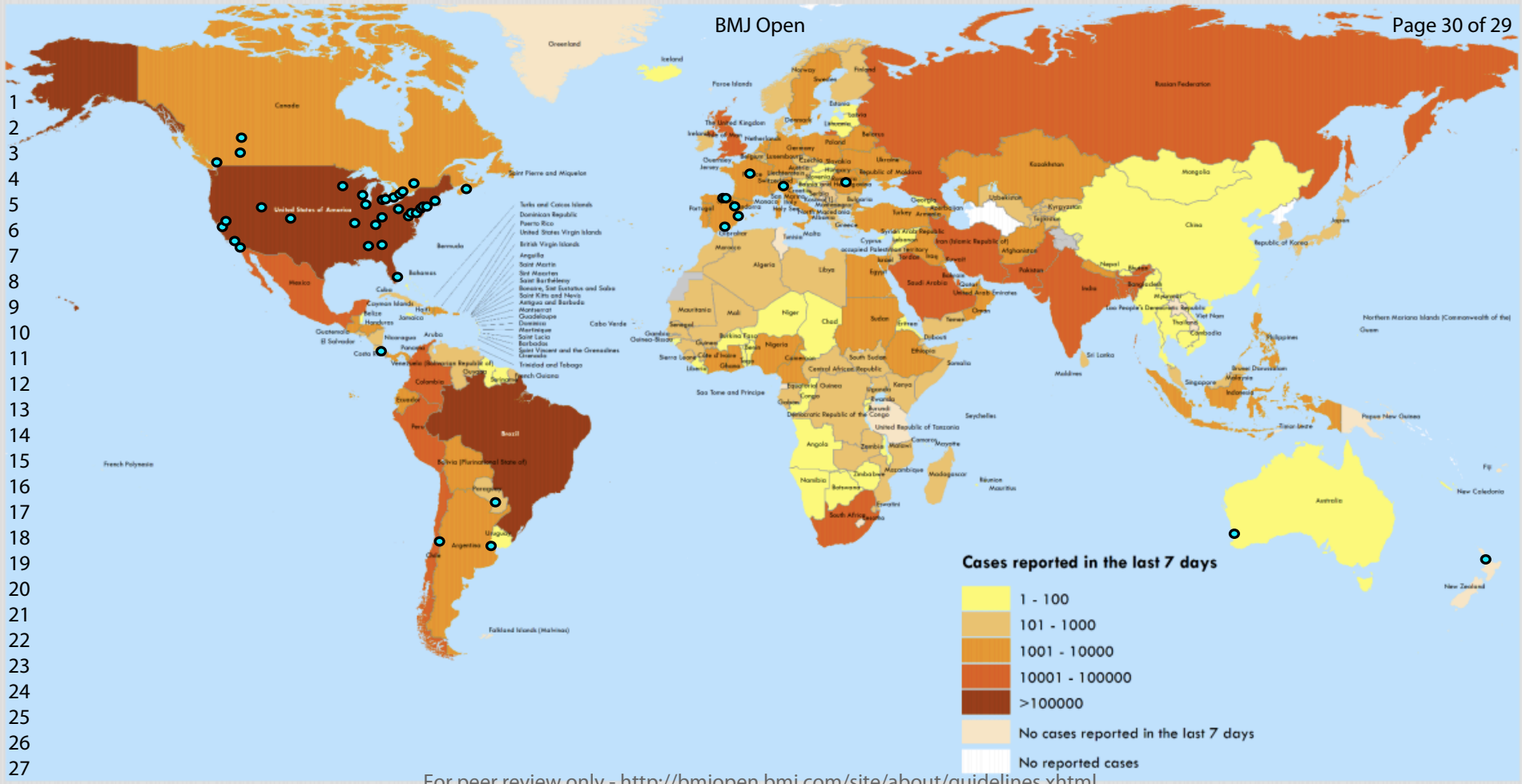

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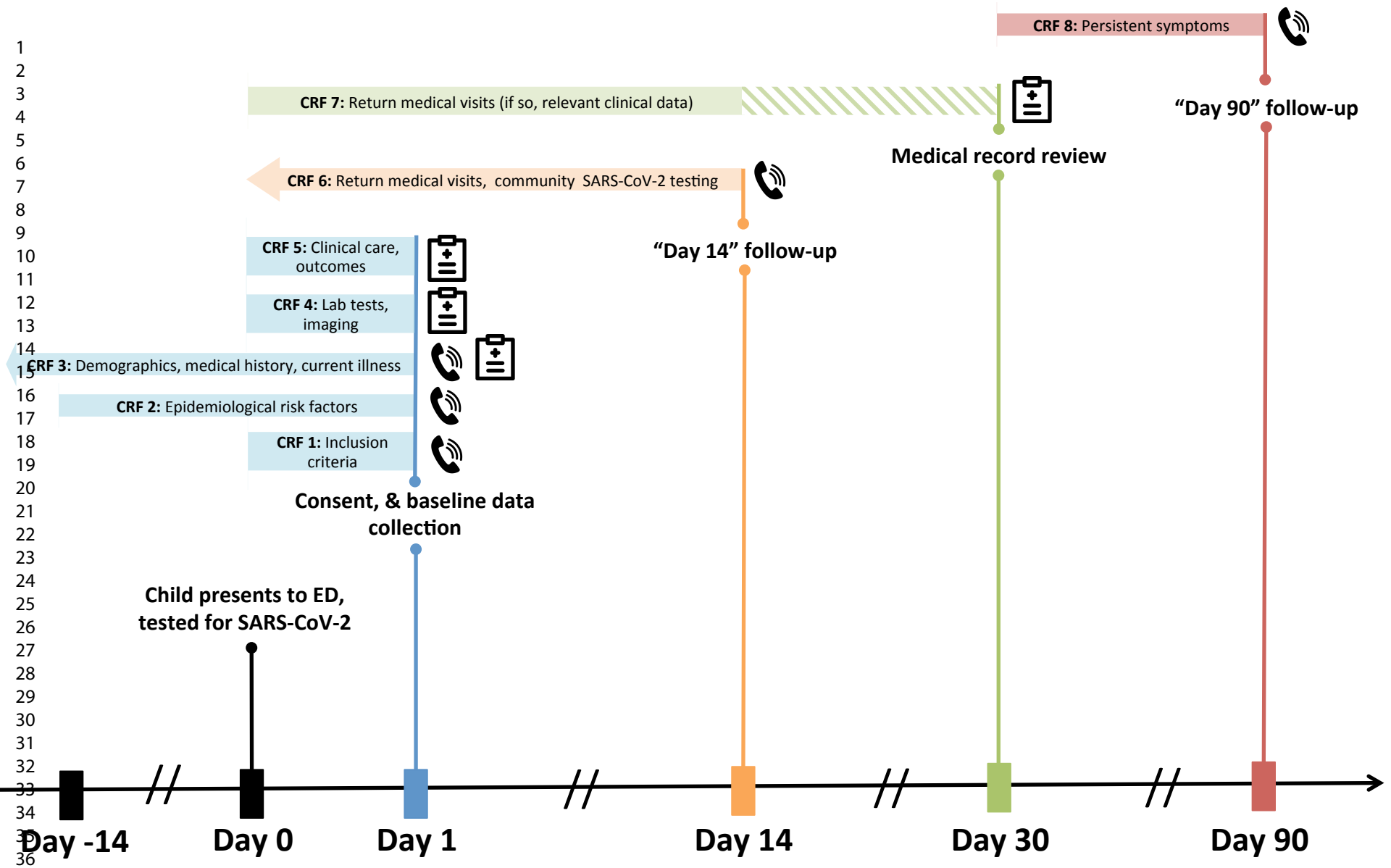

CRF = Case Report Form = Telephone (or other method if preferred) interview with caregiver = Medical chart/record review

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Prospective Cohort Study of Children with Suspected SARS-CoV-2 Infection Presenting to Pediatric Emergency Departments: A Pediatric Emergency Research Networks (PERN) Study Protocol

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Title: Prospective Cohort Study of Children with Suspected SARS-CoV-2 Infection Presenting to Pediatric Emergency Departments: A Pediatric Emergency Research Networks (PERN) Study Protocol

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Abbreviations:

CDC - United States Centers for Disease Control and Prevention

COVID-19 - 2019 novel coronavirus related disease

CRF – case report form

ED – emergency department

PECARN – Pediatric Emergency Care Applied Research Network

PEM CRC – Pediatric Emergency Medicine Collaborative Research Committee

PERC – Pediatric Emergency Research Canada

PERN – Pediatric Emergency Research Network

PHAC – Public Health Agency of Canada

PREDICT – Pediatric Research in Emergency Departments International Collaborative

REDCap - Research Electronic Data Capture

REPEM – Research in European Pediatric Emergency Medicine

RIDEPLA – Red de Investigacion y Desarollo de la Emergencia Pediatrica Latinoamerica

RISEUP-SPERG - Red de Investigación de la Sociedad Española de Urgencias de Pediatría / Spanish Pediatric Emergency Research Group

SARS-CoV-2 - severe acute respiratory syndrome coronavirus-2

UNICEF – United Nations Children's Fund

WHO – World Health Organization

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Abstract

Introduction: Relatively limited data are available regarding pediatric COVID-19. Although most children appear have mild or asymptomatic infection, infants and those with comorbidities are at increased risk of experiencing more severe illness and requiring hospitalization due to COVID-19. The recent but uncommon association of SARS-CoV-2 infection with development of a multisystem inflammatory syndrome has heightened the importance of understanding pediatric SARS-CoV-2 infection.

Methods and Analysis: The PERN-COVID-19 cohort study is a rapid, global, prospective cohort study enrolling 12,500 children who are tested for acute SARS-CoV-2 infection. 47 emergency departments across 12 countries on four continents will participate. At enrolment, regardless of SARS-CoV-2 test result, all children will have the same information collected, including clinical, epidemiological, laboratory, imaging, and outcome data. Interventions and outcome data will be collected for hospitalized children. For all children, follow-up at 14 and 90 days will collect information on further medical care received, and long-term sequelae, respectively. Statistical models will be designed to identify risk factors for infection and severe outcomes.

Ethics and Dissemination**:** Sites will seek ethical approval locally, and informed consent will be obtained. There is no direct risk or benefit of study participation. Weekly interim analysis will allow for real-time data sharing with regional, national, and international policy makers. Harmonization and sharing of investigation materials with the World Health Organization, will contribute to synergizing global efforts for the clinical

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characterization of pediatric COVID-19. Our findings will enable the implementation of countermeasures to reduce viral transmission and severe COVID-19 outcomes in children.

Registration: NCT04330261

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Article Summary

Strengths and limitations of this study

- This multi-site international research project has the unique ability to create a very large global dataset of children with COVID-19 and other infectious etiologies that will include extensive details on exposures, symptoms, investigations, treatments and outcomes.
- This study builds upon an existing multi-center research network to enable the rapid launch of a global study to address the COVID-19 pandemic.
- By collecting data on both SARS-CoV-2-positive and -negative children, we will be able to conduct comparisons to develop models, using epidemiological and clinical characteristics, to predict pediatric SARS-CoV-2 infection.
- In the context of the quickly evolving COVID-19 pandemic, varying and evolving testing and control strategies are being put in place globally, which may limit ability to combine and generalize findings across different study sites.
- As testing at some sites may overwhelm research capacity, we will be unable to collect data on 100% of SARS-CoV-2 tested children.

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INTRODUCTION

Pediatric 2019 novel coronavirus related disease (COVID-19) following severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection is not yet well characterized, and detailed reports on this topic are sparse.[1-7] Reported infections are less common in persons younger than 18 years compared with older age groups. As of early June 2020, in reports with sample sizes of COVID-19 cases ranging from 4,695 to 149,082, from China, the United States, Italy, and Spain, individuals younger than 18 years have constituted less than 2% of the total study cohort.[3 8-10]

For reasons that remain elusive, children appear to be more likely than adults to present with asymptomatic or mild disease.[1 11] The proportion of children with asymptomatic infection ranges between 4% and 16%.[4 12] However, these reports likely underestimate the frequency of asymptomatic carriage, as symptomatic patients are much more likely to be tested.[13] Moreover, symptoms in children appear to be less typical with only 73% of children with confirmed infection experiencing fever, cough or shortness of breath, which are reported in over 90% of infected adults.[3] Even when symptomatic, children appear to be less likely to develop dyspnea, hypoxemia, acute respiratory distress syndrome and multiorgan system failure.[12-14] Other symptoms, such as vomiting and diarrhea are present in 5 – 15% of children;[3 4] in older children, a loss of the sense of smell (anosmia) has been noted as a possible predictor of infection.[15] Furthermore, there is emerging evidence of a delayed multi-system inflammatory syndrome in children (MIS-C) that is linked to SARS-CoV-2 exposure that has been associated with severe outcomes.[16-19]

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The reported proportion of children with COVID-19 requiring hospitalization, although seemingly lower than that of adults, is variable and not well understood. In the United States and Canada, among children who tested positive for SARS-CoV-2, between 0.9 and 20% have reportedly required hospitalization.[3 20] Children with comorbidities and those aged <1 year appear to be at particularly high risk for hospitalization, intensive care unit admission, and death.[3 4] Although prior to mid-March, 2020, only two deaths had been reported among children worldwide,[1] in a subsequent large case series of 2,572 infected children in the United States, three additional deaths were reported.[3]

Though reports related to pediatric hospitalization and mortality exist, there is a paucity of large-scale, multi-national descriptions of the clinical features and disease course of children with COVID-19. Thus, a detailed examination of the risk factors for infection, clinical characteristics of infected children, predictors of severe outcomes, and treatments provided, is urgently needed for this unique and potentially vulnerable population. As the symptoms of SARS-CoV-2 infection are a common reason for pediatric presentation to hospitals, the early identification of high-risk children and clinical phenotypes are vital to optimizing care. Moreover, as viral shedding may occur in minimally symptomatic children,[21] an in-depth study of pediatric infection characteristics, both mild and severe, will contribute to a better understanding of transmission risks.[22] It will also be important to characterize and compare COVID-19 disease with other common pediatric respiratory illnesses to contextualize the severity of illness.

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To achieve the aforementioned objectives, our study's primary aim is to fully evaluate clinical characteristics and outcomes of SARS-CoV-2 positive and SARS-CoV-2 negative children. Specifically, among children presenting to participating hospital emergency departments (EDs) with suspected infection, we will (1) describe and compare the clinical characteristics of SARS-CoV-2 positive children (i.e. nucleic acid test-positive) and SARS-CoV-2 negative children (i.e. nucleic acid test-negative), and (2) identify factors associated with severe outcomes in SARS-CoV-2 positive children (i.e. intensive care unit admission, assisted ventilation, vasoactive medication use, MIS-C, death). The secondary aims of this study include (1) describing and comparing health care resource utilization for patient management (e.g. isolation, testing, imaging, supportive care) of both SARS-CoV-2 positive and SARS-CoV-2 negative children according to changes in national and regional policies, and (2) describing the effects of changing case screening policies for the detection of SARS-CoV-2 in children.

METHODS AND ANALYSIS

Study Design and Setting

The Pediatric Emergency Research Network (PERN; https://pern-global.com/) represents the largest global pediatric acute care research collaboration, spanning 35 countries in four World Health Organization (WHO) regions representing >200 pediatric hospitals providing care to >5 million children annually.[23] PERN represents a collaboration between seven existing pediatric emergency care medicine research networks –Pediatric Emergency Research Canada (PERC),[24 25] Pediatric Research in Emergency Departments

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International Collaborative (PREDICT),[26] the Pediatric Emergency Medicine Collaborative Research Committee (PEM CRC) of the American Academy of Pediatrics, the Pediatric Emergency Care Applied Research Network (PECARN), Research in European Pediatric Emergency Medicine (REPEM), Red de Investigacion y Desarollo de la Emergencia Pediatrica Latinoamerica (RIDEPLA), and Red de Investigación de la Sociedad Española de Urgencias de Pediatría / Spanish Pediatric Emergency Research Group (RISEUP-SPERG).[27]

In early 2019, the network launched the PERN-Pneumonia prospective cohort study to identify clinical predictors of severe outcomes in children diagnosed with community-acquired pneumonia (CAP). This global study includes 70 pediatric ED sites across 13 countries, including the United States, Canada, Spain, Italy, France, Switzerland, Romania, Argentina, Chile, Costa Rica, Paraguay, Australia, New Zealand, and Singapore. The existence of the PERN-Pneumonia study has provided a unique opportunity to expeditiously initiate a prospective cohort study of children potentially infected by SARS-CoV-2. By building on the PERN-Pneumonia study's infrastructure (e.g. ethics approvals, data sharing agreements, electronic database, study teams), we were able to rapidly initiate the PERN-COVID-19 study to fill critical gaps in the understanding of COVID-19 in children.

PERN-COVID-19 is a prospective cohort study of children with suspected acute SARS-CoV-2 infections who present for care in one of 47 participating pediatric EDs located in 12 countries on 4 continents (see Figure 1). Study recruitment began on March 16th, 2020

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at the Alberta Children's Hospital in Calgary, Canada. Most other participating sites initiated recruitment between mid-April and mid-May, 2020.

Participants and Recruitment

Eligible participants are those younger than 18 years of age who present to a participating ED for care and who are tested for SARS-CoV-2 because of suspected acute infection (i.e. symptoms, travel history, or exposure history) according to local institutional policy. This recruitment strategy will identify children who are both SARS-CoV-2 positive and SARS-CoV-2 negative. The indications for testing children identified as potentially infected will differ by country, region, and over time; however standardization of these protocols is beyond the control of this study. Participants are excluded if the caregivers and/or children do not provide informed consent and assent, as required, respectively.

This pragmatic observational study does not specify the SARS-CoV-2 testing criteria, the specimen type collected for testing, or the SARS-CoV-2 nucleic acid test performed. In some sites, a combination of nucleic acid and serological tests may be performed. Information on *all* SARS-CoV-2 tests performed on study participant specimens will be collected. It is recognized that the standard procedures and criteria for SARS-CoV-2 testing are continuously evolving, often based on access to swabs, reagents and the regional epidemiology of disease. Therefore, detailed information on these policies will be reported weekly by sites. Local practices and illness severity will dictate decisions regarding isolation, investigations, treatments and hospitalization.

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Protocol implementation will vary by site to enhance feasibility. Sites may recruit participants in real-time as they present at the ED, or after the ED visit (e.g. via a daily list of all children who presented to the ED and underwent SARS-CoV-2 testing). Contact procedures (e.g. in-person or via telephone) and the consent process (e.g. written or verbal) will adhere to each site's approved ethics agreements. In the instance of verbal consent attained via telephone, a detailed consent form is then emailed to the caregiver. All consent is recorded in the participant's case report forms. Sensitive to the child's clinical condition and isolation policies, a research team member at each institution will contact the guardian to obtain informed consent and assent, as appropriate. The initial contact with hospitalized patients may occur in-person within the hospital or via telephone and will always occur by telephone if the patient has returned home (i.e. not admitted or already discharged).

When the study was initiated, testing was limited at most sites and sites were instructed to attempt to recruit all children screened for SARS-CoV-2 infection. However, over time, the number of children screened increased, at which time the protocol was revised to have sites attempt to consecutively recruit the first five children tested each day. In sites located in areas where community prevalence of COVID-19 was very low, we moved to recruit the first two children tested each day. As enrolment may occur prior to SARS-CoV-2 test results becoming available, if none of the enrolled children on a given day are ultimately SARS-CoV-2 test-positive, then we will attempt to enroll up to two additional test-positive children. This is performed by returning to the list of children tested, and continuing consecutively, attempting to recruit children with known positive test results.

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Data Collection

Participant demographic, epidemiological and clinical data will be collected at the time of enrolment in the ED, or shortly after. Clinical data will be collected throughout the period of hospitalization (if relevant). At 14 and 90 days following the index ED visit, information on healthcare revisits and persistent symptoms will be collected, respectively. (Figure 2) Follow-up data collection time points were selected based on the presumed natural history of COVID-19 (i.e. symptom progression 7 – 10 days after onset) while accounting for both short- and longer-term potential complications.[28] To complete case report forms (CRFs), study staff will consult hospital medical records and caregivers. A medical record review to verify 14-day outcome data will be performed which will also minimize loss-to-follow-up. We anticipate that children lost to follow-up without a hospital revisit did not experience an adverse outcome as study sites all serve as regional tertiary care centers, and thus it is unlikely that a critically ill child would both be lost to follow-up and would be cared for elsewhere. Follow-up will be performed via telephone, text, or email as per caregiver preference and as feasible based on-site resources and approvals. Our data forms are harmonized with the WHO recommended CRFs for clinical characterization of COVID-19 (https://www.who.int/docs/default-source/coronaviruse/who-ncov-crf.pdf?sfvrsn=84766e69_4). All research staff will be trained using a standardized and detailed manual of operations that includes explanations and examples for any potentially subjective questions in the study's data collection forms.

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Baseline data: A study team member will complete the enrolment CRFs using the participants medical records and through a caregiver interview. Data collected will include: calendar date and site of enrolment, epidemiological risk factors (e.g. recent travel, exposures), demographics (e.g. age, sex), health information (e.g. past medical history, vaccination status, comorbidities), onset of current illness (e.g. timing, symptoms), imaging and laboratory investigations performed in the ED and treatments and care received (e.g. intravenous fluids, antivirals, antibiotics).

Hospitalization data: Enrolment CRFs will further capture management and outcome data related to events occurring during the initial hospitalization, if required. Data collected will include length of hospital stay, level of hospital care required (e.g. intensive care unit), laboratory tests, interventions, and complications.

14-day follow-up: Day 14 follow-up will be conducted through telephone, text, or email survey as per participant preference to determine if any additional healthcare visits or SARS-CoV-2 testing occurred. As appropriate, additional data related to medical care and treatments provided along with complications, will be collected. If, at Day 14, a child has been continuously hospitalized since the time of initial ED presentation, this information will be captured.

Medical record review: To minimize missing data and supplement caregiver reports regarding additional medical care, a medical record review will occur 30 days after enrolment. This review will identify additional healthcare visits occurring up until 14

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days following the initial ED visit. If the child was hospitalized during an eligible revisit, all outcome data available until the time of the review will be extracted.

90-day follow-up: Day 90 follow-up will be conducted through telephone, text, or email survey as per participant preference to determine if the participant is experiencing any ongoing symptoms that may be associated with the illness that prompted the initial ED presentation. Study team members will ask specifically about respiratory symptoms, psycho-behavioral concerns, and other general, persistent, new, or worsening health problems. If, at Day 90, a child has been continuously hospitalized since the time of initial ED presentation, this information will be captured.

Site testing criteria and regional pandemic control measures: Every week, participating sites will complete a standardized log of their institution's testing policies (e.g. symptoms and other risk factors prompting SARS-CoV-2 testing of children). In addition, they will record regional and national isolation and travel recommendations along with other pandemic control measures. Form completion will rely on institutional official documents, regional and national governmental websites, and other sources, as required.

Data Storage

A Research Electronic Data Capture (REDCap) database that is encrypted, password protected, and de-identified, is serving as the master study database. Due to our desire to launch recruitment as quickly as possible, some study sites initiated data collection using

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paper CRFs and subsequently back-entered data into the REDCap database once it was made available.

Sample Size

At the time of study development, there were many unknown factors related to the epidemiology of COVID-19 that precluded a robust sample size estimate. Our study design aims to enable the recruitment of more positive than negative cases relative to the prevalence in the general population, creating a cohort whereby 20 – 40% of enrolled participants are confirmed to be SARS-CoV-2 positive. According to preliminary data from the United States the proportion of infected children with severe outcomes may be as high as 2%.[3] Among children admitted or with a high likelihood of requiring hospitalization who were tested for SARS-CoV-2 in Spain, approximately 10% needed intensive care.[9] In calculating a sample size we estimated that 2% of SARS-CoV-2 positive cases will experience severe outcomes. This is conservative estimate as the power of our study for assessing discriminative performance depends on the number of the less-frequent outcome level (i.e. severe vs. non-severe outcomes in SARS-CoV-2 positive children). For the severe outcomes, the predictive model will be limited to approximately 10 degrees of freedom. Recruiting 12,500 SARS-CoV-2 screened participants (~250 screened children, on average/site) to identify 50 severe outcomes in SARS-CoV-2 positive children using the most conservative assumptions (12,500 x 20% x 2%) we will have 93.9% power to detect when the predictive model discriminating severe from non-severe outcomes truly (i.e. in the larger population) has a c-statistic of 0.70. These calculations used a variance inflation factor of 2.0 to account for model complexity

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(as measured by degrees of freedom).[29] Power increases with higher assumed values for the c-statistic and with a higher number of assumed cases, attaining near certainty (>99.9%) to detect c=0.70 for the model of SARS-CoV-2 positive vs. SARS-CoV-2 negative children (the other primary objective of this study). The principal investigators will analyze data and recruitment totals, alongside updated information from other studies on the behavior of COVID-19, weekly, in order to determine the optimal data dissemination plans. Sample size calculations were performed using the SAS ROCPOWER macro.[30]

Data Analysis

The following definitions will be used during data analysis:

- SARS-CoV-2 negative - Patient screened (i.e. tested) but with a negative test result for SARS-CoV-2.
- SARS-CoV-2 positive - Patient screened (i.e. tested) with laboratory confirmed SARS-CoV-2 infection.
- Severe outcomes - Positive pressure ventilation (invasive or noninvasive) OR intensive care unit admission with ventilatory or inotropic support or > 48 hour hospitalization OR multi-system hyper-inflammatory syndrome OR death; other outcomes may be added as the understanding of the epidemic evolves.
- 90-day outcomes / persistent symptoms – a child will be considered as having a persistent symptom if the parents have indicated, at the 90-day follow-up, that respiratory, psychosocial, or 'other' symptoms that began in the immediate time period surrounding the ED visit are persisting until the present day.

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Statistical Analysis: The collected epidemiological, demographic, clinical, and laboratory, and follow-up data for SARS-CoV-2 positive and SARS-CoV-2 negative participants will be summarized and compared using one-way analysis of variance, Kruskal-Wallis, or Pearson Chi-square tests, as appropriate. Bivariable analysis will be used to compare stratified (e.g. by age category, region) severe outcome risk estimates among SARS-CoV-2 positive children to each other, as well as to similarly stratified severe outcome risk estimates among children who are SARS-CoV-2 negative. Conditional multiple logistic regression models, with matched groups based on hospital of enrolment, will be used to identify a set of independent variables that are able to: 1) discriminate among the two main case-statuses (i.e. SARS-CoV-2 positive and SARS-CoV-2 negative), and 2) predict severe outcomes of COVID-19. For each of these two types of models, subgroup analyses using only a subset of the population of interest (e.g. children younger than 90 days of age, children with chronic illnesses, etc.) may be conducted. As there is a potential for misclassification with respect to infection status (e.g. false negatives) due to the sensitivity and specificity of the SARS-CoV-2 tests used, sensitivity analyses using measurement error models and other strategies will be conducted.[31,32] The selection of variables for inclusion in the models will rely heavily on expert judgment among study investigators and will be supplemented by literature review. Strategies such as elastic-net regression will be used in order to improve the external generalizability of the model. Data on health care resource use across the two main case-statuses will be compared using similar methods, with alternative specifications of link and distribution functions from the generalized linear model, as

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appropriate to account for outcome variable distributions. All data will be interpreted alongside changes to case screening and testing criteria and regional pandemic control measures. Our primary analyses will be complete case analyses, as we anticipate that key outcome and predictive variables will be available for a large fraction of the study population. However, sensitivity analyses evaluating the impacts of non-ignorable missingness on the soundness of our complete case inferences will be conducted and reported according to principled approaches to missing data.[33] A detailed statistical analysis plan can be found in the Appendix.

Patient and Public Involvement

Patients and/or the public were not involved in developing the research questions or designing the study methods. This study currently has no plans to involve patients in the dissemination of study results. However results will be shared via social media and using knowledge translation tools designed to inform the public.

Timeline

As of June 11th, 2020 most (31/47) study sites have obtained regulatory approvals and have initiated recruitment. We plan to continue recruitment for up to 12 months (i.e. from April 2020 to March 2021), however this will depend on the timing and intensity of the pandemic. Allowing for the completion of the 90-day follow-up period and 3 months to complete data analysis, we anticipate that all data will be available for dissemination within 18 months of study initiation.

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ETHICS & DISSEMINATION

The start-up, regulatory approvals, eligibility screening, recruitment, consent, data collection, and data entry activities for this study arm will take place locally at each site. The study was first approved in Calgary (Canada) by the University of Calgary's Conjoint Health Research Ethics Board (REB18-0107). In the United States, similar to the PERN-Pneumonia study, sites have the option to rely on the Cincinnati Children's Hospital Medical Center Institutional Review Board (IRB) to act as the central institutional review board of record for this study. As this study is non-interventional, and collects no biological specimens, the risk to participants is minimal. There are no direct benefits or remuneration offered to children or families who participate in the study.

The greatest challenge to this study is the unpredictable nature of the COVID-19 pandemic and the public health policies that are enacted to control it. In the midst of this public health emergency, our study maximizes feasibility and creates limited additional stress on healthcare systems and reduces the risk of transmission by minimizing direct contact with infected patients. All CRFs can be completed by telephone, e-mail or text messaged survey, and medical record review. As case-screening criteria will vary both by site and by time period, a limitation includes the potential for selection bias; our statistical modelling approaches are designed to account for some of this bias. There is also the potential for misclassification (e.g false negatives) within the SARS-CoV-2 positive and SARS-CoV-2 negative groups. In order to understand how the sensitivity of real-time polymerase chain reaction (RT-PCR) performed on nasopharyngeal and oropharyngeal swabs might lead to misclassification in our control group of SARS-CoV-

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2 negative children, we need to also consider the pre-test probability of being infected.[34-36] It is reasonable to believe that the pre-test probability among children tested for SARS-CoV-2 due to suspected infection in EDs would still be relatively low at any one time, due to the highly sensitive screening criteria that are commonly used (e.g. any child with fever). With a test sensitivity of 70% and a pre-test probability of 15% (a conservatively high estimate) in children with any symptom potentially suggestive of SARS-CoV-2 presenting to participating EDs, the percentage of misclassification of the SARS-CoV-2 negative control group would be 5%.[35] These limitations are addressed in our statistical analysis plan, which outlines the use of measurement error models to account for varying levels of misclassification in our study groups.

We will share the results of the data collected in real-time as rapidly and as openly as possible. We will run descriptive interim analyses weekly to enable data sharing with key national and international stakeholders, our study partners, and the public. The study team includes individuals representing several leading organizations including the Public Health Agency of Canada (PHAC), the United States Centers for Disease Control and Prevention (CDC), the World Health Organization (WHO), and the United Nations Children's Fund (UNICEF). Through close communication and sharing of data with these stakeholder partners, study results may rapidly lead to evidence-based changes to, or confirmation of, institutional, regional, national, and international COVID-19 pandemic planning, case management policies, and recommendations. As appropriate and relevant, our interim analysis outputs will be made available, via links, on our research network organization websites. Findings will be shared in briefings and via social media platforms

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as appropriate. We will participate actively in relevant academic conferences and will publish all substantial findings in peer-reviewed, open-access journals. All articles will include citations to repositories that host the data underlying the results, together with details of any software used to process results. We will review and adapt our outputs management plan throughout the conduct of our project, as per discussion with all investigators as well as key knowledge users.

Harmonization with the WHO recommended CRFs will enable us to rapidly share raw anonymous source data in keeping with the *joint statement on sharing research data and findings relevant to the novel coronavirus (nCoV) outbreak* (https://wellcome.ac.uk/coronavirus-covid-19/open-data). Anonymized data will be made available upon reasonable request. Furthermore, we will collaborate and share the PERN-COVID-19 study protocol and CRFs openly with other study groups, such as the WHO Clinical Characterization and Management Research Working Group, to support the synergizing of global efforts to study pediatric COVID-19.

This study will assemble a substantial amount of data that will be analyzed to identify predictors of severe COVID-19 in children, and risk factors for pediatric SARS-CoV-2 infection. These advances will allow for the earlier identification of confirmed SARS-CoV-2 infected children, assist with creating testing criteria, and the prioritization of those likely to have severe COVID-19. These advances have the potential to predict the presence of SARS-CoV-2 infection and severe outcomes in SARS-CoV-2 infected children. Healthcare resource utilization will be optimized, which will improve resource

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availability, thereby optimizing the care for those at greatest risk. Finally, this study will establish a global multicenter network poised to rapidly respond to novel infectious pathogens, which can urgently be reactivated for future public health crises.

Author contributions

SF, TF, NK, TK, SD and AF conceptualized the study and formulated the initial study protocol. SD, SM, MS, DT, MN, DP, AP, TK, RM, LA and KK further developed and provided critical feedback on the study protocol. AF and SF drafted the manuscript. All authors edited and approved the final version of the manuscript.

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Competing interests statement.

None of the authors have any conflicts of interest to disclose.

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FIGURES

Figure 1: Locations of 47 participating PERN-COVID-19 study sites (blue dots) against a world map highlighting number of cases reported, by country, over the past 7 days (map *adapted from the WHO Situation Report, June 11th, 2020).*[37]

Figure 2: PERN-COVID-19 study participation timeline with data collection events

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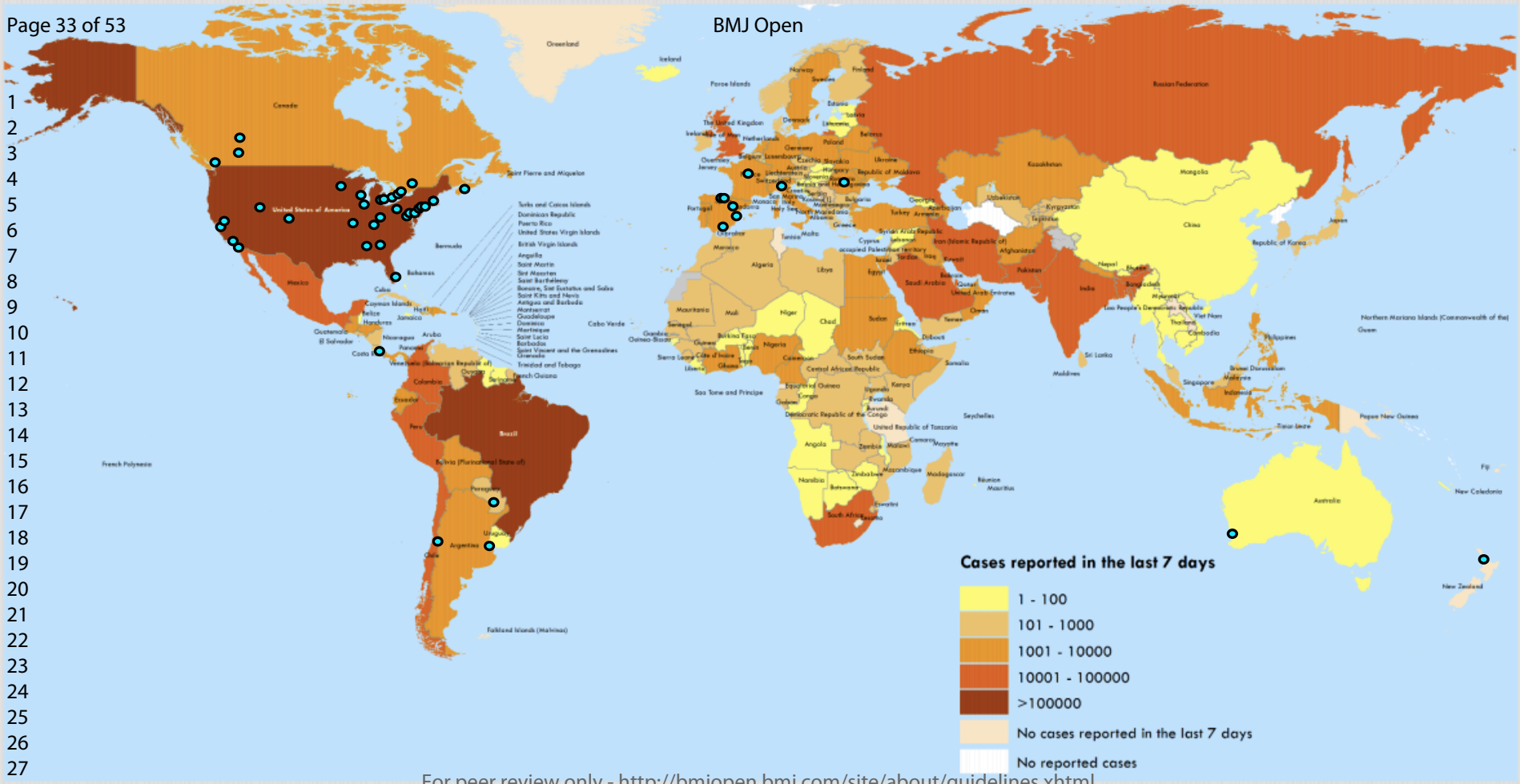

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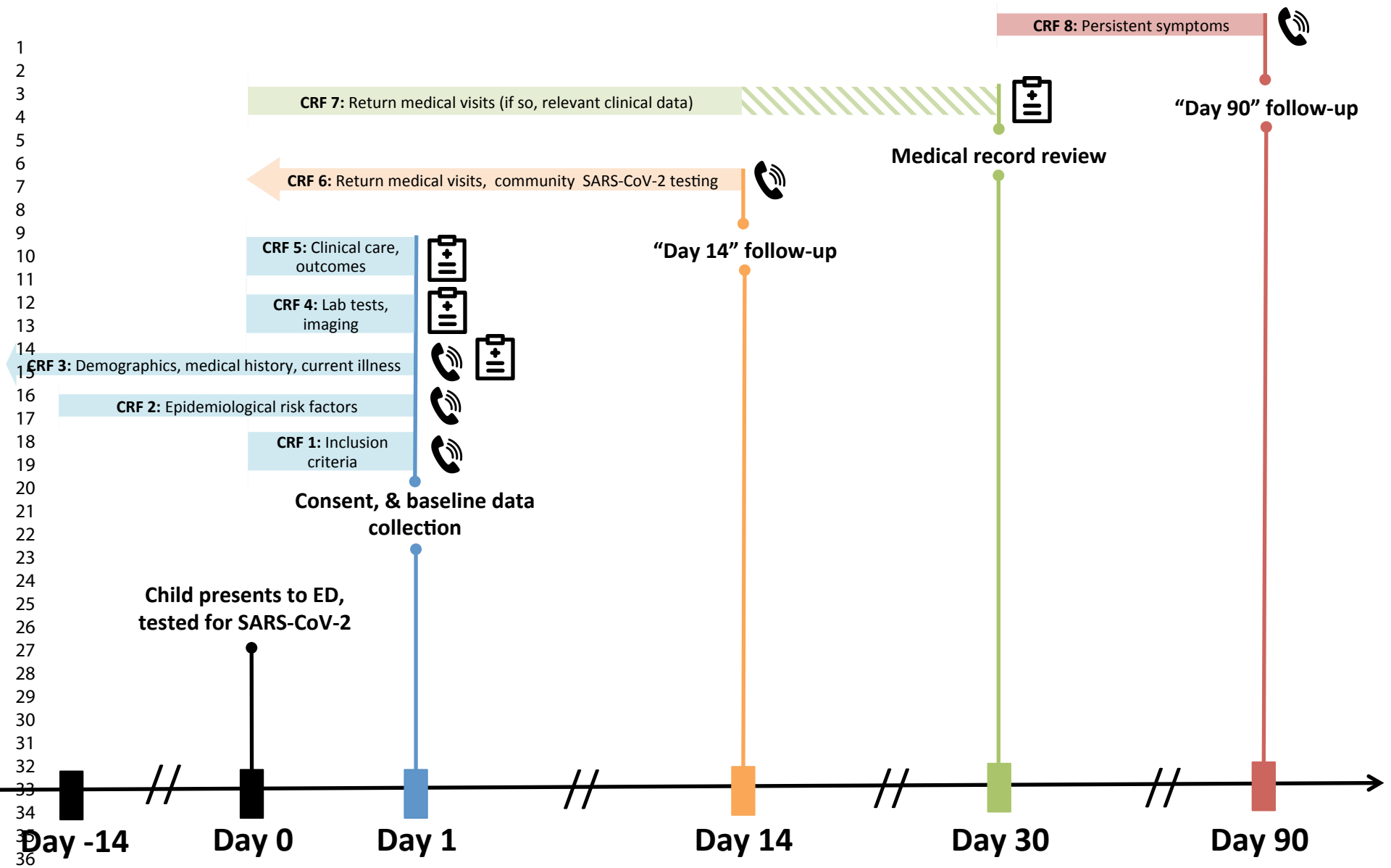

CRF = Case Report Form

= Telephone (or other method if preferred) interview with caregiver

= Medical chart/record review

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Statistical Analysis Plan (SAP)

Prospective Cohort Study of Children with Suspected SARS-CoV-2 Infection Presenting to Pediatric Emergency Departments: A Pediatric Emergency Research Networks (PERN) Study

Clinicaltrials.gov registration #: NCT04330261

SAP Version 1.0

October 31st 2020

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Background

Relatively limited data are available regarding pediatric COVID-19. Although most children appear to have mild or asymptomatic infections, infants and those with comorbidities may be at increased risk of experiencing more severe illness and requiring hospitalization due to COVID-19. The recent but uncommon association of SARS-CoV-2 infection with development of a multisystem inflammatory syndrome has heightened the importance of understanding pediatric SARS-CoV-2 infection.

Though reports related to pediatric hospitalization and mortality exist, there are few large-scale, multi-national descriptions of the clinical features and disease course of children with COVID-19. Thus, a detailed examination of the risk factors for infection, clinical characteristics of infected children, predictors of severe outcomes, and treatments provided, is urgently needed for this unique and potentially vulnerable population. As the symptoms of SARS-CoV-2 infection are a common reason for pediatric presentation to hospitals, the early identification of high-risk children and clinical phenotypes are vital to optimizing care. Moreover, as viral shedding may occur in minimally symptomatic children, an in-depth study of pediatric infection characteristics, both mild and severe, will contribute to a better understanding of transmission risks. It will also be important to characterize and compare COVID-19 disease with other common pediatric illnesses to contextualize the severity of illness.

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Objectives and hypotheses

The primary aim of this study is to fully evaluate the clinical characteristics and outcomes of SARS-CoV-2 positive and SARS-CoV-2 negative children who were tested in the emergency department (ED) due to suspected infection.

Specific primary objectives and hypotheses:

(1) Describe and compare the characteristics of SARS-CoV-2 positive children (i.e. nucleic acid test-positive) and SARS-CoV-2 negative children (i.e. nucleic acid test-negative).

→ We hypothesize that the characteristics of children positive and negative for SARS-CoV-2 will differ.

(2) Identify factors associated with severe outcomes in SARS-CoV-2 positive children (i.e. intensive care unit admission, assisted ventilation, vasoactive medication use, MIS-C, death).

→ We hypothesize that various factors will be associated with severe outcomes of SARS-CoV-2 infection in children, including but not limited to the age of the participant and the presence of underlying medical conditions.

Specific secondary objectives and hypotheses:

(1) Describe and compare health care resource utilization for patient management (e.g. isolation, testing, imaging, supportive care) of both SARS-CoV-2-positive

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and SARS-CoV-2 negative children according to changes in national and regional policies.

→ We hypothesize that health care resource utilization for patient management of SARS-CoV-2 positive and negative children will differ based on changes in national and regional policies.

(2) Describe the effects of changing case screening policies for the detection of SARS-CoV-2 in children.

→ We hypothesize that case screening policies that require either a known close-contact with a suspected case or symptoms specific to upper respiratory traction infections, will lead to decreased overall screening numbers but increased positivity rates, by site.

Study Methods

Study design

This is a cohort study of children tested for SARS-CoV-2 at 47 EDs in 13 countries. This cohort study includes a final 90-day follow-up survey.

Power considerations

At the time of study development, there were many unknown factors related to the epidemiology of COVID-19 that precluded a robust sample size estimate. Our sampling strategy aims to enable the recruitment of more positive than negative cases relative to the prevalence in the general population, creating a cohort whereby 20 – 40% of enrolled

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participants are confirmed to be SARS-CoV-2 positive. According to preliminary data from the United States, the proportion of positive children with severe outcomes may be as high as 2%.[1] Among children hospitalized or with a high likelihood of requiring hospitalization who were tested for SARS-CoV-2 in Spain, approximately 10% needed intensive care.[2] In calculating a sample size, we estimated that 2% of SARS-CoV-2 positive children will experience severe outcomes. This is a conservative estimate as the power of our study for assessing discriminative performance depends on the number of the least-frequent outcome level (i.e. severe vs. non-severe outcomes in SARS-CoV-2 positive children). For the severe outcomes, the predictive model will be limited to approximately 10 degrees of freedom. Recruiting 12,500 SARS-CoV-2 screened participants (~250 screened children, on average/site) to identify 50 severe outcomes in SARS-CoV-2 positive children using the most conservative assumptions (12,500 x 20% x 2%) we will have 93.9% power to detect when the predictive model discriminating severe from non-severe outcomes among this sample truly (i.e. in the larger population) has a c-statistic of 0.70. These calculations used a variance inflation factor of 2 to account for model complexity (as measured by degrees of freedom).[3] Power increases with higher assumed values for the c-statistic and with a higher number of assumed cases, therefore attaining near certainty (>99.9%) to detect c=0.70 for the infection risk model of SARS-CoV-2 positive vs SARS-CoV-2 negative children (the other primary objective of the study). We will analyze data and recruitment totals, alongside updated information from other studies on the behavior of COVID-19, weekly, in order to determine the optimal timing and method of data dissemination. Sample size calculations were performed using the SAS ROCPOWER macro,[4] as described by Obuchowski.[5]

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Statistical repetitive analyses

This study aims to provide frequent (up to weekly) basic descriptive analyses regarding the outcomes of children with SARS-CoV-2; the primary reason for these analyses will be to monitor data quality and workflow. We aim to perform interim analyses (at an approximate mid-point of the study in terms of participant recruitment) for all primary aims and objectives, under the condition that the sample power at that stage would allow for meaningful conclusions for that specific question – no decisions for continuing or stopping the study will be based on these analysis.

Timing of final analysis

We aim to conduct the final analyses for this study within five months following recruitment of the last enrolled participant. This five-month time period will allow for completion of the 90-day follow-up encounter for the final participant as well as an additional 30 days for final data entry and resolving data queries.

Timing of outcome assessments and timing of loss-to-follow-up

There are two key time points for assessment of outcomes, corresponding with timing to define loss-to-follow-up, among children screened for SARS-CoV-2:

- **Four weeks following the initial ED visit**, there will be an assessment of whether or not the child had a severe outcome following SARS-CoV-2 positivity.

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This outcome will be based on data collected between the participant's recruitment and that time point. At that time, participants will be considered lost to follow-up if: five successive attempts to contact the child/caregiver at the time-point two weeks following the ED visit were unsuccessful *and* a medical record review at a time point four weeks following the ED visit was not possible (e.g. unable to link child's healthcare number). In the case that a particular site or region may have a high amount of missing data for severe outcomes when relying on the medical record review (e.g. site with medical records not harmonized across a region, making it unknown if a child had a severe outcome at a different hospital) then loss to follow-up will be defined based only on the five unsuccessful attempts to contact the child/caregiver two-weeks following enrolment.

- **90 days following the ED visit**, there will be an assessment of persistent symptoms or longer-term outcomes of participating children. At this time point, a participant will be considered lost to follow-up if: five successive attempts to contact the child/caregiver between 90 and 120 days since emergency department enrolment are unsuccessful.

Study Population

Screening, eligibility, recruitment

We intend to record the number of children screened per week, overall by site, on a standardized form that collects information on screening and isolation measures in place at that hospital and in the surrounding region. These data reflect the number of children

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eligible for study inclusion at the site each week (as eligibility includes screening for SARS-CoV-2 based on suspicion of infection). The number of caregivers of children contacted for enrolment will be recorded on a confidential form that will be kept locally. We will record the number of potentially eligible participants refusing participation or who are unable to be contacted on the form. The number of eligible children contacted for recruitment, as well as the eventual number of those recruited, will be reported in subsequent manuscripts through use of flow-diagrams.

Potential confounding covariates

At present, the below list of covariates are deemed to potentially confound the results of analyses regarding the study's primary objectives to investigate risk factors for infection (comparing SARS-CoV-2 positive and SARS-CoV-2 negative children) and risk factors for severe infection (amongst SARS-CoV-2 positive children). *Although these variables have been identified as possible confounders, they may also be factors predictive of SARS-CoV-2 positivity and of severe outcomes of COVID-19.* This list may be expanded as international understanding of the natural history of SARS-CoV-2 develops.

- Site (hospital) of enrolment
- Season and/or time period of enrolment as it relates to stages of the pandemic
- Participant age
- Participant biological sex
- Presence of underlying medical conditions
- Participant ethnicity / race

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Analysis

Outcome definitions

The following definitions will be used during data analysis:

- **SARS-CoV-2 negative** - Patient screened (i.e. tested) but with a negative test result for SARS-CoV-2.
- **SARS-CoV-2 positive** - Patient screened (i.e. tested) with laboratory confirmed SARS-CoV-2 infection.
- **Severe outcomes** (within four weeks of enrolment)- Positive pressure ventilation (invasive or noninvasive) OR intensive care unit admission with ventilatory or inotropic support or > 48 hour hospitalization OR renal replacement therapy OR multi-system inflammatory syndrome OR death; other outcomes may be added as the understanding of the epidemic evolves.
- **90 day outcomes / persistent symptoms** – a child will be considered as having a persistent symptom if the parents have indicated, at 90 day follow-up, that respiratory, psychosocial, or 'other' symptoms that began in the immediate time period surrounding the ED visit are persisting until the present day. Both respiratory and psychosocial persistent symptoms are collected as a Yes/No outcome, along with free text to further describe the symptoms experienced. The presence of 'other' symptoms is collected only as free text; which of these symptoms (e.g. chronic fatigue) are considered as among those possibly linked to COVID-19 will be

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determined based on expert consensus and through scientific literature published at the time of analysis.

Analysis methods

In all cases, effect size estimation with 95% confidence intervals will be prioritized. Statistical significance will be considered at the traditional level of $p<0.05$ for comparative analyses. In cases where multiple testing is a concern, we will use methods to control the false discovery rate at 10% within the family of related inferences.[6]

Statistical analysis methods related to the first primary objective of the study

The first primary objective of this study is to describe and compare the characteristics of SARS-CoV-2 positive children (i.e. nucleic acid test-positive) and SARS-CoV-2 negative children (i.e. nucleic acid test-negative). This will be accomplished through three types of analyses:

1) **Descriptive analysis characterizing SARS-CoV-2 positive children:** We will describe in detail the follow-up of the cohort of SARS-CoV-2 positive children, from the time of their ED visits until 90 days later. Descriptive statistics will be used to summarize participant characteristics and the risk of various outcomes at each follow-up time-point. The descriptive statistics used to summarize participant characteristics (demographic, epidemiological, laboratory, clinical) and outcomes will include proportions (with 95% confidence intervals), means (with standard deviations), or medians (with interquartile ranges), as appropriate depending on the variable type and

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value distribution. Loss-to-follow-up occurring between each follow-up time point will be reported.

2) Unadjusted (bivariable) analysis of the entire cohort of children tested for SARS-CoV-2

Two types of unadjusted bivariable analyses will be done:

- Among SARS-CoV-2 positive children, stratified outcome risks will be estimated based on variables including the age of participants, the country of enrolment, and the specific site of enrolment (when possible based on the number of children enrolled at the site). Stratified risk estimates of severe outcomes will be presented along with 95% confidence intervals, and will be compared to each other using the Chi-square or Fisher's exact test (when the number of events is less than 10 for any stratum). Patient characteristics, outside of the stratified variable, will be summarized and compared using one-way analysis of variance, Kruskal-Wallis, or Pearson Chi-square tests, as appropriate.
- The stratified outcome risk estimates in SARS-CoV-2 positive children derived through the above analyses will be compared to these risks in selected subsets of the SARS-CoV-2 negative controls. The subsets of participants selected for comparison may include but will not be limited to: 1) SARS-CoV-2 negative children with specific symptom complexes (e.g. symptoms of an upper respiratory tract infection such as rhinorrhea and cough) 2) SARS-CoV-2 negative children, regardless of presenting symptoms or diagnosis. Stratified risk estimates for SARS-CoV-2 positive and SARS-CoV-2 negative participants will

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be presented along with 95% confidence intervals, and will be compared using the Pearson Chi-square, Fisher's exact (when the number of events is less than 10 for either group), one-way analysis of variance, or Kruskal-Wallis tests, as appropriate. Patient characteristics, outside of the stratified variable, will be summarized and compared using one-way analysis of variance, Kruskal-Wallis, or Pearson Chi-square tests, as appropriate.

3) **Adjusted analyses:** Multiple logistic regression models will be used to identify a set of independent variables (e.g. age, biological sex, presence of an underlying condition, ethnicity/race, etc.) able to discriminate between the two main case-statuses (SARS-CoV-2 positive vs SARS-CoV-2 negative). From site-to-site, there will be variability in the sampling fractions (SARS-CoV-2 positive, SARS-CoV-2 negative), hence it will be important to control for these effects when fitting the multiple logistic regression models. We anticipate that our primary modeling strategy will be conditional logistic regression where the matched groups are based on the ED site. As a backup strategy in case there are computational or theoretical difficulties with use of conditional logistic regression models with ED sites considered as the matched sets, we will either use alternative matched sets (e.g. grouping of sites by region and sampling fraction), or unconditional logistic regression models that include terms for site effects. These models may need to use survey weights to address concerns with sampling fractions. The overall discriminative capacity of the model will be estimated along with the 95% confidence interval by first estimating Somers' D, and the D estimate will be transformed to a c-statistic using the formula

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c=0.5*(D+1).[7] We will also estimate out-of-sample performance using 10-fold cross validation. Treatment of missing data and selection of variables to include in models are discussed in later sections of this statistical analysis plan.

Subgroup and sensitivity analyses:

- There is interest in models for specific subsets of the pediatric population, such as: children younger than 90 days of age, school-aged children, and children with chronic illnesses. Two approaches may be used to develop these models. One would be development of a model anew as described above for the larger population. Alternatively, in the case that a model is already available for a larger population, one tailored to the subpopulation (e.g. removing unnecessary variables and refitting coefficients).
- As the sensitivity and specificity of SARS-CoV-2 testing are not 100%, misclassification of children with respect to infection status (e.g. false negatives and positives) could potentially result in bias. To explore the potential impacts of misclassification on our inferences, we will conduct and report various sensitivity analyses under a variety of assumptions regarding the extent of misclassification. We will compare the resulting inferences to our primary inferences in order to allow a judgment of the extent of this misclassification. In some sensitivity analyses, we will use measurement error models for misclassified response variables and assume relevant values for the misclassification parameters.[8 9] Another type of sensitivity analysis will exclude participants with factors related to increased pre-test probability from the SARS-CoV-2 negative control group.

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These, include symptoms experienced, lengthy time since symptom onset, and history of close contact with a known case.

Statistical analysis methods related to the second primary objective

The second primary objective is to identify factors associated with severe outcomes in children positive with SARS-CoV-2. This will be done through use of similar multiple logistic regression models, as described above. The salient concerns regarding the variation from site-to-site in terms of sampling fractions is only relevant to the extent that there may be differences among the SARS-CoV-2 positive participants with respect to severity. However, outside of a few sites in very high transmission regions (e.g. New York City at the beginning of the pandemic), we believe most sites will enroll a high fraction of all SARS-CoV-2 positive children that they screen. Therefore, we will not be restricted to conditional logistic regression and other methods reserved for highly stratified data. Subgroup analyses will be considered for outcomes with sufficient sample sizes. These may be performed for specific subsets of the study population that are of particular interest or vulnerability (e.g. children of particular ethnicity/race, children in specific age categories, children with chronic conditions). However, as we expect very few severe outcomes of SARS-CoV-2 infection overall, the modeling strategies for these subgroup analyses will need to be simplified. Treatment of missing data and selection of variables to include in models are discussed in later sections of this statistical analysis plan.

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Statistical analysis methods related to the first secondary objective

The first secondary objective is to describe and compare health care resource use for patient management (e.g. isolation, testing, imaging, supportive care) of both SARS-CoV-2 positive and SARS-CoV-2 negative children according to changes in national and regional policies. The analysis will use methods as described for the first primary objective for binary outcomes. For count and continuous outcomes, analogous generalized linear models will be used, as appropriate, with choices for link and distribution functions determined by outcome variable distributions. Treatment of missing data and selection of variables to include in models are discussed in later sections of this statistical analysis plan.

Statistical analysis methods related to the second secondary objective of the study

The second secondary objective is to describe the effects of changing case screening policies for the detection of confirmed SARS-CoV-2 positive children. Sites complete a standardized form that collects information on the number of children screened at that ED along with the number of children found positive for SARS-CoV-2 (regardless of whether or not these children were enrolled in the study) on a weekly basis. Furthermore, sites indicate the case-screening criteria used each week at that ED. The proportion of children that test positive for SARS-CoV-2 each week at each site will be estimated along with 95% confidence intervals, and this will be summarized and compared using descriptive statistics (Pearson Chi-square) across categories of case-screening criteria. The case-screening criteria used and the proportion of children positive for SARS-CoV-2 at each site will be summarized graphically by region and time-period. We will analyze

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these data using time-series methods where the unit of analysis is the weekly information pertaining to each site. Heterogeneity in test-positivity rate will be assessed using a Poisson regression model for over-dispersed autocorrelated data. Time-varying independent variables will be used to operationalize specific components of the screening policy, e.g. fever present in child, close-contact known, etc.

Choice of variables to be included in predictive models

The selection of variables for inclusion in models will rely on expert judgment supplemented by a literature review. Candidates for inclusion in the model will be evaluated based on the following criteria: presumed major confounders, variables considered potentially predictive of the dependent variable (SARS-CoV-2 positivity or severe outcomes) based on PERN-COVID-19 study investigator consensus, factors already found significantly predictive of the dependent variable (SARS-CoV-2 positivity or severe outcomes) in any age group through already published studies. We will consider using elastic-net regression in order to improve the external generalizability of the model. We anticipate that this will result in a parsimonious model.

Treatment of missing data

The proportion of missing data for each variable of interest (characteristics and outcomes) will be reported, as will be the number of participants lost to follow-up at each follow-up time point. Outcome data that would be obtained through follow-up phone calls at day 14 and day 90, and through the medical record review performed at day 30, are likely not to be missing at random, although this is an untestable assumption.

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Similarly, some data may be more prone to non-ignorable missingness (e.g. person-reported infection prevention measures, provider-ordered laboratory data) whereas other data relating to participant demographic characteristics (e.g. age), and some clinical characteristics (such as symptoms experienced) may be deemed missing at random (MAR). Our primary analysis will be a complete case analysis, as we anticipate that key outcome and predictive variables will be available for a large fraction of the study population. However, the validity of the complete case analysis depends on the validity of the missing-at-random assumption. To evaluate the impact of non-ignorable missingness on the soundness of our complete case inferences, we will conduct sensitivity analyses using multiple imputation but alter imputation models to reflect varying degrees of non-missingness (e.g. assuming a higher likelihood of a severe outcome than was predicted in the complete case model). Sensitivity analyses will be conducted and reported according to principled approaches to missing data.[10]

Other analyses and considerations

To mitigate the impact of potential misclassification (i.e. false negatives) within the SARS-CoV-2 negative control group, we will further perform a statistical exploration of the proportion of children with positive SARS-CoV-2 test results in relation to time since first symptom onset. This will include sensitivity analyses that consider the types of symptoms experienced.

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Statistical software

The statistical software that will be used to carry out the analyses will include the following: SAS 9.4 (SAS Institute, Cary NC), SPSS 25.0 (IBM Corp), Stata 16 (StataCorp LP 2019), R statistical software (R Foundation for Statistical Computing; https://www.R-project.org/).

Reporting

Reporting for models will adhere to the TRIPOD checklist.[11]

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