DAIT-COVID-19-001

HUMAN EPIDEMIOLOGY AND RESPONSE TO SARS-COV-2 (HEROS)

V3.0/SEPTEMBER 2, 2020

NIAID Funding Mechanism: Administrative Supplements to multiple NIAID grants

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Confidentiality Statement

National Institute of Allergy and Infectious Diseases

Protocol Synopsis

Title	Human Epidemiology and Response to SARS-CoV-2
Short Title	HEROS
Number of Sites	Thirteen US Sites (additional sites may be eventually involved)
Study Primary Objective	Determine the incidence of SARS-CoV-2 infection (via detection of viral RNA in nasal secretions) in children and their household contacts (caregivers and siblings) during the study period.
Study Design	Prospective surveillance for SARS-CoV-2 in children that are currently enrolled in NIH-funded studies (index participant) and their household contacts
Primary Endpoint	The cumulative incidence of SARS-CoV-2 RNA detection in nasal samples among index participants and their household contacts over the study period.
Secondary Endpoint(s)	• The percent of index participants and their household contacts with detectable SARS-CoV-2-specific antibodies in serum over the study period. • The cumulative incidence of SARS-CoV-2 detection in nasal samples among index participants with asthma and other atopic disease over the study period as compared to index participants without any atopic disease. • The percent of index participants with asthma and other atopic disease with detectable SARS-CoV-2-specific antibodies in serum over the study period as compared to index participants without any atopic disease. • Changes in the nasal transcriptome that are associated with detection of SARS-CoV-2 in nasal samples among index participants and their household contacts over the study period. • Changes in the nasal transcriptome that are associated with detection of SARS-CoV-2 in nasal samples among index participants with asthma and other atopic disease over the study period as compared to index participants without any atopic disease. • Symptoms (including upper and lower airway, gastrointestinal, and systemic symptom as assessed via questionnaires) that are associated with detection of

	SARS-CoV-2 in nasal samples among index participants and their household contacts over the study period. • The cumulative incidence of SARS-CoV-2 detection in nasal samples among index participants using topical, systemic, or inhaled steroids during the study period as compared to index participant that are not using topical, systemic, or inhaled steroids. • The association of baseline demographic and environmental factors or history of bronchiolitis with the cumulative incidence of SARS-CoV-2 detection in nasal samples among index participants and their household contacts over the study period.
Accrual Objective	Up to 2000 families
Study Duration	a minimum of 6 months from time of enrollment to end of study
Inclusion Criteria	Household members who meet all of the following criteria are eligible for enrollment as study participants: a. The index participant and/or caregiver understands the study procedures, is willing to conduct them at home, and has the ability to use either a computer or a smart phone to link to and respond to the study questionnaires. If the family does not have access to a computer or a smart phone, they are willing to speak with a study member by phone to answer the questionnaires b. The index participant is 21 years old and younger, lives with caregiver(s), and is or has been a participant in a NIH-funded clinical study from which information on respiratory conditions, including asthma, and other atopic and allergic diseases is available c. The index participant and caregiver will reside in the United States, including Puerto Rico, for the duration of the study d. The index participant will live with the caregiver for at least 50% of the time for the duration of the study e. An English or Spanish speaker is available to serve as the primary contact and as the person who will be responsible for the completion of questionnaires and the collection of study biological samples

	f. Qualifying siblings must be under 21 years of age and live in the same home as the Index participant and caregiver
Exclusion Criteria	Individuals who meet any of the following criteria are not eligible for enrollment as study participants: Past or current medical problems, which, in the opinion of the site investigator, may pose risks from participation in the study, may interfere with the participant's ability to comply with study requirements or may impact the quality or interpretation of the data obtained from the study
Study Stopping Rules	• If protocol continuation poses major new risks to participants or study staff • If, as a result of the COVID-19 pandemic circumstances, protocol feasibility becomes highly questionable

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Glossary of Abbreviations

CFR	Code of Federal Regulations
COVID-19	Coronavirus Disease 2019
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DAIT	Division of Allergy, Immunology, and Transplantation
DSMB	Data Safety Monitoring Board
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICH	International Conference on Harmonization
IND	Investigational New Drug
IRB	Institutional Review Board
MOP	Manual of Procedures
NIAID	National Institute of Allergy and Infectious Diseases
PI	[Site] Principal Investigator
SACCC	Statistical And Clinical Coordinating Center
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Suspected Adverse Reaction
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SOP	Standard Operating Procedure
SUSAR	Serious Unexpected Suspected Adverse Reaction

1. Background and Rationale

COVID-19, the infectious disease caused by SARS-CoV-2, is rapidly affecting humans around the globe. While initial epidemiological data have focused on cases that resulted in severe respiratory disease seen predominantly in adults, little information regarding the infection burden in children is available. This is complicated by the observation that many virologically-confirmed cases in children are asymptomatic (Dong et al, *Pediatrics*, PMID 32179660). Undocumented, and likely infectious, cases could result in exposure to a far greater proportion of the community than would otherwise occur. Indeed, it has been proposed that undocumented (or silent) infections are the source for almost 80% of documented infections (Li et al, *Science*, PMID 32179701); thus, it is critical to determine the silent and symptomatic infection rate in children. To overcome challenges for clinical study implementation imposed by current healthcare access restrictions, this surveillance study will enroll and prospectively observe eligible children that are current participants in NIH-funded pediatric research studies and their family members. These children and their families are known to study site personnel and because, as part of their participation in the various NIH-funded research studies, most of these children have already been exposed to the procedures that are involved in a surveillance study. This study can therefore be rapidly implemented and realistically conducted remotely without necessitating any visits to a clinical research center.

In addition to the need for surveying children for asymptomatic SARS-CoV-2 infection, this study will allow a comparison between children with asthma and other atopic conditions and children without those conditions. Although, as of the current writing of this protocol, asthma has not been identified as a risk factor for severe COVID-19 disease (Zhang et al, *Allergy*, PMID 32077115), there is evidence that children with asthma and other atopic conditions have increased susceptibility to viral respiratory infections (Esquivel et al, *AJRCCM*, PMC5649984) and that viral respiratory infections may result in worsening of underlying airway disease (Jartti et al, *J Allergy Clin Immunol*, PMID 28987219). No data currently exist as to whether this is true for SARS-CoV-2 infection or whether allergic airway disease could be protective.

2. Study Objectives

2.1 Primary Objective

Determine the incidence of SARS-CoV-2 infection (via detection of viral RNA in nasal secretions) in children and their household contacts (caregivers and siblings) during the study period.

2.2. Secondary Objectives

a. Determine SARS-CoV-2 antibody development in children and their household members.
b. Compare SARS-CoV-2 infection status (detection of viral RNA in nasal secretions) and virus-specific antibody development for children with asthma and other atopic conditions (e.g. eczema) versus children without asthma or other atopic conditions.
c. Determine mucosal immune responses to SARS-CoV-2 infection through gene expression profiling and examine whether these responses are influenced by the presence of asthma or other atopic condition.
d. Determine whether topical, systemic, or inhaled steroids use, as directed by their care provider, modify the risk of SARS-CoV-2, the severity of infection, or expression of the SARS-CoV-2 receptor.
e. Determine whether baseline demographic and environmental factors, such as age, sex, race, history of influenza vaccination, rural versus urban living, medications (such as ACE inhibitors), and smoking exposure modify the risk of SARS-CoV-2 infection or the severity of infection.

f. Assess whether a history of RSV infection or bronchiolitis during infancy modifies severity of SARS-CoV-2 infection.

2.3. Exploratory Objectives

a. Investigate the transmissibility of SARS-CoV-2 infection among household members.
b. Investigate whether SARS-CoV-2 infection will be associated with more respiratory symptoms in children with asthma and other atopic conditions, as compared to children without asthma or other atopic conditions.
c. Investigate whether SARS-CoV-2 infection will be associated with baseline nasal microbiome or with changes in the nasal microbiome and whether the underlying atopic status plays a role in this relationship.
d. Investigate whether SARS-CoV-2 infection, as identified by the presence of virus in nasal secretions, will be associated with the presence of virus in stool.
e. Determine whether IgA antibody specific for common coronaviruses (229E, OC43, NL63, HKU1) in the blood at baseline modifies the risk of SARS-CoV-2 infection or the severity of infection.
f. Investigate earlier SARS-CoV-2 exposure by assaying historical samples from enrolled participants.
g. Identify protective/risk factors for disease acquisition integrating all available data using machine learning approaches and network analysis to provide efficient representation of complex interactions.

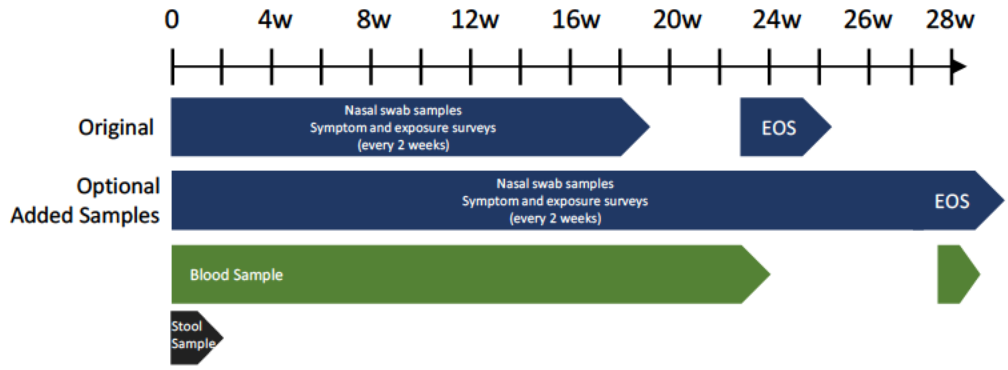
3. Study Design

3.1. Description of Study Design

This is a prospective surveillance study in which subjects that are currently enrolled in NIH-funded studies (index participant) and their household contacts, including caregiver(s) and possibly a sibling, will be asked to enroll in the SARS-CoV-2 surveillance study. A minimum of 2 family members (index participant and a caregiver) and up to a maximum of 4 total members (additional caregiver and/or sibling) will be enrolled per family. The enrollment goal is approximately 2000 families. The enrollment period will be approximately 8 weeks, and each participant will participate for a minimum of 6 months with possible extension of the observation period. During the study, biological samples will be collected by the family at pre-determined intervals and symptom and exposure surveys will be completed remotely via a smart phone, on-line, or phone communications at the time the biological samples are collected (Figure 3.1 Study Overview). The Schedule of Events (Table A) provides more complete details of the study events and timing of these events. All biological samples (e.g. nasal swabs, peripheral blood, stool) will be collected by the caregiver at home using materials provided to the family. Peripheral blood will only be collected from participants 2 years of age and older. At the end of study, additional samples (e.g. nasal secretion and/or saliva samples) may be collected by the family or study staff at a site visit, if feasible.

If any member of the household develops symptoms compatible with COVID-19, the family will be instructed to complete a symptom survey for the affected household member. If completion of the symptom algorithm meets a study-specified threshold, this will be considered the first illness event for the family/household and an additional nasal swab will be collected from all study participants in the household and an additional stool sample (via swab) will be collected from the affected household member if they are a study participant. Blood will be collected from all study participants that are 2 years of age and older three weeks following this first illness event during the study period. Additional nasal swabs and stool samples will be collected from the index participants with every illness that meets the study-specified symptom threshold. For family members other than the index participant, additional samples associated with illnesses will be collected with the first illness event only.

Figure 3.1 Study Overview



3.2. Primary Outcome

The cumulative incidence of SARS-CoV-2 RNA detection in nasal samples among index participants and their household contacts over the study period.

3.3. Secondary Outcome(s)

a. The percent of index participants and their household contacts with detectable SARS-CoV-2-specific antibodies in serum over the study period.
b. The cumulative incidence of SARS-CoV-2 detection in nasal samples among index participants with asthma and other atopic disease over the study period as compared to index participants without any atopic disease.
c. The percent of index participants with asthma and other atopic disease with detectable SARS-CoV-2-specific antibodies in serum over the study period as compared to index participants without any atopic disease.
d. Changes in the nasal transcriptome that are associated with detection of SARS-CoV-2 in nasal samples among index participants and their household contacts over the study period.
e. Changes in the nasal transcriptome that are associated with detection of SARS-CoV-2 in nasal samples among index participants with asthma and other atopic disease over the study period as compared to index participants without any atopic disease.
f. Symptoms (including upper and lower airway, gastrointestinal, and systemic symptom as assessed via questionnaires) that are associated with detection of SARS-CoV-2 in nasal samples among index participants and their household contacts over the study period.
g. The cumulative incidence of SARS-CoV-2 detection in nasal samples among index participants using topical, systemic, or inhaled steroids during the study period as compared to index participant that are not using topical, systemic, or inhaled steroids.
h. The association of baseline demographic and environmental factors or history of bronchiolitis with the cumulative incidence of SARS-CoV-2 detection in nasal samples among index participants and their household contacts over the study period.

3.4. Exploratory Outcome(s)

a. Symptoms associated with detection of SARS-CoV-2 in nasal samples.
b. Nasal microbiome outcomes of alpha and beta diversity among index participants and their household contacts with detectable SARS-CoV-2 in nasal samples over the study period.
c. The percent of participants with symptomatic SARS-CoV-2 infection in whom the virus can be detected in stool.
d. Levels of IgA antibodies specific for common coronaviruses (229E, OC43, NL63, HKU1) in the blood at baseline.
e. The percent of index participants with detectable SARS-CoV-2-specific antibodies in samples that were collected and stored prior to the current study period.

3.5 Randomization

N/A

4. Selection of Participants and Clinical Sites/Laboratories

4.2. Rationale for Study Population

The study population will include index participants and their families. The intent is to recruit index participants who have asthma and/or other atopic or allergic conditions, as well as healthy index participants, with extensive medical information and information on atopic and allergic status available as a result of their participation in the NIH-funded research study. As many of these studies are birth cohort studies, there is also extensive information on the parents. Furthermore, most of these families have experience with collection of respiratory samples and are familiar with respiratory questionnaires.

4.3. Inclusion Criteria

Household members who meet all of the following criteria are eligible for enrollment as study participants:

a. The index participant and/or caregiver understands the study procedures, is willing to conduct them at home, and has the ability to use either a computer or a smart phone to link to and respond to the study questionnaires. If the family does not have access to a computer or a smart phone, they are willing to speak with a study member to answer the questionnaires.

b. The index participant is 21 years old and younger, lives with caregiver(s), and is or has been a participant in a NIH-funded clinical study from which information on respiratory conditions, including asthma, and other atopic and allergic diseases is available.

c. The index participant and caregiver will reside in the United States, including Puerto Rico, for the duration of the study.

d. The index participant will live with the caregiver for at least 50% of the time for the duration of the study.

e. An English or Spanish speaker is available to serve as the primary contact and as the person who will be responsible for the completion of questionnaires and the collection of study biological samples.

f. Qualifying siblings must be under 21 years of age and live in the same home as the index participant and caregiver.

4.4. Exclusion Criteria

Individuals who meet any of the following criteria are not eligible for enrollment as study participants:

Past or current medical problems, which, in the opinion of the site investigator, may pose risks from participation in the study, may interfere with the participant's ability to comply with study requirements or may impact the quality or interpretation of the data obtained from the study

5. Known and Potential Risks and Benefits to Participants

5.1 Risks of Study Procedures

5.1.1 Nasal Swabs and Nasal Secretions

a. Nasal swab and nasal secretion collection may cause localized discomfort. Rarely, mild epistaxis may occur.

b. There is a risk of irritation if the liquid reagent in the nasal swab collection kit comes in contact with the skin. Gloves will be provided to reduce the risk of skin contact.

c. Risk of infection: It is unknown whether the collection of the biospecimens outlined in this protocol increases the risk of infection to household members beyond that of living in the same household with study participants. There is a distinction between what should be expected in a healthcare setting and the home. In this respect, home collection probably does not merit use of the level of personal protective equipment (PPE) recommended for healthcare workers. Because it is not known whether the collection of the biospecimens outlined in this protocol increases the risk of infection to household members beyond that of living in the same household with study participants, we include viral transmission as a potential risk of study participation. Because we do not know if there is an increased risk of infection transmission, as a precaution, the study will provide, recommend, and teach proper use of barrier protection to those assisting with biospecimen collection (collection of anterior nasal swab in age 10 and under, inferior turbinate swab for age 11+, stool swab, capillary blood collection).

Personal Protective Equipment (PPE) plan: The proposed PPE plan for this study is based on available data and guidance from the CDC at the time the study was implemented to prevent any significant additional infectious risk to the family members performing the swabs given both the nature of the procedure being non-aerosol generating and the ongoing level of contact within the household.

1. **Masks.** We recognize that the CDC at the time of writing of this protocol does still recommend use of an N95 or higher-level respirator during collection of a nasopharyngeal (NP) sample for SARS-CoV-2 testing by healthcare providers. However, there are no recommendations for collection by household members nor any recommendations for collecting anterior nares and mid-length, inferior turbinate samples. The CDC guidance does acknowledge that not all procedures are equally likely to generate infectious aerosols and that NP swabs therefore would be a lower priority for use of N95 masks than more invasive procedures such as intubation, if availability of N95 masks is limited. The collection of anterior nares swabs and inferior turbinate swabs, which are proposed to be performed in this study, is less likely to induce coughing and possible aerosol generation compared with NP swabs, although even NP swabs are not considered AGP. Thus, we believe that there is lesser utility of an N95 in the setting of such sample collection. In addition, an

N95 mask cannot be fit tested in this scenario, and without fit testing there isn't any assurance that an N95 mask will provide any better protection than a surgical mask.

2. **Other barrier protection:** The CDC guidance for specimen collection by healthcare providers also specifies the use of a gown in addition to the PPE we are recommending. We do not view a gown in the home as necessary given the differences between the healthcare and home environments. When family members have physical contact with the child throughout the rest of the day without such a barrier, the benefit of the gown is questionable. We are recommending gloves for the dual purpose of barrier protection and protection from inadvertent contact with the liquid reagent provided in the tubes into which the swabs will be placed, as the liquid reagent may cause mild irritation of the skin.

3. **Ethical use of PPE:** At the time of development of this protocol, PPE shortages, including N95 masks are currently (March – April 2020) posing a tremendous challenge to the US healthcare system because of the COVID-19 pandemic. Healthcare facilities are having difficulty accessing the needed PPE and are having to identify alternate ways to provide patient care. There is an Emergency Use Authorization (EUA) of Respiratory Protective Devices; on February 4, 2020, the HHS Secretary declared that circumstances exist to justify the authorization of emergency use of additional respiratory protective devices in healthcare settings during the COVID-19 outbreak. Thus, recommending PPE for this protocol in excess of what has been included and in the absence of any likely benefit would not be responsible use of limited resources and could not be endorsed.

   Summary: In summary, it is unknown whether the collection of the biospecimens outlined in this protocol increases the risk of infection to household members beyond that of living in the same household with study participants. Because of this uncertainty, viral transmission is included as a potential risk of study participation, and a barrier protection plan is recommended. However, the collection of these samples by household members does not merit use of the level of PPE recommended for healthcare workers. Thus, use of a surgical mask, eye shield, gloves, and education on proper use, in addition to hand hygiene, are deemed to provide protection for household members assisting with biospecimen collection. These recommendations were developed based on there being a clear distinction between what should be expected in a healthcare setting and the home, and the procedures being conducted. It is not known whether our recommendation of barrier protection precautions for those living in the same household who assist with biospecimen collection are even necessary, but the benefits seem plausible, and the harms unlikely.

5.1.2 Blood Collection

The risks associated with drawing blood via the OnDemand device include syncope, local discomfort where the lancet is inserted, and, in rare cases, local infection. Participants are instructed to remain seated while using the OnDemand device and during blood collection and to lay down if a participant feels light-headed or experiences dizziness. Universal precautions will be followed to reduce the risk of infection.

5.1.3. Stool and Saliva Collections

There are no significant risks associated with saliva sample collection.

There is a risk of irritation if the liquid reagent in the stool swab collection kit comes in contact with the skin. Gloves will be provided to reduce the risk of skin contact.

5.1.4. Questionnaires/Surveys

There is a possibility that participants may find questions too personal. Participants may refuse to answer any questions that make them feel uncomfortable. Participants will provide name, address, phone number, and date of birth. This information will be shared with the sponsor (NIAID/DAIT), the Data Management Coordinating Center (DMCC) at Vanderbilt University, the company that is sending the sample kits to the participants home, and the researchers and staff that are part of this study.

5.1.5. Breach of Confidentiality

As in every research study, unauthorized access to identified data is a risk. The REDCap data system into which participants will directly enter personal data is an established data system that provides several levels of security.

5.2. Potential Benefits

This study will provide no direct benefit for participants. The public health benefit for this study is to collect data regarding incidence of symptomatic and asymptomatic SARS-CoV-2 in a large convenience sample in order to inform decisions regarding interventions to control spread of SARS-CoV-2 infection and possibly design proactive interventions to prevent future COVID-19 outbreaks. This study will provide timely and useful evidence and may enable public health authorities to be more effective in their efforts to protect and promote public health related to SARS-CoV-2.

6. Study Procedures

6.1. Enrollment and Training

Potential study participants (usually the primary care provider for minor children) will be contacted by a member of the clinical research site staff via text, email, or phone call who will direct them to the link to the study HEROS home web page. If interested in participating in the study, the participant/caregiver will be given instructions to view the study web portal. The potential participant will read an information sheet that includes details about the study, study requirements, and study risks, and will provide assurance that each participating family member has read the information sheet and agrees to participate for themselves, index participants, and other family members. The participant will then be directed to complete an electronic registration form and to complete a baseline questionnaire. Once this process is completed, the participant is considered enrolled in the study and will be assigned a unique participant number. All participating family members will be assigned unique participant numbers. Upon completion of these tasks, the sample kit distribution center will mail each household a set of sample collection kits for initiation of bio-sampling.

Once enrolled, the primary contact/caregiver and each participant will be requested to undergo a web-based training that will describe in detail the processes of sample collection and handling. Study staff will be available by phone, Skype, text, or video conferencing for further instructions and clarifications on sample collection procedures.

At Week 18, the primary contact/caregiver will be electronically sent an information sheet that includes details about a study extension that will include collecting 4 additional nasal swabs for a total of 14 nasal swabs over 28 weeks. The information sheet will require that each participating family member attest that they have read the information sheet. The household will have the option to continue with the original visit and sample collection schedule (10 nasal swab collections over 24 weeks), to participate in the study extension with 4 additional nasal swab collections, or to request further information via contact with their local study site.

6.2. Index participants and Household Contacts Study Assessments

6.2.1 Caregiver-Collected Samples

At the times shown in the Schedule of Events (Table A), the primary contact/caregiver will collect nasal swabs from the index participants and all family members that are enrolled in the study at the beginning of the study (Week 2) and every 2 weeks thereafter for 9 collections, then a final 10th nasal swab collected at the end of the study (total 10 nasal swabs collected over 24 weeks). If the household agrees to participate in the study extension, 4 additional nasal swabs will be collected between Week 18 and Week 28 (Table A). Stool samples via swabs will be collected from the index participants and all family members that are enrolled (starting at Week 2) into the study (Table A). Blood samples will be collected via the OnDemand device from the index participants and all family members that are enrolled in the study and 2 years of age and older (Table A). Nasal secretion and/or saliva samples may also be collected from the index participants and all enrolled family members at Week 24. Samples will be shipped as instructed in the sample kit package. Details of the nasal swab, stool collection, blood collection, nasal secretion, and saliva procedures will be provided in the sample kit package.

6.2.2. Questionnaires

At the times shown in the Schedule of Events (Table A), the primary contact/caregiver will have the responsibility to ensure that on-line questionnaires regarding current symptoms and recent exposures will be completed for all participants. A symptom and exposure survey will be completed every 2 weeks starting at Week 2 to coincide with nasal sample collection. A health check survey to detect any illness in the household in the intervening weeks will be completed every 2 weeks starting at Week 1. The caregiver will be instructed on how to access and complete the on-line questionnaires.

6.3. Unscheduled Assessments During Illness

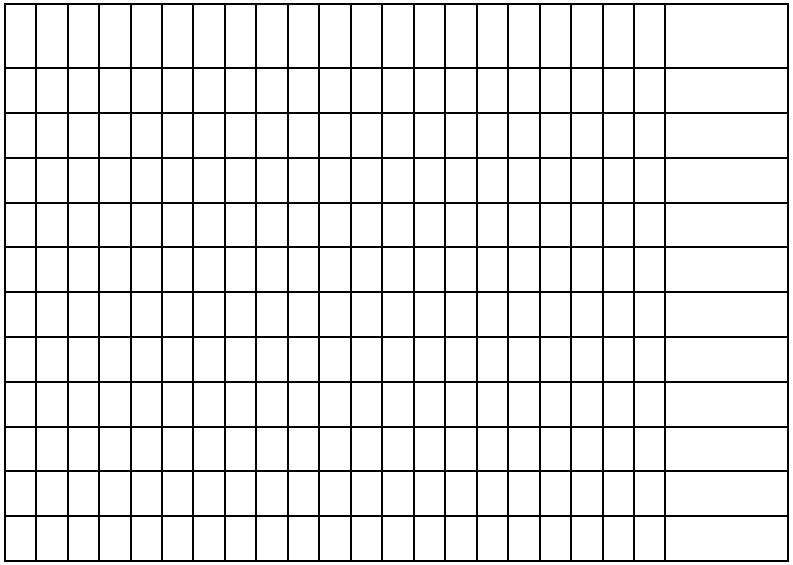
6.3.1. First Illness. If any member of the household, including study participants and other people living in the same household that are not enrolled in the study, develop symptoms consistent with a viral illness, the caregiver will be instructed to fill in a symptom survey. If completion of the symptom survey meets a study-specified threshold in an illness algorithm, the caregiver will be instructed to collect, within 24 hours, unscheduled nasal swabs from all study participants and a stool sample from the affected participant. If the affected household member is not a study participant, she/he will be asked to enroll in the study only for this illness event and to provide a nasal swab and a stool sample. In addition, blood will be collected via a OnDemand device from all study participants that are 2 years old or older three weeks after the first illness event threshold is met. If the affected household member was not a study participant, she/he will also be asked to provide the 3-week blood sample. If the affected household member was not a study participant and refuses to register into the study or provide samples, then this illness event will not be recorded as the first Illness event for the household.

6.3.2. Subsequent Illnesses. Subsequent illnesses will only be investigated if the index participant develops symptoms consistent with a viral illness that meet the same study-specific threshold as in the "first illness". In such case, an extra nasal swab and a stool sample will be collected only from the index participant within 24 hours.

6.4. Sample Collection/Questionnaire Completion Windows

Sample collection and completion of the study questionnaires should take place within the time limits specified in the Schedule of Events (Table A).

Table A. Schedule of Events for All Participants



Weeks	0	1	2*	3	4*	5	6*	7	8*	9	10*	11	12*	13	14*	15	16*	17	18*	19	20*	21	22*	23	24*	25	26*	27	28*	Illness Event
Information Sheet Agreement to participate	X																		X											
Registration Form	X																													
Baseline Enrollment Questionnaire	X																													
Nasal Swab			X		X		X		X		X		X		X		X		X		X_4		X_4		X		X_4		X_4	X_2
Nasal Secretion																									X_3					
Saliva Collection																									X_3					
Blood Collection			X[1]																						X_5				X_5	X_6
Stool Collection			X																											X_2
Symptom and Exposure Survey			X		X		X		X		X		X		X		X		X		X_4		X_4		X		X_4		X_4	X_2
Health Check Survey		X		X		X		X		X		X		X		X		X		X_4		X_4		X_4		X_4		X_4		
End of Study Questionnaire																									X					

*The window for sample collection and completion of Symptom and Exposure surveys is (+/-) 4 business days

[1]There is no window for the baseline (Week 2) blood collection.

[2]Additional nasal swab and a stool samples will be collected when a household member shows signs of a viral illness and a study-specified threshold for symptom algorithm has been met. For the first illness, the nasal swab sample will be collected within 24 hours from all study participants, including the affected household member, and a stool sample from just the affected household member. Subsequent illnesses will be assessed only if the index participant is affected; in this case a swab and a stool sample will be obtained within 24 hours only from the index participant.

[3]A nasal secretion and/or saliva sample may be collected at End of Study.

[4]Nasal swabs will be collected at Week 20, 22, 26 and 28 and Health Check Surveys at Week 19, 21, 23, 25, and 27 from participants that agree to participate in the study extension.
[5]An end of study blood sample will be collected from all study participants that are at least 2 years old at Week 24 or at Week 28, if the participant decided to continue in the study with the original visit plan or agreed to participate in the extension, respectively.
[6]An additional blood sample will be collected from all study participants that are at least 2 years old three weeks after a first illness in the household and a study-specified threshold for the symptom algorithm has been met.

7. Laboratory Assays

- SARS-CoV-2 detection and nasal transcriptomics. RNA extracted from all swabs will be used to perform RT-qPCR for SARS-CoV-2. The remaining RNA and DNA will be stored for possible detection (and quantification) of other respiratory viruses, for generating the host transcriptome response to infection (from airway epithelial and any immune cells that were present on the nasal swab), and for delineating the nasal microbiome at the time the swab was collected.
- Viral Serology (antibody detection/quantification) on stored serum. The optimal assay for detection of virus-specific antibody has not yet been identified in the greater scientific community. Serum samples will be stored until such an assay becomes available.
- SARS-CoV-2 detection in stool. RNA extracted from all stool swabs will be used to perform RT-qPCR for SARS-CoV-2. The remaining RNA will be stored for possible detection (and quantification) of other respiratory viruses.

8. Biospecimen Storage

All biological samples will be collected by the caregiver and mailed to the study biorepository.

9. Criteria for Participant and Study Completion and Premature Study Termination

9.1. Participant Completion

Participation of the index participants, caregiver, and sibling(s) will be complete at Week 24 (original schedule of events) or Week 28 if the household agrees to the study extension.

9.2. Participant Stopping Rules and Withdrawal Criteria

Participants may be prematurely terminated from the study for the following reasons:

- The participant elects to withdraw from all future study activities
- The participant is “lost to follow-up” (i.e., no further follow-up is possible because attempts to reestablish contact with the participant have failed)
- The participant dies
- The Investigator no longer believes participation is in the best interest of the participant
- If the index participant’s enrollment is terminated, the caregivers’ and siblings’ participation will be terminated; however, termination of enrollment of the caregiver or sibling will not result in termination of the index participant

9.3. Participant Replacement

Participants who withdraw or are withdrawn will not be replaced.

9.4. Study Stopping Rules

The study may be prematurely terminated for the following reasons:

- If protocol continuation poses major new risks to participants or study staff
- If, as a result of the COVID-19 pandemic circumstances, protocol feasibility becomes highly questionable

10. Safety Monitoring and Reporting

10.1 Overview

This section defines the types of safety data that will be collected under this protocol and outlines the procedures for appropriately collecting, grading, recording, and reporting those data. Adverse events (AEs) that are classified as serious will be reported promptly to DAIT/NIAID. Appropriate notifications will also be made to the site principal investigators.

10.2 Definitions

10.2.1 Adverse Event

For this surveillance study, an adverse event (AE) is defined as any untoward or unfavorable medical occurrence in a participant that is associated with a study procedure mandated by the protocol and occurs within 48 hours of this procedure. This definition excludes all untoward or unfavorable medical occurrences not related to a study procedure, including hospitalizations or deaths. The study mandated procedures are listed in the Schedule of Events (Table A). Criteria for determining the relatedness of an AE to a study procedure and grading its severity are provided in Sections 10.3.1 *Grading Criteria* and 10.3.2 *Attribution Definitions*. The worsening of a participant's pre-existing medical condition will not be considered an AE unless the worsening is related to a study mandated procedure.

10.2.2 Serious Adverse Event (SAE)

SAEs are very unlikely to occur and reportable SAEs for this surveillance study will be limited to those related to study procedures. An SAE is defined as an AE meeting 1 of the following conditions:

- Death.
- A life-threatening event: An AE is considered "life-threatening" if, in the view of either the investigator or the DAIT Medical Monitor, its occurrence places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization.
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- Important medical events that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

Any other condition that, in the judgment of the investigator, represents a significant hazard, such as an important medical event that does not result in one of the above outcomes, may be considered an SAE when the event is related to a study procedure and jeopardizes the participant or requires medical or surgical intervention to prevent one of the outcomes listed above.

10.3 Grading and Attribution of Adverse Events

10.3.1 Grading Criteria

The study site will grade the severity of adverse events experienced by the study subjects according to the criteria set forth in the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE V5.0). This document (referred to herein as the NCI-CTCAE manual) provides a common language to describe levels of severity, to analyze and interpret data, and to articulate the clinical significance of all adverse events. The NCI-CTCAE has been reviewed by the DAIT/NIAID Medical Monitor and has been deemed appropriate for the subject population to be studied in this protocol.

Adverse events will be graded on a scale from 1 to 5 according to the following standards in the NCI-CTCAE manual:

Grade 1 = mild adverse event.

Grade 2 = moderate adverse event.

Grade 3 = severe and undesirable adverse event.

Grade 4 = life-threatening or disabling adverse event.

Grade 5 = death.

10.3.2 Attribution Definitions

For the purpose of this surveillance study, only AEs related to a study-mandated procedure will be reportable and by definition will always be assessed as related. The degree of certainty about relatedness will be graded using the 2 categories below.

Table 12.3.2 Attribution of Adverse Events

Code	Descriptor	Relationship (to study procedure)
RELATED CATEGORIES		
2	Possibly Related	The adverse event has a reasonable possibility to be related; there is evidence to suggest a causal relationship.
3	Related	The adverse event is clearly related.

10.4 Collection and Recording of Adverse Events

10.4.1 Collection Period

Adverse events will be collected from the time of first procedure, until a participant completes the study, until 48 hours after he/she prematurely withdraws, or is withdrawn from the study.

10.4.2 Collecting Adverse Events

Adverse events (including SAEs) may be discovered through any of these methods:

- Interviewing the participant through specific questions that will be incorporated in the study questionnaires
- Receiving an unsolicited complaint from the participant

10.4.3 Recording Adverse Events

Throughout the study, the clinical site investigators will record adverse events and serious adverse events as described previously (Sections 10.2.1, 10.2.2) on the appropriate AE/SAE eCRF

Once recorded, an AE/SAE will be followed until it resolves with or without sequelae, or until the end of study participation, or until 48 hours after the participant prematurely withdraws or is withdrawn from the study, whichever occurs first.

10.5 Pregnancy Reporting

A pregnancy will not be reported as an AE and is not an exclusionary condition for this surveillance study

10.6 Review of Safety Information

10.6.1 Medical Monitor Review

The DAIT/NIAID Medical Monitor will receive monthly reports from the Statistical and Clinical Coordinating Center (SACCC) compiling new and accumulating information on AEs and SAEs recorded by the study site(s) on appropriate eCRFs.

The DAIT/NIAID Medical Monitor will also assess whether a study stopping rule has been met and will recommend either halting of the study for review of the safety information or study termination.

11. Statistical Considerations and Analytical Plan

11.1 Overview

A prospective longitudinal cohort of children and their families will allow us to estimate the incidence of SARS-CoV-2 infection and investigate the association of risks factors for infection while accounting for follow-up and censoring. This study will permit us to gain insights into the complex interaction of SARS-CoV-2 exposure, particularly within families, with participant sex, age, susceptibility, immunological profiles and clinical outcomes.

11.2 Analysis Plan

Population description

Baseline characteristics of 2000 index children and their families that include age, sex, household members, co-morbidities, proportion with evidence of SARS-CoV-2 infection at baseline, and follow-up will be described using standard statistical techniques such as proportions for categorical variables and means and standard deviations (SD), or medians and interquartile ranges as appropriate.

Primary outcome: The cumulative incidence of SARS-CoV-2 RNA detection in nasal samples among index participants and their household contacts over the study period

Time to event analyses will be conducted among participants that are SARS-CoV-2 serologically negative at entry. We will use Kaplan-Meier cumulative morbidity curves for the primary analysis. The primary endpoint will be calculated at the end of follow-up or fate defined as follows. Follow-up time will be the time from entry until the first of the following events:

- Tests positive for SARS-CoV-2 RNA in nasal samples
- Is lost to follow-up or withdraws from the study
- End of study (24 weeks)

Fate at the end of follow-up will be:

- 1 (positive): if the patient tests positive for SARS-CoV-2.
- 0 (censored): if the patient has no evidence of having had disease by the end of follow-up.

Attack rates
SARS-CoV-2 attack rate per person-week will be calculated. Attack rates within families will also be estimated.

Secondary outcome: time to the index participants and their household members with detectable SARS-CoV-2-specific antibodies in serum over the study period.

Cox regression on seroconversion status at 24 weeks: Hazard ratios will be modeled using Cox Regression to compare demographic and clinical factors to the time to detectable SARS-CoV-2-specific antibodies in serum.

11.3 Sample Size Calculations

Sample size considerations were based on the margin of error or precision. We plan to enroll and study 2000 index children representing 2000 family units. Power estimates were based on precision represented with width of the 95% confidence interval and using the Wilson interval (Software Stata version 16). Below are estimates for varying observed incidence of SARS-CoV-2 infection among these 2000 family units:

3%, the 95% confidence interval for the true incidence as 2.3% -- 3.84%;
5%, the 95% confidence interval for the true incidence as 4.1% -- 6.0%;
10%, the 95% confidence interval will be as 8.7% -- 11.4%
and 20% this confidence interval will be 18.3% - 21.8%.

12. Identification and Access to Source Data

12.1. Source Data
A source document is a document in which data are collected for the first time. In HEROS, the source documents are the electronic case report forms (eCRFs) completed by the participants in an online electronic data capture system hosted by Vanderbilt. Throughout the study, Vanderbilt will transfer deidentified HEROS data to the SACCC where deidentified historic data imported from the index participant's parent study will be merged with the HEROS data and laboratory results and stored.

12.2. Access to Source Data
The site investigators and site staff are bound to maintain the strict confidentiality of medical and research information that may be linked to identified individuals.

12.3 Genomic Data Sharing Policy
DNA from participants in the HEROS study will be stored for analysis that will be limited to studies of SARS-CoV-2 infection. The NIH Genomic Data Sharing (GDS) policy requires deidentified genomic data from a NIH-funded study to be shared via dbGaP. However, GDS provides an exception to allow for controlled access to the data. The protocol chair for HEROs will submit a request for this exception which allows for deposition of summary (high level general) data with a 'controlled access guard' so that a future investigator would need to ask NIAID for permission to access the COVID-19 collected summary data and will be required to indicate that data analysis will be restricted to COVID-19 research.

13. Quality Assurance and Quality Control
The site principal investigator is required to keep accurate records to ensure that the conduct of the study is fully documented. The NIAID Division of Allergy, Immunology, and Transplantation (DAIT) is responsible for regular inspection of the conduct of the trial, for verifying adherence to the protocol, and for confirming the completeness, consistency,

and accuracy of all documented data. On a frequency determined by DAIT/NIAID, a clinical monitor from the SACCC will conduct a review of the conduct of the study by remote data review. Site study staff and participants will complete electronic case report forms and questionnaires online via a web-based electronic data capture system and data will be stored remotely at a central database. Data quality will be ensured through the electronic data capture system's continuous monitoring of data and real-time detection and correction of errors. All elements of data entry (e.g., time, date, verbatim text, and the name of the person performing the data entry) will be recorded in an electronic audit trail to allow all changes in the database to be monitored and maintained. In addition, SACCC data managers and statisticians will monitor data completeness and other elements of data quality throughout the trial and provide periodic reports on data quality.

14. Protocol Deviations

Since this is a Public Healthy Surveillance study and not human subject research, we will not be collecting protocol deviations. Missed samples and incomplete questionnaires are considered missing data.

15. Ethical Considerations

15.1. Informed Consent Process

The proposed prospective observational study fits the Public Health Surveillance exception at 45CFR46.102(l)(2). The exception allows for no IRB involvement since the study would not be considered human subject research and therefore not subject to the Common Rule. The informed consent is an information sheet about the study. The primary caregiver of the participant will read the information sheets and any questions will be addressed to the study investigators. If the caregiver wants to continue with the surveillance study and each member of the household that will take part in the study has reviewed and agrees with the requirements for participation in the information sheet, the caregiver will check "yes" and continue into the study web portal.

15.2 Privacy and Confidentiality

A participant's privacy and confidentiality will be respected throughout the study. It is possible that the study team may be required by law to share the surveillance data, including individually identifiable information, to a public health authority other than the National Institute of Health. The Human Health Services protection of human subjects regulations do not prevent investigators or institutions from fulfilling this requirement. The participants are informed that the results from the study will be confidential to the extent permitted by law.

16. Publication Policy

A publication policy of study results will be developed by the study investigators and the data coordinating centers prior to the completion of the study.