Protocol

Protocol for: Price AM, Olson SM, Newhams MM, et al. BNT162b2 protection against the omicron variant in children and adolescents. N Engl J Med. DOI: 10.1056/NEJMoa2202826

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

This supplement contains the following items:

1. Original and final protocol; original and final statistical analysis plan
2. Summary of changes

COVID-19 Vaccine Effectiveness in Preventing Severe COVID-19-Related Complications in U.S. Children and Adolescents

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Original Protocol & Statistical Analysis Plan Version: Version 1d, August 12th, 2021

Final Protocol & Statistical Analysis Plan Version: February 24, 2022

Contents – Original Protocol and Statistical Analysis Plain

Original Protocol and Statistical Analysis Plan (Version Aug 12, 2021)

Purpose: The influenza and other emerging respiratory pathogens surveillance registry was initiated in April 2020 at the request of the U.S. Centers for Disease Control and Prevention (CDC) across over 60 pediatric hospitals that are members of the Pediatric Acute Lung Injury and Sepsis Investigator's Network. Its purpose was to describe in detail the demographics and clinical characteristics, including clinical course and treatment, of children infected with SARS-CoV-2 who require hospitalization and to provide real-time reporting to government agencies for public health. Previously children were thought to have mild disease but as of April 26 European countries began reporting an increase of severe inflammatory syndrome among children with COVID-19. Over the past year, the US has observed over 3000 cases of this syndrome which is called multisystem inflammatory syndrome in children (MIS-C). This surveillance registry aims to provide a better understanding and etiology of this syndrome related to COVID-19 as well as acute COVID-19 in children and adolescents. The PALISI Overcoming COVID-19 registry is the largest pediatric COVID-19 registry in the United States and is complementary to state departments of health efforts to collect information on these pediatric cases and report to CDC.

In 2021, multiple vaccines targeting SARS-CoV-2 that have demonstrated efficacy for preventing COVID-19 in phase III clinical trials. Implementation of SARS-CoV-2 vaccination, initially in high-priority populations followed by the general public, is underway in US adults and now in children down to age 12 years. Given the rapid pace of vaccine development and the critical role of vaccines to control the pandemic, data on the protective benefits under real-world conditions (vaccine effectiveness) in children are urgently needed. Although severe complications related to SARS-CoV-2 in children are rare, it is estimated that over 300 children have died and children comprise over 14% of COVID-19 cases. Although vaccine studies in <5,000 children can accurately evaluate immunogenicity, these are insufficient numbers of patients to evaluate efficacy against severe complications such as life-threatening organ involvement. One of the major goals of this registry will be to monitor the real-world impact of the COVID-19 vaccine on COVID-19 hospitalizations and MIS-C.

Overall objectives of the surveillance registry protocol:

The purpose of the Overcoming COVID-19 public health surveillance registry initiated in April 2020 is to describe the incidence of acute respiratory failure in SARS-CoV-2 infected children admitted to participating hospitals. Specifically, the registry has the following aims:

Aim 1.) 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.

Aim 2.) 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.

Aim 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.

Aim 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.

Aim 5.) To compare the endpoints outlined in aims 1-4 for critically ill 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.

This supplementary protocol, to be initiated in June 2021, for enrollment of case-patients hospitalized after vaccine introduction in mid-May 2021, includes the following specific aims:

Aim 1.) To estimate vaccine effectiveness for the SARS-CoV-2 vaccines in use in the United States to prevent COVID-19 hospitalization among children, including subgroups of age, race/ethnicity, underlying conditions, dual infections (with other pathogens including influenza), and duration of protection.

Aim 2.) To estimate SARS-CoV-2 vaccine effectiveness for the different SARS-CoV-2 vaccines in use in the United States for prevention of COVID-19 hospitalization in children.

Aim 3.) To estimate SARS-CoV-2 vaccine effectiveness against circulating SARS-CoV-2 variants for prevention of COVID-19 hospitalization in children.

Aim 4.) To monitor the relationship of COVID-19 and influenza vaccine effectiveness, when influenza circulates in the 2021-2022 winter season.

Aim 5.) To estimate vaccine effectiveness of maternal receipt of vaccination during pregnancy in infants (<6 months age).

1. Background:

In early 2020, the CDC asked the Pediatric Acute Lung Injury and Sepsis Investigator's (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)[1]. Acute COVID-19 is associated with high mortality in hospitalized adults causing profound hypoxia and acute respiratory distress syndrome; survivors have prolonged recovery.[2] In contrast, the majority of children infected in China, where the outbreak first began, had a mild clinical course or were asymptomatic.[3] The majority of children who were hospitalized for COVID-19 had underlying health conditions putting them at risk for complications. 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.[4] 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 a public health surveillance registry in early 2020 allowed us to capture data on 213 U.S. cases of MIS-C across 53 centers in 26 states.[5] In early February 2021, from almost 1,200 cases in the registry the two major types of severe COVID-19-related complications in children and adolescents were compared, including acute COVID-19 and MIS-C, revealing some overlap between the two syndromes.[6] There are now over 3,000 MIS-C cases reported across the U.S.

As the pandemic progressed, more adults were vaccinated against COVID-19 in the U.S., and SARS-CoV-2 viral variants emerged with higher transmissibility, the proportion of children and adolescents comprising hospitalized cases of COVID-19 rose. Multiple vaccines targeting severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes COVID-19, have demonstrated efficacy for preventing COVID-19 in phase III clinical trials.[7,8] Implementation of SARS-CoV-2 vaccination, initially in high-priority populations followed by the general public, is underway in the United States. Given the rapid pace of vaccine development and the critical role of vaccines to control the pandemic, data on the protective benefits under real-world conditions (vaccine effectiveness) are urgently needed.[9] This is especially important in children and adolescents, for whom studies have focused on vaccine immunogenicity and have not been powered to evaluate the effect on uncommon complications such as MIS-C or acute COVID-19 with respiratory failure.

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2. Non-Research Determination of Public Health Surveillance Activity

The world is in year two of a pandemic caused by severe acute respiratory virus coronavirus 2 (SARS-CoV-2) which as of May 2020 has 170 million cases of coronavirus disease 2019 (COVID-19) and an estimated 3.4 million deaths (https://covid19.who.int/ accessed 5.27.2021). The purpose of the activities described above are to identify, monitor, assess, and investigate COVID-19-related complications in children and adolescents and the protective benefits of COVID-19 vaccination in children and adolescents (vaccine effectiveness). The **public health surveillance** activities above are **requested and authorized by the U.S. CDC** and will be conducted with their support. The activities are **limited to those necessary** to identify, monitor, assess and investigate severe complications and vaccine effectiveness. The activities above serve the purpose **of informing the CDC on taking certain action**, such as disseminating information to the public, or issuing orders or guidance. The activities above are supported by a contract with the CDC (#75D30121C10297). Testing of respiratory biospecimens for SARS-CoV-2 variants of concern and analysis of the data will be in direct collaboration with the CDC. The intended benefits of the activities above are for the residents of the United States and its outlying territories. The CDC non-research determination for these activities is appended at the end of this protocol.

3. COVID-19 Vaccine Effectiveness Surveillance Study Design:

This is a prospective case: control study. The current study intends to enroll hospitalized index children and adolescents (age <19 years) at enrolling sites who are diagnosed with confirmed COVID-19 (SARS-CoV-2 positive by PCR or antigen) or MIS-C. Thus, participation is initiated when the index enrollee meets eligibility criteria. Identification of patients will be through screening daily of positive SARS-CoV-2 specimen test results and by screening of charts of the hospital units. The index patient/family will be approached and it will be explained that we are conducting a study to assess the real-world of the effectiveness of the COVID-19 vaccine on behalf of the CDC. Once an index patient is enrolled, an interview is conducted to determine their race, ethnicity, symptoms, prior illness, exposures, and vaccine history for COVID-19 and influenza virus. Proof of vaccination is obtained through multiple methods. Once enrolled, two SARS-CoV-2 test negative control patients (one symptomatic, one asymptomatic) are identified who are matched for age category (<6 months, 6 months-5 years, 6-11 years, 12-15 years, 16-18 years inclusive) and the same data are collected. Patients may be contacted to be enrolled after they have been discharged from the hospital. We will attempt to contact the patient/family using the phone number provided in their medical record. Interest to participate will be assessed by asking the patient and/or parent if they are willing to share information about their vaccine history for COVID-19. Case and control definitions and the algorithm for enrollment (Figure 1) are below.

3a. Definitions

Hospitalized Index Cases: Child admitted to the hospital for an acute illness testing positive for SARS-CoV-2 (PCR, nucleic acid amplification, or antigen) or meeting diagnostic criteria for MIS-C (PCR, nucleic acid amplification, antigen or antibody).

SARS-CoV-2 Syndrome Positive, Test-negative Control: Children admitted to the hospital for an acute illness with symptom overlap with COVID-19 who has tested negative for SARS-CoV-2.

SARS-CoV-2 Syndrome Negative Control: Children admitted to the hospital for a reason other than an acute respiratory illness and who do not have a clinical suspicion of COVID-19.

3b. Inclusion/Exclusion Criteria

Index Case

1. Age <19 years old.
2. Hospital admission or in an emergency department awaiting admission. Patients transferred from another hospital may be enrolled. The time of initial hospital presentation is the time of admission to the first hospital.
3. Meets at least 1 of the following:
    a. Clinically obtained test from a respiratory sample that is positive for acute SARS-CoV-2 via RT-PCR, nucleic acid amplification tests, or antigen testing AND/OR
    b. Antibody positive for SARS-CoV-2 and meets CDC criteria for MIS-C
4. Patient lives in the same state as the site hospital OR, if the patient lives out of state site must be able to access the patient's home state's immunization registry
5. Patients <6 months of age cannot be enrolled during their birth hospitalization

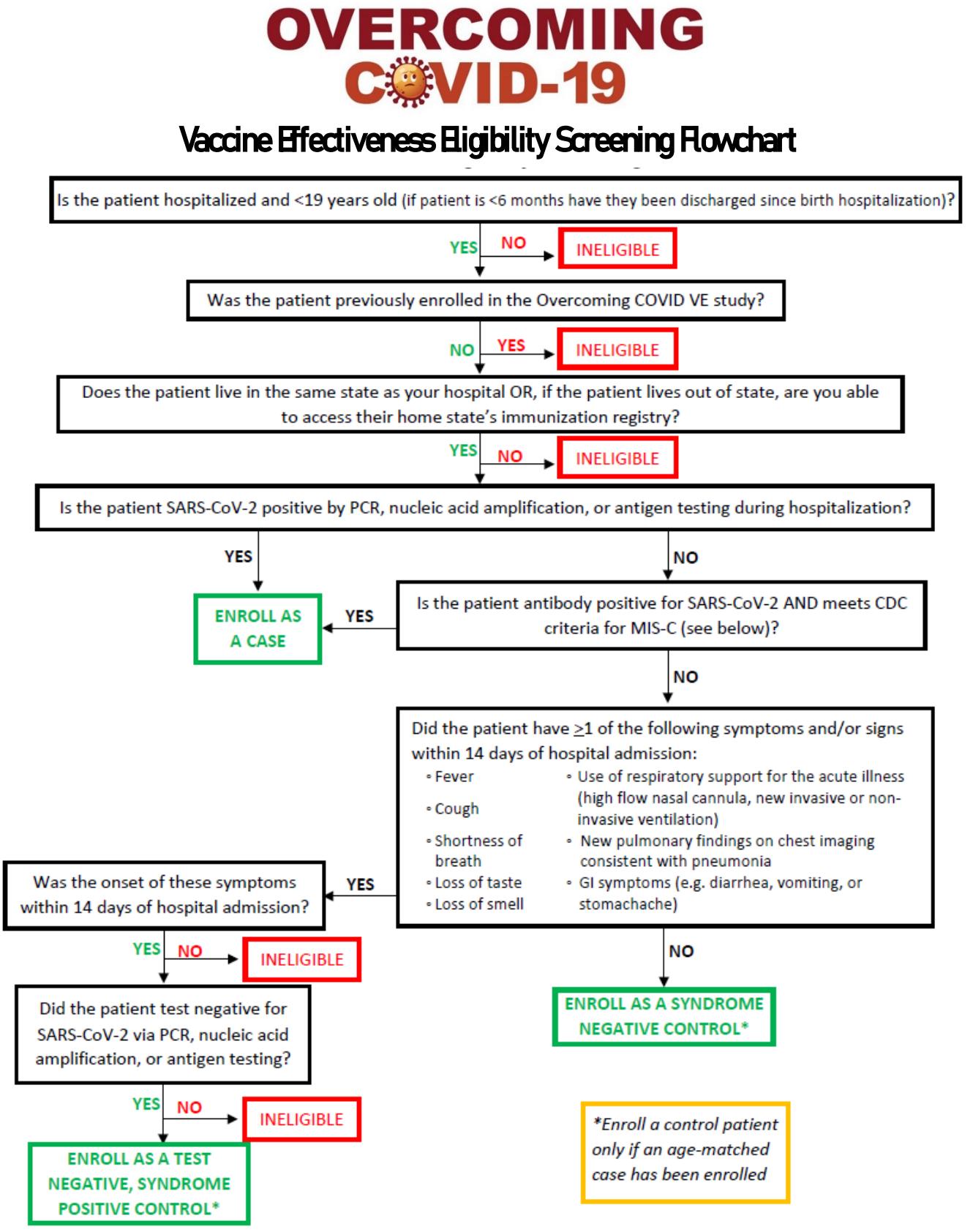
Syndrome-positive, Test-negative Control

1. Age <19 years old.
2. Hospital admission or in an emergency department awaiting admission within 14 days of onset of symptoms (see inclusion criterion #4). Patients transferred from another hospital may be enrolled. The time of initial hospital presentation is the time of admission to the first hospital.
3. Clinically obtained test from a respiratory sample that is negative for acute SARS-CoV-2 (see inclusion criterion #4). Examples of acute SARS-CoV-2 tests include RT-PCR tests, nucleic acid amplification tests, and antigen tests. Serology testing may not be used for eligibility.
4. Symptoms and/or signs believed to be due to COVID-19, including ≥1 sign or symptom of the following: fever, cough, shortness of breath, loss of taste, loss of smell, use of respiratory support (high flow oxygen by nasal cannula, invasive or non-invasive ventilation) for the acute illness, new pulmonary findings on chest imaging consistent with pneumonia, GI symptoms (e.g. diarrhea, vomiting, or stomachache).
5. Not enrolled in the study in the past 12 months.
6. Patient lives in the same state as the site hospital OR, if the patient lives out of state site must be able to access the patient's home state's immunization registry
7. Patients <6 months of age cannot be enrolled during their birth hospitalization

Syndrome-negative Control

1. Age <19 years old.
2. Hospital admission or in an emergency department awaiting admission.
3. None of the following signs or symptoms consistent that overlap with COVID-19 in the past 14 days: fever, cough, shortness of breath, loss of taste, loss of smell, use of respiratory support (high flow oxygen by nasal cannula, new invasive or non-invasive ventilation) for the acute illness, new pulmonary findings on chest imaging consistent with pneumonia, GI symptoms (e.g. diarrhea, vomiting, or stomachache).
4. Not enrolled in the study in the past 12 months.
5. Patient lives in the same state as the site hospital OR, if the patient lives out of state site must be able to access the patient's home state's immunization registry
6. Patients <6 months of age cannot be enrolled during their birth hospitalization
7. Patients with or without SARS-CoV-2 testing can be included

Figure 1: Eligibility, Screening and Enrollment Flowchart



CDC MIS-C Criteria

Inclusion Criteria

- Fever ≥38 °C (100.4 °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

3c. Patient Location and Sites

We will enroll patients from the population of children admitted to PALISI Overcoming COVID-19 Network hospitals and medical centers. We have contacted over 60 individual PALISI Network sites identified as willing and able to participate in this surveillance registry. A subset of these sites will participate in the vaccine effectiveness study.

3d. Data and Sample Collection

All procedures for this public health activity 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). Data collected from the medical record includes patient demographics, social vulnerability index (SVI) score, SARS-CoV-2 testing, reasons for hospitalization, hospital admission and discharge dates, medical history including presence of chronic medical conditions, and course of illness and treatment in the hospital. To determine the patient's overall SVI score the enrolling site will enter the patient's address into the CDC's SVI Interactive Map (https://svi.cdc.gov/map.html). The site will then record the patient's overall SVI in REDCap and will not record the patient's address in REDCap.

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.

Bi-weekly summary reports will be disseminated to the CDC to ensure real-time tracking of vaccine effectiveness. Reports will also be made available upon request. These reports will include the number of patients that met the case criteria that were enrolled and the number of matched controls.

The primary exposure variable in vaccine effectiveness analyses will be receipt of a SARS-CoV-2 vaccine. During 2020-21 season, we will also collect influenza vaccination information to evaluate relationship with SARS-CoV-2 vaccination. Therefore, we will undertake intensive vaccine verification efforts including the following steps:

1. at the time of enrollment, obtain patient/surrogate report of SARS-CoV-2 vaccination, and, if necessary, written authorization for release of information from the pediatrician's office (or other health care provider), records from pharmacies, employers, and other non-traditional vaccination locations.
2. ask patient/surrogate to view their "SARS-CoV-2 vaccine card," which is a paper form used to document SARS-CoV-2 vaccine receipt by many vaccination centers.
3. systematic search of local electronic medical records.
4. search of state vaccination registry.
5. contact relevant pharmacies, clinics (e.g. primary care provider), payors and other venues for evidence of vaccination.
6. call patients/surrogates to clarify discordant information between initial self-/surrogate-report and results of systematic searches of medical records, registries, and vaccination venues.

For consistency, the verification process will encompass similar efforts to confirm absence of vaccination among those who self-reported no vaccination as to confirm the presence of vaccination among those who self-report vaccination. State registries will be reviewed twice: once during the vaccine verification for each patient at the time of enrollment and once at least 28 days later to capture any delays in data transfer to the registry.

When feasible (e.g. allowed at the enrolling site), a nasal respiratory sample will be collected from the patient for public health purposes to sequence the SARS-CoV-2 virus to identify variants that are potentially clinically relevant. If collecting a fresh specimen is not feasible, a residual SARS-CoV-2 positive respiratory specimen can be collected after it is 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. Dates are needed to fully and accurately track the epidemic and thus serve the national interest. 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 sample collection.

4. Human Subjects Issues

4a. Waiver of Signed Consent and HIPAA Authorization

Because 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. Contact with the parents and patients will be done via the phone in test positive patients and over the phone or in person otherwise. 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 or through a survey interview of the patient or parent (for race, ethnicity, symptoms and vaccine history). For all patients <18 years, we will interview at least one parent. For cognitively capable patients 10 years and over, we will also interview the child.

We propose to conduct this public health surveillance 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. In the case that the parent/patient declines to participate in the interview, we will collect data from the clinical chart and check the clinical records and vaccine registry for confirmation of vaccination. For this public health surveillance 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. Thus, conduct of this study would not be practicable without a waiver of signed informed consent.

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 or through a brief interview or check of vaccine records. 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 collected from the patient for public health purposes or 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 sample collection.

4b. Risks

The only procedures for this public health 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.

Biweekly 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.

5. Statistical Analysis Plan

Case-control investigations will be conducted among children <19 years of age to estimate COVID-19 VE against hospitalized illness by comparing odds of prior COVID-19 vaccination among those hospitalized with illness consistent with COVID-19 who test positive for SARS-CoV-2 (cases) to hospitalized children who test negative or are syndrome negative for SARS-CoV-2 (controls).

5a. Vaccination status definition (exposure)

COVID-19 vaccine verification will occur using a systematic process. Patients, parents/guardians of patients, or proxies are interviewed about receipt of one or more doses of a COVID-19 vaccine. If no COVID-19 vaccine is self-reported or vaccine history cannot be completed, local hospital EMR or vaccine registry searches will be completed (first search shortly after enrollment and second search approximately 28 days after enrollment). If receipt of at least one COVID-19 vaccine is self-reported, vaccine verification will continue until all options for verification have been exhausted and the vaccine

dose(s) cannot be verified. When all reported vaccine doses have been verified, the vaccine verification process will stop. Sources of documentation include CDC vaccine card, local hospital EMR, state vaccine registry (including search shortly after enrollment and approximately 28 days after enrollment), and vaccine records requested from other sources including clinics or pharmacies (if the patient reported receiving a vaccine at one of these sources and receipt cannot be verified using the above sources).

Patients vaccinated after illness onset (or hospital admission in the syndrome-negative control group) will be classified as unvaccinated, and patients who received a first dose of a licensed SARS-CoV-2 vaccine 0-13 days before illness onset will be excluded from the primary analysis given unlikely vaccine-associated protection during this interval shortly following vaccination.

Definition 1: Documented vaccination
Requires documented evidence of vaccination, operationalized as a non-missing date of vaccination obtained from a vaccination record card, electronic medical record (EMR), local vaccine registry, or other documented source (including other clinics or pharmacies).

Definition 2: Self-reported vaccination with date
Requires patient/proxy to answer affirmatively to yes/no receipt of COVID-19 vaccine AND be able to provide either an exact or approximate date of vaccination, in order to establish that the vaccine was received at least two weeks prior to onset. If patient cannot answer that question, they are classified as having missing date of vaccination and self-reported vaccination is also classified as missing/unknown.

Definition 3: Self-reported vaccination with date and location ("plausible self-report")
Same as definition 2 except that patient/proxy must also verbally provide a location of vaccination. Usually, any reasonable location is accepted.

Definition 4: Self-report with date OR documented
Classified as vaccinated if patient meets either definition 1 or definition 2

Definition 5: Plausible self-report OR documented
Classified as vaccinated if patient meets either definition 1 or definition 3

5b. SARS-CoV-2 case status definitions (outcome)

Patients will be enrolled into Cohort 1 (case-patients), Cohort 2 (syndrome-positive controls), or Cohort 3 (syndrome-negative controls). New or stored upper respiratory specimens or salivary specimens will be routinely collected from enrolled case-patients as available for centralized public health RT-PCR testing. Patients enrolled in Cohorts 2 or 3 who had negative or no initial clinical SARS-CoV-2 testing will be reclassified as an "analytical case" if SARS-CoV-2 testing is positive during that hospital admission.

Classification of cases and controls for the analysis is shown below in Table 1:

Table 1. Classification of cases and control for analysis.

Status of patient at enrollment	Clinical SARS-CoV-2 test results	Public Health SARS-CoV-2 RT-PCR results	Classification for Analysis
Enrollment case	≥1 positive	Positive	Analytical case
Enrollment case	≥1 positive	Negative	Analytical case
Enrollment case	≥1 positive	Not done / inconclusive	Analytical case

Exclusion criteria for analysis:

- Missing/unknown case status
- Missing/unknown vaccination status
- First dose of vaccine 0 to 13 days before illness onset (excluded from primary analysis)
- Illness onset >10 days before date of first SARS-CoV-2 test or >72 hours from hospital admission date
- Received a COVID-19 vaccine not authorized for use in the United States
- Exclusion of Moderna and Janssen COVID-19 vaccine until vaccines are authorized for use in US children and coverage increases to >20% in the control patients.

5c. Sample size calculations

Table 2 provides the estimated number of cases and test-negative controls required for a crude VE analysis using a range of assumptions for VE, precision (95% confidence interval), and vaccine coverage among control patients.

Table 2. Sample size calculators for VE analysis

VE estimate	Confidence interval	Vaccine coverage in controls	Number of cases	Number of test-negative controls
90%	67.0–97.0%	70%	30	30
90%	67.0–97.0%	50%	43	43
90%	67.0–97.0%	30%	81	81
80%	60.0–90.0%	70%	75	75
80%	60.0–90.0%	50%	90	90
80%	60.0–90.0%	30%	148	148
70%	51.5–81.5%	70%	147	147
70%	51.5–81.5%	50%	160	160
70%	51.5–81.5%	30%	243	243

5d. Key study definitions

Key study definitions for the VE analysis and clinical outcomes for specified severity outcomes are shown in Table 3A and 3B below:

Table 3A. Study definitions.	
Category / Group	**Description**
Vaccination status	
Full vaccination	Study patient who received all doses of an authorized COVID-19 vaccine ≥14 days prior to illness onset (or date of hospitalization in syndrome-negative controls).
Partial vaccination	Study patient who received one of two doses of a two-dose COVID-19 vaccine ≥14 days prior to illness onset (or date of hospitalization in syndrome-negative control patients). These patients either have not received a second dose of vaccine or received the second dose 0-13 days prior to illness onset. Secondary analyses may also consider VE within different timeframes from date of vaccination.
Full or partial vaccination (one or more doses)	Study patient who has received either full or partial vaccination with a COVID-19 vaccine.
Unvaccinated	Study patient who did not receive any doses of an authorized COVID-19 vaccine ≥14 days prior to illness onset or who was vaccinated after illness onset. A patient who received vaccination 0-13 days before illness onset will be excluded from the primary VE analyses but will be considered in secondary analyses. This vaccination group may serve as an indicator of bias in primary VE analyses (selection bias or confounding not accounted for in VE models), as vaccine effectiveness is not expected in the period shortly following the first dose of a COVID-19 vaccine.
Alternative times from vaccination to illness onset	If feasible we may perform additional sub-analyses of VE using other discrete time periods between vaccination and illness onset, such as (for a 2-dose vaccine series): 0-14 days from first dose of vaccine (partial vaccination) 15-28 days from first dose of vaccine (partial vaccination) 29-42 days from first dose of vaccine (partial vaccination) >42 days from first dose of vaccine (partial vaccination) 0-7 days from second dose of vaccine 8-14 days from second dose of vaccine >14 days from second dose of vaccine Future analyses will evaluate potential waning vaccine effectiveness over time in future analyses, e.g. for each 30-day interval from date of vaccination.
Severity	
Severe case	Several definitions for severity will be used including but not limited to case patients who are: hospitalized in ICU, hospitalized with acute organ failure, hospitalized with vasopressor-dependent shock, hospitalized with death, hospitalized with non-invasive or invasive mechanical ventilation, or severity defined by other parameters (e.g., Food and Drug Association criteria).
Non-severe case	Case patient who do not meet criteria for the severity case definition.

Genetic strain	
SARS-CoV-2 strain	Available specimens with a cycle threshold (Ct) value ≤30 will undergo genetic sequencing with lineage determination. VE by group (B.1.1.7, B.1.351, or P.1 viruses, or other variants) will be assessed if sufficient sample size. For specimens with higher Ct values, PCR analysis using targeted primers to detect SARS-CoV-2 strains will be conducted.

Table 3B. Clinical outcome definitions

Clinical Outcome	Description
Window of outcome assessment	All outcomes are assessed between initial hospital presentation and the earlier of hospital discharge or the end of hospital day #28 (calendar day). Once a patient is discharged from the acute care hospital participating, outcome assessment ends. Clinical events, such as vasopressor use and mechanical ventilation that occur during the index hospitalization but before enrollment (defined as the time of upper respiratory sample collection) are included as study outcomes.
ICU admission	Admission to or boarding for an ICU bed at any time during hospitalization.
Vasopressor support	Use of a vasopressor by continuous intravenous/intraosseous infusion for at least 1 hour to increase or maintain blood pressure at any time during hospitalization.
Invasive mechanical ventilation	Receipt of positive pressure ventilation through an endotracheal tube or tracheostomy tube for at least 1 hour at any time during hospitalization. Patients on chronic invasive mechanical ventilation prior to the current illness are not eligible for the invasive mechanical ventilation outcome.
Non-invasive ventilation	Receipt of positive pressure ventilation through nasal prongs or a facemask for at least 1 hour at any time during hospitalization. CPAP and BiPAP for respirator support, other than for treatment of chronic sleep apnea, fulfill the criteria for the non-invasive mechanical ventilation outcome. Patients chronically on invasive or non-invasive mechanical ventilation prior to the current illness are not eligible for the non-invasive mechanical ventilation outcome.
In-hospital 28-day mortality	Death after hospital presentation and before the earlier of hospital discharge or the end of hospital day #28.

5e. Model building strategy for final VE analysis

Patient description:

A model building strategy will be applied for VE assessment using test-negative or syndrome-negative control groups. Characteristics of SARS-CoV-2-positive and SARS-CoV-2-negative patients (or syndrome-negative controls) and vaccinated and unvaccinated patients will be described by counts and percentages or medians and interquartile ranges and compared using Pearson X^2 test or Fisher exact test for categorical variables and Wilcoxon rank-sum test or *t* test for continuous variables.

Adjusted COVID-19 VE:

Crude (unadjusted) VE will first be calculated. Adjusted VE will then be calculated by comparing the odds of COVID-19 vaccine receipt among cases and controls using unconditional multivariable logistic regression with SARS-CoV-2 positivity as the outcome and vaccination status as the exposure. VE is calculated as (1 – *adjusted odds ratio*) × 100%.

Several variables will be included *a priori* in VE regression models. These include enrollment location (specific hospital or geographic region), age, sex, race/ethnicity, and calendar time. These variables are included because they are established or suspected confounders.

Additional variables will be considered as model covariates that may confound the relationship of interest if associated with both vaccination status and risk of hospitalized COVID-19 illness.

We will examine the association of these other potential confounders. Variables with the strongest association with the exposure and the outcome that change the OR by >5% will be selected for inclusion in the model. If several of these potential confounders performed similarly, we will use the most parsimonious set of variables. We will examine a range of health status indicators as potential confounders, including measures of baseline health status (e.g., ≥1 underlying health conditions, specific health conditions). As factors related to social vulnerability and community exposures/behaviors are also potential confounders, we will also consider measures of SES and social vulnerability (e.g., CDC Social Vulnerability Index) and reported behaviors/exposures (e.g. mask use, influenza vaccination during the current season).

We will estimate VE separately for full vaccination, partial vaccination, and receipt of one or more doses (either full or partial vaccination), as well as for subgroups of interest or using alternative times since vaccination. VE will also be estimated based on documented vaccination alone (Definition 1 above) as well as either documented vaccination or plausible self-report including location and date(s) [Definition 5 above]. Patients self-reporting COVID-19 vaccination without details about location and date(s) will be excluded from the analysis given low confidence in vaccination status. Similar approaches to model building will also be used in estimating VE using the syndrome-negative control group. If estimates are similar between test-negative and syndrome-negative control VE models, control groups will be pooled to increase sample size and precision of VE estimate.

Effect modification:

Potential effect modifiers of vaccine effectiveness, such as presence of underlying conditions, may also be considered. Likelihood ratio tests will be used to compare P-values of the interaction term (a P-value <~0.15 is suggestive of effect modification). VE estimates will be presented stratified by level of an effect modifier.

5f. Other analytic considerations

Missing illness onset date:

Some patients or proxies may not be able to provide the date of illness onset. For the main VE analysis, we will include these patients. We may perform sensitivity analyses restricting the VE analysis only to patients with a known date of illness onset, using a multiple imputation approach to impute illness

onset date in reference to time of testing for those with missing values, or assigning illness onset date as the median days between illness onset and date of hospital admission in patients with complete data.

Specification of race/ethnicity:

We may be unable to obtain race and ethnicity data for all patients. This will be handled analytically, e.g., including an unknown race/ethnicity category if this group is large.

Specification of age:

Specification of age varies depending on subset being analyzed. Alternative specifications included continuous/linear (if data suggested no evidence of nonlinearity) or 3-or 4-part categorization if nonlinearity is present (alternatively, cubic splines can be used). In models stratified by age group, age (continuous) is typically included in the model to account for residual confounding by age within age category (sample size permitting).

Specification of calendar time:

Calendar time of symptom onset is specified in the VE model by classifying based on calendar week based on the date of illness onset or date of hospitalization. We will consider adjusting for calendar time in different intervals (e.g., weekly, biweekly, monthly).

Discordant dates of vaccination:
Dates of COVID-19 vaccination through documented sources such as vaccine record cards or immunization registries are likely to be more accurate than self-reported dates and will therefore be used preferentially.

Contents – Final Protocol and Statistical Analysis Plain

Final Protocol and Statistical Analysis Plan (Version February 24, 2022)

Purpose: The influenza and other emerging respiratory pathogens surveillance registry was initiated in April 2020 at the request of the U.S. Centers for Disease Control and Prevention (CDC) across over 60 pediatric hospitals that are members of the Pediatric Acute Lung Injury and Sepsis Investigator's Network. Its purpose was to describe in detail the demographics and clinical characteristics, including clinical course and treatment, of children infected with SARS-CoV-2 who require hospitalization and to provide real-time reporting to government agencies for public health. Previously children were thought to have mild disease but as of April 26 European countries began reporting an increase of severe inflammatory syndrome among children with COVID-19. Over the past year, the US has observed over 3000 cases of this syndrome which is called multisystem inflammatory syndrome in children (MIS-C). This surveillance registry aims to provide a better understanding and etiology of this syndrome related to COVID-19 as well as acute COVID-19 in children and adolescents. The PALISI Overcoming COVID-19 registry is the largest pediatric COVID-19 registry in the United States and is complementary to state departments of health efforts to collect information on these pediatric cases and report to CDC.

In 2021, multiple vaccines targeting SARS-CoV-2 that have demonstrated efficacy for preventing COVID-19 in phase III clinical trials. Implementation of SARS-CoV-2 vaccination, initially in high-priority populations followed by the general public, is underway in US adults and now in children down to age 12 years. Given the rapid pace of vaccine development and the critical role of vaccines to control the pandemic, data on the protective benefits under real-world conditions (vaccine effectiveness) in children are urgently needed. Although severe complications related to SARS-CoV-2 in children are rare, it is estimated that over 300 children have died and children comprise over 14% of COVID-19 cases. Although vaccine studies in <5,000 children can accurately evaluate immunogenicity, these are insufficient numbers of patients to evaluate efficacy against severe complications such as life-threatening organ involvement. One of the major goals of this registry will be to monitor the real-world impact of the COVID-19 vaccine on COVID-19 hospitalizations and MIS-C.

Overall objectives of the surveillance registry protocol:

The purpose of the Overcoming COVID-19 public health surveillance registry initiated in April 2020 is to describe the incidence of acute respiratory failure in SARS-CoV-2 infected children admitted to participating hospitals. Specifically, the registry has the following aims:

Aim 1.) 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.

Aim 2.) 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.

Aim 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.

Aim 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.

Aim 5.) To compare the endpoints outlined in aims 1-4 for critically ill 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.

This supplementary protocol, to be initiated in June 2021, for enrollment of case-patients hospitalized after vaccine introduction in mid-May 2021, includes the following specific aims:

Aim 1.) To estimate vaccine effectiveness for the SARS-CoV-2 vaccines in use in the United States to prevent COVID-19 hospitalization among children, including subgroups of age, race/ethnicity, underlying conditions, dual infections (with other pathogens including influenza), and duration of protection.

Aim 2.) To estimate SARS-CoV-2 vaccine effectiveness for the different SARS-CoV-2 vaccines in use in the United States for prevention of COVID-19 hospitalization in children.

Aim 3.) To estimate SARS-CoV-2 vaccine effectiveness against circulating SARS-CoV-2 variants for prevention of COVID-19 hospitalization in children.

Aim 4.) To monitor the relationship of COVID-19 and influenza vaccine effectiveness, when influenza circulates in the 2021-2022 winter season.

Aim 5.) To estimate vaccine effectiveness of maternal receipt of vaccination during pregnancy in infants (<6 months age).

4. Background:

In early 2020, the CDC asked the Pediatric Acute Lung Injury and Sepsis Investigator's (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)[10]. Acute COVID-19 is associated with high mortality in hospitalized adults causing profound hypoxia and acute respiratory distress syndrome; survivors have prolonged recovery.[11] In contrast, the majority of children infected in China, where the outbreak first began, had a mild clinical course or were asymptomatic.[12] The majority of children who were hospitalized for COVID-19 had underlying health conditions putting them at risk for complications. 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.[13] 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 a public health surveillance registry in early 2020 allowed us to capture data on 213 U.S. cases of MIS-C across 53 centers in 26 states.[14] In early February 2021, from almost 1,200 cases in the registry the two major types of severe COVID-19-related complications in children and adolescents were compared, including acute COVID-19 and MIS-C, revealing some overlap between the two syndromes.[15] There are now over 3,000 MIS-C cases reported across the U.S.

As the pandemic progressed, more adults were vaccinated against COVID-19 in the U.S., and SARS-CoV-2 viral variants emerged with higher transmissibility, the proportion of children and adolescents comprising hospitalized cases of COVID-19 rose. Multiple vaccines targeting severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes COVID-19, have demonstrated efficacy for preventing COVID-19 in phase III clinical trials.[16,17] Implementation of SARS-CoV-2 vaccination, initially in high-priority populations followed by the general public, is underway in the United States. Given the rapid pace of vaccine development and the critical role of vaccines to control the pandemic, data on the protective benefits under real-world conditions (vaccine effectiveness) are urgently needed.[18] This is especially important in children and adolescents, for whom studies have focused on vaccine immunogenicity and have not been powered to evaluate the effect on uncommon complications such as MIS-C or acute COVID-19 with respiratory failure.

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5. Non-Research Determination of Public Health Surveillance Activity

The world is in year two of a pandemic caused by severe acute respiratory virus coronavirus 2 (SARS-CoV-2) which as of May 2020 has 170 million cases of coronavirus disease 2019 (COVID-19) and an estimated 3.4 million deaths (https://covid19.who.int/ accessed 5.27.2021). The purpose of the activities described above are to identify, monitor, assess, and investigate COVID-19-related complications in children and adolescents and the protective benefits of COVID-19 vaccination in children and adolescents (vaccine effectiveness). The **public health surveillance** activities above are **requested and authorized by the U.S. CDC** and will be conducted with their support. The activities are **limited to those necessary** to identify, monitor, assess and investigate severe complications and vaccine effectiveness. The activities above serve the purpose **of informing the CDC on taking certain action**, such as disseminating information to the public, or issuing orders or guidance. The activities above are supported by a contract with the CDC (#75D30121C10297). Testing of respiratory biospecimens for SARS-CoV-2 variants of concern and analysis of the data will be in direct collaboration with the CDC. The intended benefits of the activities above are for the residents of the United States and its outlying territories. The CDC non-research determination for these activities is appended at the end of this protocol.

6. COVID-19 Vaccine Effectiveness Surveillance Study Design:

This is a prospective case: control study. The current study intends to enroll hospitalized index children and adolescents (age <19 years) at enrolling sites who are diagnosed with confirmed COVID-19 (SARS-CoV-2 positive by PCR or antigen) or MIS-C. Thus, participation is initiated when the index enrollee meets eligibility criteria. Identification of patients will be through screening daily of positive SARS-CoV-2 specimen test results and by screening of charts of the hospital units. The index patient/family will be approached and it will be explained that we are conducting a study to assess the real-world of the effectiveness of the COVID-19 vaccine on behalf of the CDC. Once an index patient is enrolled, an interview is conducted to determine their race, ethnicity, symptoms, prior illness, exposures, and vaccine history for COVID-19 and influenza virus. Proof of vaccination is obtained through multiple methods. Once enrolled, two SARS-CoV-2 test negative control patients (one symptomatic, one asymptomatic) are identified who are matched for age category (<6 months, 6 months-5 years, 6-11 years, 12-15 years, 16-18 years inclusive) and the same data are collected. Patients may be contacted to be enrolled after they have been discharged from the hospital. We will attempt to contact the patient/family using the phone number provided in their medical record. Interest to participate will be assessed by asking the patient and/or parent if they are willing to share information about their vaccine history for COVID-19. Case and control definitions and the algorithm for enrollment (Figure 1) are below.

3a. Definitions

Hospitalized Index Cases: Child admitted to the hospital for an acute illness testing positive for SARS-CoV-2 (PCR, nucleic acid amplification, or antigen) or meeting diagnostic criteria for MIS-C (PCR, nucleic acid amplification, antigen or antibody).

SARS-CoV-2 Syndrome Positive, Test-negative Control: Children admitted to the hospital for an acute illness with symptom overlap with COVID-19 who has tested negative for SARS-CoV-2.

SARS-CoV-2 Syndrome Negative Control: Children admitted to the hospital for a reason other than an acute respiratory illness and who do not have a clinical suspicion of COVID-19. Stopped enrollment of syndrome negative controls on/ after December 14, 2021.

3b. Inclusion/Exclusion Criteria

Index Case

6. Age <19 years old.
7. Hospital admission or in an emergency department awaiting admission. Patients transferred from another hospital may be enrolled. The time of initial hospital presentation is the time of admission to the first hospital.
8. Meets at least 1 of the following:
    a. Clinically obtained test from a respiratory sample that is positive for acute SARS-CoV-2 via RT-PCR, nucleic acid amplification tests, or antigen testing AND/OR
    b. Antibody positive for SARS-CoV-2 and meets CDC criteria for MIS-C
9. Patient lives in the same state as the site hospital OR, if the patient lives out of state site must be able to access the patient's home state's immunization registry
10. Patients <6 months of age cannot be enrolled during their birth hospitalization

Syndrome-positive, Test-negative Control

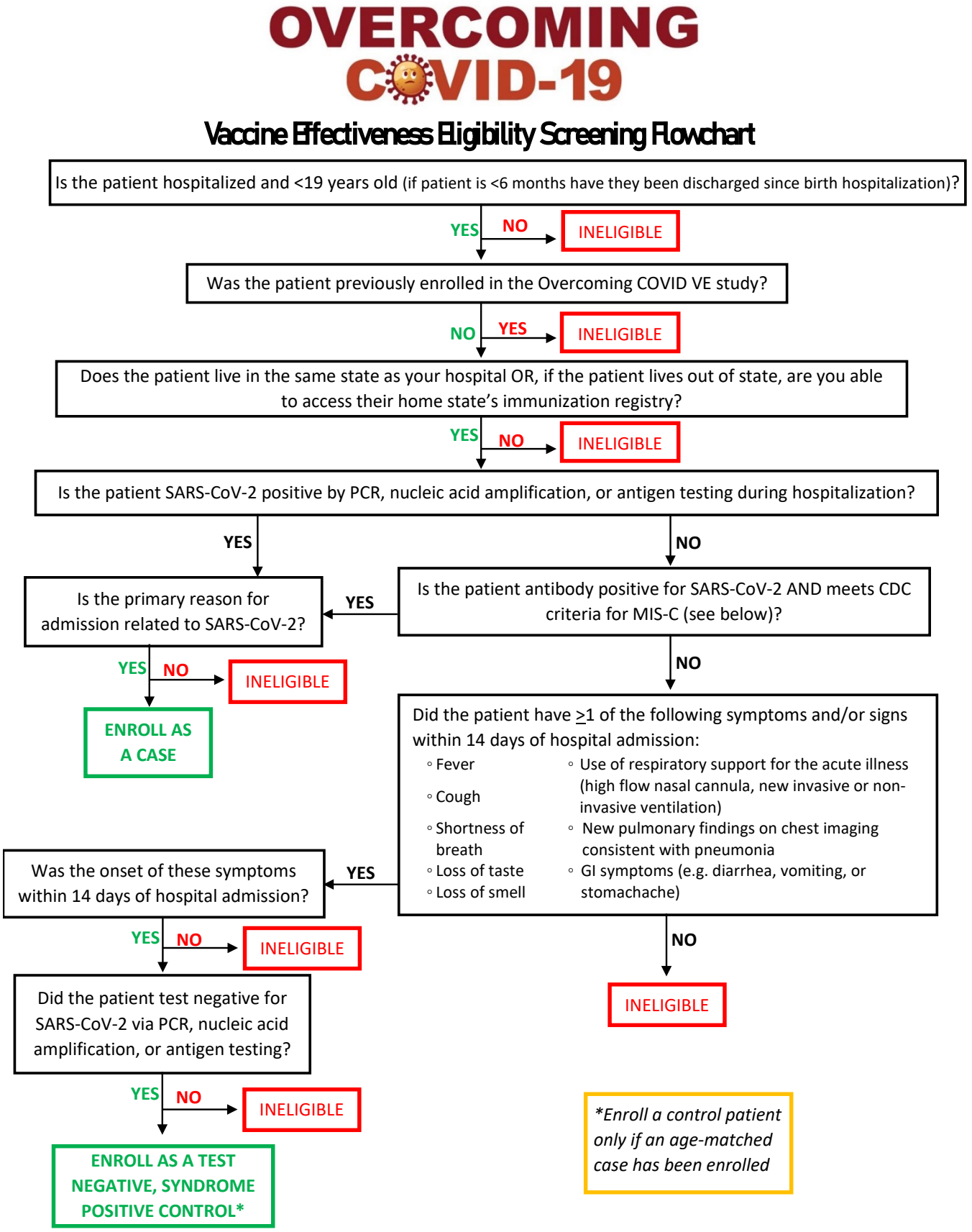
8. Age <19 years old.
9. Hospital admission or in an emergency department awaiting admission within 14 days of onset of symptoms (see inclusion criterion #4). Patients transferred from another hospital may be enrolled. The time of initial hospital presentation is the time of admission to the first hospital.
10. Clinically obtained test from a respiratory sample that is negative for acute SARS-CoV-2 (see inclusion criterion #4). Examples of acute SARS-CoV-2 tests include RT-PCR tests, nucleic acid amplification tests, and antigen tests. Serology testing may not be used for eligibility.
11. Symptoms and/or signs believed to be due to COVID-19, including ≥1 sign or symptom of the following: fever, cough, shortness of breath, loss of taste, loss of smell, use of respiratory support (high flow oxygen by nasal cannula, invasive or non-invasive ventilation) for the acute illness, new pulmonary findings on chest imaging consistent with pneumonia, GI symptoms (e.g. diarrhea, vomiting, or stomachache).
12. Not enrolled in the study in the past 12 months.
13. Patient lives in the same state as the site hospital OR, if the patient lives out of state site must be able to access the patient's home state's immunization registry
14. Patients <6 months of age cannot be enrolled during their birth hospitalization

Syndrome-negative Control (stop enrollment on/ after December 14, 2021)

8. Age <19 years old.
9. Hospital admission or in an emergency department awaiting admission.
10. None of the following signs or symptoms consistent that overlap with COVID-19 in the past 14 days: fever, cough, shortness of breath, loss of taste, loss of smell, use of respiratory support (high flow oxygen by nasal cannula, new invasive or non-invasive ventilation) for the acute illness, new pulmonary findings on chest imaging consistent with pneumonia, GI symptoms (e.g. diarrhea, vomiting, or stomachache).
11. Not enrolled in the study in the past 12 months.

12. Patient lives in the same state as the site hospital OR, if the patient lives out of state site must be able to access the patient's home state's immunization registry
13. Patients <6 months of age cannot be enrolled during their birth hospitalization
14. Patients with or without SARS-CoV-2 testing can be included

Figure 1: Eligibility, Screening and Enrollment Flowchart



CDC MIS-C Criteria

Inclusion Criteria

- Fever ≥38 °C (100.4 °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

3c. Patient Location and Sites

We will enroll patients from the population of children admitted to PALISI Overcoming COVID-19 Network hospitals and medical centers. We have contacted over 60 individual PALISI Network sites identified as willing and able to participate in this surveillance registry. A subset of these sites will participate in the vaccine effectiveness study.

3d. Data and Sample Collection

All procedures for this public health activity 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). Data collected from the medical record includes patient demographics, social vulnerability index (SVI) score, SARS-CoV-2 testing, reasons for hospitalization, hospital admission and discharge dates, medical history including presence of chronic medical conditions, and course of illness and treatment in the hospital. To determine the patient's overall SVI score the enrolling site will enter the patient's address into the CDC's SVI Interactive Map (https://svi.cdc.gov/map.html). The site will then record the patient's overall SVI in REDCap and will not record the patient's address in REDCap.

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.

Bi-weekly summary reports will be disseminated to the CDC to ensure real-time tracking of vaccine effectiveness. Reports will also be made available upon request. These reports will include the number of patients that met the case criteria that were enrolled and the number of matched controls.

The primary exposure variable in vaccine effectiveness analyses will be receipt of a SARS-CoV-2 vaccine. During 2020-21 season, we will also collect influenza vaccination information to evaluate relationship with SARS-CoV-2 vaccination. Therefore, we will undertake intensive vaccine verification efforts including the following steps:

7. at the time of enrollment, obtain patient/surrogate report of SARS-CoV-2 vaccination, and, if necessary, written authorization for release of information from the pediatrician's office (or other health care provider), records from pharmacies, employers, and other non-traditional vaccination locations.
8. ask patient/surrogate to view their "SARS-CoV-2 vaccine card," which is a paper form used to document SARS-CoV-2 vaccine receipt by many vaccination centers.
9. systematic search of local electronic medical records.
10. search of state vaccination registry.
11. contact relevant pharmacies, clinics (e.g. primary care provider), payors and other venues for evidence of vaccination.
12. call patients/surrogates to clarify discordant information between initial self-/surrogate-report and results of systematic searches of medical records, registries, and vaccination venues.

For consistency, the verification process will encompass similar efforts to confirm absence of vaccination among those who self-reported no vaccination as to confirm the presence of vaccination among those who self-report vaccination. State registries will be reviewed twice: once during the vaccine verification for each patient at the time of enrollment and once at least 28 days later to capture any delays in data transfer to the registry.

When feasible (e.g. allowed at the enrolling site), a nasal respiratory sample will be collected from the patient for public health purposes to sequence the SARS-CoV-2 virus to identify variants that are potentially clinically relevant. If collecting a fresh specimen is not feasible, a residual SARS-CoV-2 positive respiratory specimen can be collected after it is 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. Dates are needed to fully and accurately track the epidemic and thus serve the national interest. 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 sample collection.

6. Human Subjects Issues

4a. Waiver of Signed Consent and HIPAA Authorization

Because 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. Contact with the parents and patients will be done via the phone in test positive patients and over the phone or in person otherwise. 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 or through a survey interview of the patient or parent (for race, ethnicity, symptoms and vaccine history). For all patients <18 years, we will interview at least one parent. For cognitively capable patients 10 years and over, we will also interview the child.

We propose to conduct this public health surveillance 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. In the case that the parent/patient declines to participate in the interview, we will collect data from the clinical chart and check the clinical records and vaccine registry for confirmation of vaccination. For this public health surveillance 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. Thus, conduct of this study would not be practicable without a waiver of signed informed consent.

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 or through a brief interview or check of vaccine records. 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 collected from the patient for public health purposes or 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 sample collection.

4b. Risks

The only procedures for this public health 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.

Biweekly 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.

7. Statistical Analysis Plan

Case-control investigations will be conducted among children <19 years of age to estimate COVID-19 VE against hospitalized illness by comparing odds of prior COVID-19 vaccination among those hospitalized with illness consistent with COVID-19 who test positive for SARS-CoV-2 (cases) to hospitalized children who test negative or are syndrome negative for SARS-CoV-2 (controls).

5a. Vaccination status definition (exposure)

COVID-19 vaccine verification will occur using a systematic process. Patients, parents/guardians of patients, or proxies are interviewed about receipt of one or more doses of a COVID-19 vaccine. If no COVID-19 vaccine is self-reported or vaccine history cannot be completed, local hospital EMR or vaccine registry searches will be completed (first search shortly after enrollment and second search approximately 28 days after enrollment). If receipt of at least one COVID-19 vaccine is self-reported, vaccine verification will continue until all options for verification have been exhausted and the vaccine

dose(s) cannot be verified. When all reported vaccine doses have been verified, the vaccine verification process will stop. Sources of documentation include CDC vaccine card, local hospital EMR, state vaccine registry (including search shortly after enrollment and approximately 28 days after enrollment), and vaccine records requested from other sources including clinics or pharmacies (if the patient reported receiving a vaccine at one of these sources and receipt cannot be verified using the above sources).

Patients vaccinated after illness onset (or hospital admission in the syndrome-negative control group) will be classified as unvaccinated, and patients who received a first dose of a licensed SARS-CoV-2 vaccine 0-13 days before illness onset will be excluded from the primary analysis given unlikely vaccine-associated protection during this interval shortly following vaccination.

Definition 1: Documented vaccination
Requires documented evidence of vaccination, operationalized as a non-missing date of vaccination obtained from a vaccination record card, electronic medical record (EMR), local vaccine registry, or other documented source (including other clinics or pharmacies).

Definition 2: Self-reported vaccination with date
Requires patient/proxy to answer affirmatively to yes/no receipt of COVID-19 vaccine AND be able to provide either an exact or approximate date of vaccination, in order to establish that the vaccine was received at least two weeks prior to onset. If patient cannot answer that question, they are classified as having missing date of vaccination and self-reported vaccination is also classified as missing/unknown.

Definition 3: Self-reported vaccination with date and location ("plausible self-report")
Same as definition 2 except that patient/proxy must also verbally provide a location of vaccination. Usually, any reasonable location is accepted.

Definition 4: Self-report with date OR documented
Classified as vaccinated if patient meets either definition 1 or definition 2

Definition 5: Plausible self-report OR documented
Classified as vaccinated if patient meets either definition 1 or definition 3

5b. SARS-CoV-2 case status definitions (outcome)

Patients will be enrolled into Cohort 1 (case-patients), Cohort 2 (syndrome-positive controls), or Cohort 3 (syndrome-negative controls). New or stored upper respiratory specimens or salivary specimens will be routinely collected from enrolled case-patients as available for centralized public health RT-PCR testing. Patients enrolled in Cohorts 2 or 3 who had negative or no initial clinical SARS-CoV-2 testing will be reclassified as an "analytical case" if SARS-CoV-2 testing is positive during that hospital admission.

Classification of cases and controls for the analysis is shown below in Table 1:

Table 1. Classification of cases and control for analysis.

Status of patient at enrollment	Clinical SARS-CoV-2 test results	Public Health SARS-CoV-2 RT-PCR results	Classification for Analysis
Enrollment case	≥1 positive	Positive	Analytical case
Enrollment case	≥1 positive	Negative	Analytical case
Enrollment case	≥1 positive	Not done / inconclusive	Analytical case

Exclusion criteria for analysis:

- Missing/unknown case status
- Missing/unknown vaccination status
- First dose of vaccine 0 to 13 days before illness onset (excluded from primary analysis)
- Illness onset >10 days before date of first SARS-CoV-2 test or >72 hours from hospital admission date
- Received a COVID-19 vaccine not authorized for use in the United States
- Exclusion of Moderna and Janssen COVID-19 vaccine until vaccines are authorized for use in US children and coverage increases to >20% in the control patients.
- Exclusion of third dose recipients until coverage increases in control patients.

5c. Sample size calculations

Table 2 provides the estimated number of cases and test-negative controls required for a crude VE analysis using a range of assumptions for VE, precision (95% confidence interval), and vaccine coverage among control patients.

Table 2. Sample size calculators for VE analysis

VE estimate	Confidence interval	Vaccine coverage in controls	Number of cases	Number of test-negative controls
90%	67.0–97.0%	70%	30	30
90%	67.0–97.0%	50%	43	43
90%	67.0–97.0%	30%	81	81
80%	60.0–90.0%	70%	75	75
80%	60.0–90.0%	50%	90	90
80%	60.0–90.0%	30%	148	148
70%	51.5–81.5%	70%	147	147
70%	51.5–81.5%	50%	160	160
70%	51.5–81.5%	30%	243	243

5d. Key study definitions

Key study definitions for the VE analysis and clinical outcomes for specified severity outcomes are shown in Table 3A and 3B below:

Table 3A. Study definitions.	
Category / Group	**Description**
Vaccination status	
Full vaccination	Study patient who received all doses of an authorized COVID-19 vaccine ≥14 days prior to illness onset (or date of hospitalization in syndrome-negative controls).
Partial vaccination	Study patient who received one of two doses of a two-dose COVID-19 vaccine ≥14 days prior to illness onset (or date of hospitalization in syndrome-negative control patients). These patients either have not received a second dose of vaccine or received the second dose 0-13 days prior to illness onset. Secondary analyses may also consider VE within different timeframes from date of vaccination.
Full or partial vaccination (one or more doses)	Study patient who has received either full or partial vaccination with a COVID-19 vaccine.
Unvaccinated	Study patient who did not receive any doses of an authorized COVID-19 vaccine ≥14 days prior to illness onset or who was vaccinated after illness onset. A patient who received vaccination 0-13 days before illness onset will be excluded from the primary VE analyses but will be considered in secondary analyses. This vaccination group may serve as an indicator of bias in primary VE analyses (selection bias or confounding not accounted for in VE models), as vaccine effectiveness is not expected in the period shortly following the first dose of a COVID-19 vaccine.
Alternative times from vaccination to illness onset	If feasible we may perform additional sub-analyses of VE using other discrete time periods between vaccination and illness onset, such as (for a 2-dose vaccine series): 0-14 days from first dose of vaccine (partial vaccination) 15-28 days from first dose of vaccine (partial vaccination) 29-42 days from first dose of vaccine (partial vaccination) >42 days from first dose of vaccine (partial vaccination) 0-7 days from second dose of vaccine 8-14 days from second dose of vaccine >14 days from second dose of vaccine Future analyses will evaluate potential waning vaccine effectiveness over time in future analyses, e.g. for each 30-day interval from date of vaccination.
Severity	
Severe case	Several definitions for severity will be used including but not limited to case patients who are: hospitalized in ICU, hospitalized with acute organ failure, hospitalized with vasopressor-dependent shock, hospitalized with death, hospitalized with non-invasive or invasive mechanical ventilation, or severity defined by other parameters (e.g., Food and Drug Association criteria).
Non-severe case	Case patient who do not meet criteria for the severity case definition.

Genetic strain	
SARS-CoV-2 strain	Available specimens with a cycle threshold (Ct) value ≤30 will undergo genetic sequencing with lineage determination. VE by group (B.1.1.7, B.1.351, or P.1 viruses, or other variants) will be assessed if sufficient sample size. For specimens with higher Ct values, PCR analysis using targeted primers to detect SARS-CoV-2 strains will be conducted.

Table 3B. Clinical outcome definitions

Clinical Outcome	Description
Window of outcome assessment	All outcomes are assessed between initial hospital presentation and the earlier of hospital discharge or the end of hospital day #28 (calendar day). Once a patient is discharged from the acute care hospital participating, outcome assessment ends. Clinical events, such as vasopressor use and mechanical ventilation that occur during the index hospitalization but before enrollment (defined as the time of upper respiratory sample collection) are included as study outcomes.
ICU admission	Admission to or boarding for an ICU bed at any time during hospitalization.
Vasopressor support	Use of a vasopressor by continuous intravenous/intraosseous infusion for at least 1 hour to increase or maintain blood pressure at any time during hospitalization.
Invasive mechanical ventilation	Receipt of positive pressure ventilation through an endotracheal tube or tracheostomy tube for at least 1 hour at any time during hospitalization. Patients on chronic invasive mechanical ventilation prior to the current illness are not eligible for the invasive mechanical ventilation outcome.
Non-invasive ventilation	Receipt of positive pressure ventilation through nasal prongs or a facemask for at least 1 hour at any time during hospitalization. CPAP and BiPAP for respirator support, other than for treatment of chronic sleep apnea, fulfill the criteria for the non-invasive mechanical ventilation outcome. Patients chronically on invasive or non-invasive mechanical ventilation prior to the current illness are not eligible for the non-invasive mechanical ventilation outcome.
In-hospital 28-day mortality	Death after hospital presentation and before the earlier of hospital discharge or the end of hospital day #28.

5e. Model building strategy for final VE analysis

Patient description:

A model building strategy will be applied for VE assessment using test-negative or syndrome-negative control groups. Characteristics of SARS-CoV-2-positive and SARS-CoV-2-negative patients (or syndrome-negative controls) and vaccinated and unvaccinated patients will be described by counts and percentages or medians and interquartile ranges and compared using Pearson X^2 test or Fisher exact test for categorical variables and Wilcoxon rank-sum test or *t* test for continuous variables.

Outcomes:

Based on sample size calculations as presented in Table 2 with observed vaccination coverage, We will consider VE against primary analytic outcomes of highest disease severity among hospitalized patients, as defined by admission to intensive care unit (ICU) or receipt of receipt of life-supporting interventions during hospitalization, including noninvasive or invasive mechanical ventilation, vasoactive infusions, or extracorporeal membrane oxygenation, or in-hospital death.

Adjusted COVID-19 VE:

Crude (unadjusted) VE will first be calculated. Adjusted VE will then be calculated by comparing the odds of COVID-19 vaccine receipt among cases and controls using unconditional multivariable logistic regression with SARS-CoV-2 positivity as the outcome and vaccination status as the exposure. VE is calculated as (1 – *adjusted odds ratio*) × 100%.

Several variables will be included *a priori* in VE regression models. These include enrollment location (specific hospital or geographic region), age, sex, race/ethnicity, and calendar time. These variables are included because they are established or suspected confounders.

Additional variables will be considered as model covariates that may confound the relationship of interest if associated with both vaccination status and risk of hospitalized COVID-19 illness.

We will examine the association of these other potential confounders. Variables with the strongest association with the exposure and the outcome that change the OR by >5% will be selected for inclusion in the model. If several of these potential confounders performed similarly, we will use the most parsimonious set of variables. We will examine a range of health status indicators as potential confounders, including measures of baseline health status (e.g., ≥1 underlying health conditions, specific health conditions). As factors related to social vulnerability and community exposures/behaviors are also potential confounders, we will also consider measures of SES and social vulnerability (e.g., CDC Social Vulnerability Index) and reported behaviors/exposures (e.g. mask use, influenza vaccination during the current season).

We will estimate VE separately for full vaccination, partial vaccination, and receipt of one or more doses (either full or partial vaccination), as well as for subgroups of interest or using alternative times since vaccination. We will estimate VE by specific age groups, including: 12-15 years and 16-18 years. VE will also be estimated based on documented vaccination alone (Definition 1 above) as well as either documented vaccination or plausible self-report including location and date(s) [Definition 5 above]. Patients self-reporting COVID-19 vaccination without details about location and date(s) will be excluded from the analysis given low confidence in vaccination status. Similar approaches to model building will also be used in estimating VE using the syndrome-negative control group. If estimates are similar between test-negative and syndrome-negative control VE models, control groups will be pooled to increase sample size and precision of VE estimate. Firth penalized regression was used for models with ≤5 vaccinated cases.

Effect modification:

Potential effect modifiers of vaccine effectiveness, such as presence of underlying conditions, may also be considered. Likelihood ratio tests will be used to compare P-values of the interaction term (a P-value <~0.15 is suggestive of effect modification). VE estimates will be presented stratified by level of an effect modifier.

5f. Other analytic considerations

Missing illness onset date:

Some patients or proxies may not be able to provide the date of illness onset. For the main VE analysis, we will include these patients. We may perform sensitivity analyses restricting the VE analysis only to patients with a known date of illness onset, using a multiple imputation approach to impute illness onset date in reference to time of testing for those with missing values, or assigning illness onset date as the median days between illness onset and date of hospital admission in patients with complete data.

Specification of race/ethnicity:

We may be unable to obtain race and ethnicity data for all patients. This will be handled analytically, e.g., including an unknown race/ethnicity category if this group is large.

Specification of age:

Specification of age varies depending on subset being analyzed. Alternative specifications included continuous/linear (if data suggested no evidence of nonlinearity) or 3-or 4-part categorization if nonlinearity is present (alternatively, cubic splines can be used). In models stratified by age group, age (continuous) is typically included in the model to account for residual confounding by age within age category (sample size permitting).

Specification of calendar time:

Calendar time of symptom onset is specified in the VE model by classifying based on calendar week based on the date of illness onset or date of hospitalization. We will consider adjusting for calendar time in different intervals (e.g., weekly, biweekly, monthly).

Discordant dates of vaccination:
Dates of COVID-19 vaccination through documented sources such as vaccine record cards or immunization registries are likely to be more accurate than self-reported dates and will therefore be used preferentially.

8. Summary of Changes to the protocol and the statistical analytic plan (February 24, 2022)

Changes on October 27, 2021

- Firth penalized regression was used for models with ≤5 vaccinated cases.
- Based on sample size calculations as presented in Table 2 with observed vaccination coverage, considered VE against primary analytic outcomes of highest disease severity among hospitalized patients, as defined by admission to intensive care unit (ICU) or receipt of receipt of life-supporting interventions during hospitalization, including noninvasive or invasive mechanical ventilation, vasoactive infusions, or extracorporeal membrane oxygenation, or in-hospital death.
- Subgroup analysis included:
    - Age groups: 12-15 years vs 16-18 years
- Exclusion of Moderna and Janssen COVID-19 vaccine until vaccines are authorized for use in US children and coverage increases to >20% in the control patients.
- Vaccine effectiveness guidelines for enrolling controls (appendix)

Changes on December 14, 2021

- On December 14, 2021, all sites stopped enrollment of syndrome negative controls. Analyses using the full cohort admitted on July 1, 2021 will include hospitalized controls with a negative SARS-CoV-2 RT-PCR or antigen test result, with or without Covid-19-like symptoms. An updated flow chart describing enrollment after December 14, 2022 is updated in Section 3b. Inclusion/Exclusion Criteria, Figure 1: Eligibility, Screening and Enrollment Flowchart.
    - Rationale was based on similarity in control groups from a prior analysis (Olson et al. NEJM 2022; 386:713-723; DOI: 10.1056/NEJMoa2117995), which helped investigators achieve initial aim of comparing the two control groups early in the Covid-19 vaccine introduction phase.

- Analyses will exclude third dose recipients until coverage increases in control patients to >20%.

9. Appendix: Vaccine Effectiveness Guidelines for Enrolling Controls

Vaccine Effectiveness Guidelines for Enrolling Controls

- A case (SARS-CoV-2 positive patient) in the same age range must have already been enrolled at your site
    - Enroll 2 controls per case
        - 1 test negative, syndrome positive control (see eligibility flowchart)
        - 1 syndrome negative control (see eligibility flowchart – stopped enrollment on/ after December 14, 2021)
    - Age matching
        - < 6 months
        - ≥ 6 months to < 6 years
        - ≥ 6 years to < 12 years
        - ≥ 12 to < 16 years
        - ≥ 16 to < 19 years
    - Time matching
        - Controls should be hospitalized within 3 weeks of case being enrolled. This can be 3 weeks before or 3 weeks after case was enrolled.
        - If after 3 weeks you cannot find 1 type of control you can enroll a 2nd of the already enrolled control type
            - For example: You enrolled a case and have enrolled an age-matched syndrome negative control. It has now been 3 weeks since you enrolled the case and you have not been able to identify and enroll an age-matched test negative, syndrome positive control. You can enroll a 2nd age-matched syndrome negative control.