

**Respiratory Virus Transmission Network – National
Protocol, Version 1.0**



[Participant-friendly project name]

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Table of Contents

1	Study objectives.....	1
2	Definitions of common terms.....	1
3	Study design.....	1
4	Selection of study subjects.....	2
4.1	Inclusion criteria.....	2
4.1.1	Index cases.....	2
4.1.2	Household contacts.....	2
4.1.3	Household units.....	3
4.2	Exclusion criteria.....	3
4.2.1	Index cases.....	3
4.2.2	Household contacts.....	3
4.2.3	Households.....	3
5	Study procedures.....	4
5.1	Period of study enrollment.....	4
5.2	Recruitment: potential participant identification and screening.....	4
5.2.1	Index cases.....	4
5.2.2	Household contacts.....	4
5.2.3	Point of Contact (POC).....	4
5.3	Screening, consent, and enrollment using the study website.....	5
5.3.1	Screening.....	5
5.3.2	Informed consent and enrollment.....	5
5.3.3	Data retention.....	5
5.4	Study contact.....	5
5.5	Biospecimen collection.....	6
5.5.1	Daily collection of COVID-19 test samples.....	6
5.5.2	Blood Sample collection.....	6
6	Data collection.....	6
6.1	Screening questions.....	6
6.2	Enrollment questions.....	7
6.3	Daily diary.....	7
6.4	10-day questions and closeout questions.....	7
6.5	Vaccination.....	7

7	Participant compensation	7
8	Laboratory methods	8
8.1	Detection of novel coronaviruses and influenza viruses	8
8.1.1	For screening index cases	8
8.1.2	For detecting and characterizing respiratory virus during follow-up	8
8.1.3	For detecting respiratory virus antibodies using blood drop collection in follow-up.....	8
8.2	Specimen storage, transport, and shipping.....	8
8.3	Additional testing.....	9
9	Quality assurance.....	9
9.1	Quality of screening, enrollment.....	9
9.2	Quality of self-collected specimens and laboratory analyses.....	9
10	Data management.....	9
10.1	Data sharing and use	9
11	Regulatory and ethical considerations.....	10
11.1	Protection of human subjects	10
11.2	Participant confidentiality	10
11.3	Informed consent of index and household contacts	11
11.4	Risk and benefits to participants.....	11
11.4.1	Risks.....	11
11.4.2	Benefits.....	11
11.5	Return of results.....	11

1 Study objectives

Transmission of respiratory viruses in the household plays a large role in the spread of respiratory viruses in the community. Studying patterns of transmission within households, how these patterns are affected by duration and type of contact, available vaccines or treatments, and other factors, is important for making recommendations to prevent respiratory virus transmission during pandemics. This protocol and associated objectives will allow the timely study of household transmission of SARS-CoV-2 virus.

The primary objectives of this study are to:

- a. Estimate attack rates of SARS-CoV-2 virus among household contacts using a national framework to identify and recruit index cases and their household contacts.
- b. Estimate attack rates of SARS-CoV-2 virus among household contacts of vaccinated and unvaccinated index cases to estimate the impact of COVID-19 vaccine on transmission.
- c. Estimate attack rates of SARS-CoV-2 virus among vaccinated and unvaccinated household contacts to estimate the impact of SARS-CoV-2 virus vaccination on the risk of infection.
- d. Identify individual-level and household-level factors associated with increased or decreased risk of SARS-CoV-2 virus and transmission in households.
- e. Provide surveillance of SARS-CoV-2 virus variants on vaccine breakthroughs among vaccinated index cases and surveillance on variants among unvaccinated index cases.

2 Definitions of common terms

Several terms are used commonly throughout the study protocol, and below are their definitions.

Household: a shared living space between ≥ 2 people, excluding correctional facilities, long-term care facilities, boarding schools, hostels, dormitories, or other similar institutionalized/congregate settings.

Acute respiratory illness: fever, cough, sore throat, shortness of breath, fatigue, muscle or body aches, headache, new loss/change of taste/smell, or congestion/runny nose of ≤ 5 days' duration.

Asymptomatic infection: evidence of laboratory-confirmed SARS-CoV-2 virus without the presence of symptoms on the day of testing.

Index case: the first person with laboratory-confirmed SARS-CoV-2 virus identified in the household.

Household contact: any person who routinely sleeps (slept in the household about half the nights in the last month) in the same household as the index case and slept in the household for ≥ 1 night in the time from 1 day prior to illness onset or positive test date in the index case.

Secondary attack rate: The secondary attack rate is the proportion of household contacts who were not ill/infected at the time of illness onset or laboratory confirmed SARS-CoV-2 virus in the index case.

3 Study design

The study objectives will be met through observation of a cohort of household contacts who are exposed to a household contact with laboratory-confirmed SARS-CoV-2 virus. The study will identify an individual with acute SARS-CoV-2 virus and recruit and attempt to enroll both the index case and their household

contacts who meet eligibility criteria. Once the index case and his/her household have been enrolled, study data collection will begin. Data and biospecimen collection will include enrollment questions; a daily diary during the 10-day collection period regarding symptoms and household interactions from all participating individuals in the household; questions completed at 10 days following sample collection; final questions completed 4-6 weeks after study initiation (and associated with final sample collection); 10 daily respiratory specimens collected from each participating individual in the household; and collection of a blood specimen (from blood collected via a Tasso device) at study initiation and 4–6 weeks after enrollment.

Households will be recruited into this study from individuals in the U.S. who utilize national laboratories providing SARS-CoV-2 virus testing to the public. Both symptomatic and asymptomatic potential participants will have testing completed at a national laboratory testing location or from a mailed testing kit. National laboratories were selected for their ability to offer a broad geographic and demographic testing base, testing offered to individuals from the public for multiple reasons (e.g. symptoms, exposure, other reason), rapid turn-around time from test to results, and testing available to the public for SARS-CoV-2.

4 Selection of study subjects

4.1 Inclusion criteria

4.1.1 Index cases

An **index case** is eligible to be included in the study if s/he:

- Has laboratory-confirmed SARS-CoV-2 virus by either rapid diagnostic assay or RT-PCR.
- At the time of testing, is in the age range approved by FDA to receive the COVID-19 vaccine (age 5 and older as of November 2021); AND
- Has not been hospitalized since the date of illness onset; AND
- Has acute respiratory illness with onset no more than 5 days prior (Days 0-6) to the testing date or reports being asymptomatic; AND
- Indicates they routinely live with ≥ 1 household contact; AND
- Lives, and has plans to live, in his/her household for the 10-day follow-up period.

4.1.2 Household contacts

A **household contact** is eligible to be included in the study if s/he:

- Routinely sleeps in the same household as the index case; AND
- Slept in the household for ≥ 1 night during the period from the day before index case's illness onset date (or the day before the index case was tested, in the instance of an asymptomatic index case) through the current date; AND
- Expects to or has plans to sleep in the household for some part of the 10-day follow-up period.

4.1.3 Household units

A **household** is considered for inclusion if:

- The index case is eligible and enrolled in the study and can be linked within the same household to ≥ 1 eligible and enrolled household contact; AND
- There is ≥ 1 enrolled household contact who was not ill on the day of illness onset of symptoms in the index case (or the date the index case was tested, in the instance of an asymptomatic index case).

4.2 Exclusion criteria

4.2.1 Index cases

An **index case** will be excluded from the study if s/he:

- Does not live in a household (e.g. lives in a correctional facility, skilled nursing facility, long-term care facility, boarding school, hostel, or in a dormitory); OR
- Indicates that at least one other person in the household had an acute respiratory illness in the 7 days before or that began the same day as the index case's symptom onset; OR
- Indicates that at least one other person in the household tested positive in the 7 days before or on the same day as the index case; OR
- Is less than the age range approved by FDA to receive the COVID-19 vaccine (age 5 and older as of November 2021); OR
- Indicates that s/he is only partially vaccinated with the COVID-19 vaccine (e.g. has received only 1 dose of a 2-dose COVID-19 vaccine series); OR
- Lives in a household where package shipments cannot be delivered (e.g., contact is via post office (PO) box only).

4.2.2 Household contacts

Household contacts must be of an appropriate age for authorized use of SARS-CoV-2 sample collection devices used (currently ≥ 2 years) for collection.

4.2.3 Households

A **household** will be excluded from the study if:

- Seven or more days have elapsed between illness onset in the index case and the first day of specimen collection. Data and specimen collection must begin 0-6 days after the index case's illness onset, or the date the index case was tested if asymptomatic; OR
- More than 33% of household contacts do not intend to enroll. (For example, in a two-person household, both persons must participate or else the household is excluded from eligibility. In a 3-person household, two or more household contacts must participate. In households with 4-5 people, three or more must participate; in households with six participants, four people must

participate; in households with seven people, five or must participate, and in households with eight people, five or more people must participate.)

5 Study procedures

5.1 *Period of study enrollment*

Enrollment will begin as soon as IRB review and approval have been completed. Enrollment will continue for approximately 9 months and/or until in excess of the target completion of at least 450-500 index cases and their eligible household contacts (approximately 1,000-1,100 participants completing study activities).

5.2 *Recruitment: potential participant identification and screening*

Recruitment will focus on a national distribution of individuals with a positive SARS-CoV-2 virus result. If needed, recruitment may be adjusted to focus on specific geographic locations.

5.2.1 Index cases

Index cases are individuals who test positive for SARS-CoV-2 virus at a national laboratory and who use the national laboratory's electronic personal test reporting portal to obtain their results. When a potential participant (index case) logs into their personal test reporting account to see their test results within 0-4 days of their test date, they will receive a recruitment message in the test result summary screen inviting them to potentially participate in the study if found eligible. The SARS-CoV-2 virus test result(s) must be available to the individual in their electronic personal test reporting account in order for them to receive the study recruitment message and the link to the study website. These individuals will volunteer to begin the study screening, consent (or parental permission for all children and child agreement for age 7 to <18) and enrollment process by linking to the study website (hosted by Westat). Index cases also may serve as the point of contact (POC) for the household (as described in 5.2.3 below), though this role is not required of the index case.

5.2.2 Household contacts

Household contacts will be identified as potential participants in the study only if index cases are found to be eligible during the study screening process and the index case consents or assents (in case of children) to the study. Potential household contact(s) will be provided more information about the study and recruited to the study by the index case (or responsible parent or guardian for children). The household contact must link to the study website to complete the study informed consent/assent process before being considered enrolled in the study. A household contact may serve in the role of POC for the household (as described in 5.2.3 below).

5.2.3 Point of Contact (POC)

Either an adult the index case or an adult household contact may serve in the role of POC for the household if this person is eligible and has consented to study participation. The POC also may serve as a proxy in providing information if authorized by a consenting adult, assenting youth household participant or a consenting parent or guardian for their legal minor (under age 7). The POC will serve as the primary person for study-related communications in the household. The POC will also be responsible for scheduling follow-up activities for household contacts who will not complete information for themselves on the website (e.g., child under age 7 or other participant authorizing the POC to serve as a proxy).

5.3 Screening, consent, and enrollment using the study website

The study website will use plain language that explains the purpose of the study and describes the study activities. The study website page will describe the background and purpose of the study and will provide information about the compensation involved in their participation. The website will provide Frequently Asked Questions and will provide study contact information (email and toll-free number) for further questions. All participant materials and communications will be provided in English and Spanish and will be Section 508 compliant.

5.3.1 Screening

After linking to the study website and entering the study page, potential index case participants will be presented with screening questions to determine the index case's study eligibility according to Westat IRB approved procedures. Screener questions are described in Section 6.1.

If the index case meets eligibility criteria and the index case (or parent/guardian) indicates that the household contacts and household are potentially eligible per inclusion and exclusion criteria listed above, then the primary household POC will be identified if needed.

5.3.2 Informed consent and enrollment

If the potential index case and their household is found to be eligible for participation in the screening questions, they will be asked to complete an electronic informed consent process and provide an electronic signature on the consent (or assent) document that will be collected via the study website. The consent process will include a review of study requirements with the index case and each eligible household contact (or POC) and will obtain and document consent and child agreement as applicable. The consent document includes language for attestation or verification of COVID-19 vaccination and archiving residual research specimens at CDC or a designated laboratory (see Informed Consent document). The index case and all eligible household contacts must complete the consent process within a period of one calendar day in order to enroll in the study.

5.3.3 Data retention

Westat will maintain all data provided by potential and enrolled participants during the screening and enrollment process in a secure and confidential manner. The screening questions will collect information on potentially eligible participants and whether they meet inclusion/exclusion criteria according to information known at the time of enrollment. We will record data entered from all potential participants who begin the screening and enrollment process so that de-identified data can be analyzed, as possible, for participation status by age, gender, geographic location, vaccination history and other demographic factors.

5.4 Study contact

Westat staff will schedule initial electronic contact with both index cases and household contacts (or their POCs) following consent. They will receive a study welcome message explaining that the study sample collection supplies have been shipped to the household address and that they will need to collect samples from all household participants in the study for 10 days. Westat will provide study participants with study contact information and remind them that we will contact them daily (by email and/or text) and that they are expected to complete information on the study website on a daily basis. Westat also will provide them with study contact information in case they need assistance in any aspect of completing the study tasks.

Westat will package study sample collection supplies into kits and ship them to enrolled households by overnight express delivery service to the households. The kits will contain sufficient quantities for all

samples to be collected (e.g., COVID-19 test samples and blood samples) from all household participants. Instructions for specimen collection, storage and shipment also will be included.

If any participant is delinquent in daily completion of their sample collection and daily diary, Westat will conduct additional contact with the participant, including emails, texts (opt-out) and phone calls to the individual participant or his/her POC. Additionally, 4–6 weeks after sample collection begins in each household, Westat will schedule one final contact for the self-collection of the blood and completion of closeout questions.

The study materials will also provide an explanation that each member of the household (including the index case) should seek medical care for any illness, as they would routinely receive if they were not enrolled in the study. This study is observational, it is not meant to replace appropriate medical care, and should not preclude outpatient medical visits, emergency room visits, hospitalization, or medical prescriptions. The laboratories involved in testing specimens from household contacts will be required to report positive laboratory testing results and specified demographic information to local public health authorities. Westat will work with national laboratories to obtain SARS-CoV-2 test results and provide them to all consented study participants in a timely manner.

5.5 *Biospecimen collection*

5.5.1 Daily collection of COVID-19 test samples

Each enrolled participant (index cases and household contacts) will be instructed to collect COVID-19 test samples (by a saliva sample or anterior nasal swabs) on a daily basis for 10 days. The sample will be collected regardless of whether the individual has signs and symptoms of SARS-CoV-2 virus infection. Participants can collect the COVID-19 test sample themselves or have another member of their household collect the swab for them; for example, parents/guardians or the household POC may collect nasal swabs for children.

5.5.2 Blood Sample collection

Each enrolled participant (index cases and household contacts) will be instructed to use a Tasso device to collect small drops of blood from his/her arm into a small tube. Blood will be collected regardless of whether the individual has signs and symptoms of SARS-CoV-2 virus infection. Participants can collect the blood drops themselves or have another member of the household assist in collecting the blood for them; for example, parents/guardians or the household POC may assist in collecting blood drops for children. All participants will be instructed to collect blood drops both on the first day of biospecimen collection and at the conclusion of the study (ideally 4–6 weeks after the household is enrolled).

6 Data collection

All data collection from participants will take place using the study website. Questions include screener questions, enrollment questions, daily symptom diaries, and 10-day and closeout questions. These data collection instruments are described below.

6.1 *Screening questions*

Potential index case participants will be directed to the screening questions when they link to the study website. The questions will include at a minimum eligibility questions as well as the age, gender, race/ethnicity, and if they have any symptoms. All data completed, whether partial or complete, will be

recorded. These data will be assessed to compare index cases who were and were not enrolled in the study.

6.2 Enrollment questions

Each consenting index case and household contact, or his/her parent/guardian, will be administered questions on participant demographics, high-risk conditions, prior and current symptoms, prior and current SARS-CoV-2 vaccination status, interactions with other participants and people outside the home, and other social or medical history, such as other vaccination history (e.g., influenza virus vaccination status). Patterns of interaction with other household participants will be assessed. Questions will include duration as well as type of interaction. Participants may also be asked about prior and current use of COVID-19 or influenza antivirals or other medication pertinent to treatment of respiratory viruses.

The household POC will be asked about household characteristics, including but not limited to, age and gender of enrolled and non-enrolled household contacts as well as household exposures, household income, and highest educational attainment.

6.3 Daily diary

Each consenting participant (index cases and household contacts; or the household POC/parent/guardian on behalf of children) will complete daily questions regarding presence or absence of specific symptoms whether the participant slept in the household, collected a COVID-19 test sample for the study, used antivirals (if applicable), had a related medical encounter, missed school or work, left the home and interacted with people outside their household, and how they interacted with other household contacts.

6.4 10-day questions and closeout questions

At the conclusion of the 10-day sample collection period and again at study closeout 4-6 weeks after enrollment, the index case and household contacts will be asked to complete questions including medical care sought, clinical respiratory virus testing that occurred and any changes to the household characteristics and exposures.

6.5 Vaccination

All consenting participants will be asked about COVID-19 vaccination and current and prior season influenza vaccination. These questions will be asked of participants in different ways in both the screening and enrollment questions, as appropriate. The study will gather data (for each dose, if applicable) about date of vaccination, location of vaccination, and manufacturer or type of vaccination in order to determine vaccination status. When asking about date of vaccination, the study will request for an exact or best-estimated date, whether the vaccine was given 14 or more days before illness onset, or both. For COVID-19 vaccine, participants also will be asked to attest to their vaccination status and associated details, and then asked to find, take a picture and upload an image of their vaccine record/card if possible during the 4-6 week study period.

7 Participant compensation

Each index case and/or household contact will be compensated. An electronic form of compensation will be provided based on completion level following the conclusion of the initial 10-day collection period and again at the end of the study. To acknowledge each participant for their time on this study, we will provide reimbursement for a maximum of \$100 per person, up to \$200 per household with two

participants, \$300 for three participants, and so on, up to a maximum of \$800 for eight participants. Study participants will be reimbursed according to the following standards of completion:

Criteria	Amount
Participant completes 7 days of data and biospecimen collection including enrollment questions, 7 daily diaries, a small amount of blood, and 7 daily anterior nasal swabs or saliva samples for COVID-19 testing at any point during the consecutive 10 day collection period	\$50
Participant completes 3 more days of data and biospecimen collection after the first 7 days of study activities for a total of 10 days of study activities	\$25
Participant completes closeout questions and collects a small amount of blood	\$25

8 Laboratory methods

8.1 *Detection of novel coronaviruses and influenza viruses*

8.1.1 For screening index cases

Index cases will be identified among people with SARS-CoV-2 virus rapid diagnostic assay or RT-PCR positive tests and using the national laboratories' electronic personal test reporting portals. If possible, Westat will ask national laboratories that specimens used for initial SARS-CoV-2 virus of the index case be retained by the clinical, public health, or research laboratory for further testing. Specimens will only be kept from index cases who provide consent to be included in the study.

8.1.2 For detecting and characterizing respiratory virus during follow-up

Swabs collected during follow-up will be tested for SARS-CoV-2 virus infection using RT-PCR at a research or clinical laboratory. Specimens will be considered positive based on current laboratory standards for RT-PCR interpretation. In addition, the first positive RT-PCR test sample for COVID-19 from the index case as well as each household participant will be sequenced to determine SARS-CoV-2 variant type.

8.1.3 For detecting respiratory virus antibodies using blood drop collection in follow-up

Blood specimens collected by placing blood drops from the participant's arm into a Tasso device at enrollment and closeout will be tested for antibodies against SARS-CoV-2 virus at a research or clinical laboratory.

8.2 *Specimen storage, transport, and shipping*

COVID-19 test samples and blood drops collected by participants will be stored at the designated testing laboratories according to the instructions from the national laboratories and the study. Specific testing requirements will be defined for the testing laboratories, but include up to four aliquots of each sample.

Specimen aliquots and residual blood drops may be sent to CDC or other laboratories for further laboratory tests in the future. The number of aliquots to be sent and the shipping process will be determined in consultation with CDC and subject matter experts.

8.3 Additional testing

Additional testing may be conducted on the collected COVID-19 test samples or blood drops to address the study objectives, including, but not limited to, viral sequencing, quantitative PCR, or antibody titers.

9 Quality assurance

9.1 Quality of screening, enrollment

Westat will establish a set of quality assurance procedures to ensure reliability of screening, enrollment, and follow-up practices, as well as data collection. Logic and edit checks will be imbedded in all web-based questions, allowing participant correction and quality control of the data as it is collected. Additionally, Westat will develop and apply routine quality assurance assessments for all data management and reporting, allowing identification of study-wide inconsistencies and unexpected or unsatisfactory results so that adjustments can be made as needed to study procedures.

9.2 Quality of self-collected specimens and laboratory analyses

Westat will request the laboratories assess the quality of self-collected specimens received at the laboratory prior to analysis and report those metrics. In addition, Westat will receive the quality assurance procedures, including proficiency testing, from the laboratories involved in testing study samples to ensure reliability of analyses of study specimens.

10 Data management

Data will be collected by the study into a central database and stored according to FISMA-specified data security requirements. No research subject will be identified by name, picture, or any other personally identifying manner if information from this study is presented publicly or published in a medical journal.

A Data Use Agreement will be established with the national laboratories providing approved COVID-19 PCR testing so that participants testing positive for COVID-19 are reported in a timely manner to local public health authorities as required by state and local laws. Information regarding test positive participants that is reported to local authorities include items such as name, address, demographic information, and questions on symptoms. Westat will ensure that all data transferred to national laboratories for public health reporting is limited to required information.

Westat will conduct partial de-identification of data and limited datasets will be transferred to CDC using research identification numbers. Data privacy will be maintained according to Westat IRB protocols.

To ensure uniform and consistent data collection Westat will create and administer a central database that includes agreed-upon data elements to be collected for the study.

10.1 Data sharing and use

Data and associated documentation from this study will be available only under a data use agreement that provides for: (1) a commitment to using the data only for public health reporting and research purposes; (2) a commitment that personal identification will be limited to strict protocols instituted for public health reporting; (3) a commitment to securing the data using appropriate information technology; and (3) commitments for destruction, return, or retention of data as stipulated by Federal regulations and

the IRB. Westat will comply with federal, state, and institutional requirements regarding time horizons for retention and/or destruction of research records.

Westat also will ensure that Federal data sharing guidelines are followed for the release of aggregate, de-identified data for purposes related to public health research and policy use while maintaining all confidentiality and security requirements.

11 Regulatory and ethical considerations

11.1 Protection of human subjects

Westat will serve as the single IRB of Record for this study and will oversee protections of human subjects research (45 C.F.R. § 46.114). The Westat IRB will enter into an IRB Authorization Agreement (IAA) that will include a communication plan with each entity (e.g., national laboratory subcontractors) that is contributing data to the study. IAAs and other documentation necessary in order to document compliance with the single IRB policy are maintained by Westat's IRB. Westat's IRB will use several mechanisms to communicate with the national laboratory subcontractors, including email, phone calls and direct person-to-person communications as needed.

The protocol, data collection instruments, and other documents associated with the protocol shall be approved by Westat's IRB in compliance with all applicable laws, including 45 CFR 46. Subsequently, the protocol and related documents must be re-reviewed at least annually. Westat is responsible for preparation and submission of all documents and periodic reports required by the IRB.

11.2 Participant confidentiality

All participants in the dataset will be assigned a linkable participant identification code (e.g., PID or study identification code). Westat will be responsible for assigning and maintaining the link between the participant's identifying information and study ID. Documents maintaining this link will never be transferred to the CDC or study investigators. Personal identifiers (participant's name, address, phone number and email address) will exist at Westat as part of the contact information to receive study supplies and follow-up reminders but will be replaced by a random generated code (linkable PID), which will allow linkage of data without CDC or the study investigators having any access to these personal identifiers. All study data and administrative documentation will be identified by the study identification code only, to maintain participant confidentiality.

Limited datasets will be created for the study; the study will comply with each institution's human subjects, privacy, and information security laws, if any. All study data files will be stored separately from any study records that contain names or other personal identifiers. All local databases must be secured with password protected access systems.

Listings that link study (and personal) IDs to other identifying information must be stored in a separate, locked file (or encrypted) in an area with limited access (or maintained in a directory separate from any study specific data files/sets) at each participating facility. No links between personal identifiers and study identification will be available outside of the secure study management system.

Westat will develop a Data Management Plan that details how Westat will protect any identifiers from improper use or disclosure, how Westat will destroy the identifiers after study completion, and how the protected health information will not be reused for other research.

11.3 Informed consent of index and household contacts

Electronic informed consent will be obtained from all index and household contact participants (or parent, legal guardian, or person with power of attorney for participants who cannot consent for themselves). Assent of participants under the age of majority must also be obtained if he or she is able to understand the nature, significance, and risks with the study.

The informed consent will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. Participants will be given an opportunity to print a copy of the informed consent/assent document and shipped a copy of the consent/assent form with study supplies.

Pursuant to guidance from OHRP, adolescent participants enrolled into studies with parental permission while a minor (as defined by the jurisdiction in which they live) must consent individually to remain on study when they reach the age of majority in the jurisdiction.

11.4 Risk and benefits to participants

11.4.1 Risks

The primary risks to participants include:

- Potential loss of confidentiality
- Re-identifiability and group harms within households
- Anxiety related to having a COVID-19 test
- Possibility of a false positive or false negative test
- Having to isolate due to a positive test result or exposure to an enrolled household contact who has a positive test result
- Physical discomfort related to collecting the COVID-19 test sample (e.g., nasal sample and nosebleed)
- Physical discomfort related to the arm stick for collecting the blood drops
- Feeling faint collecting blood drops as with all blood sampling procedure
- Bruising may occur around the sample collection site

The study team will take steps to keep data secure and to minimize the risks of breach of confidentiality. Because access to identifiable data is controlled, this helps to minimize the risks of re-identifiability and group harms.

11.4.2 Benefits

Benefits may accrue to household members who have a PCR positive test result using a standard, approved COVID-19 test collection device, and, upon being provided with their results, take health precautions or seek medical help for themselves as needed or avoid contact with others in their household or community to protect them from COVID-19 transmission.

There also may be future indirect benefits to the U.S. population if sufficient evidence is found to determine the impact of household transmission of and illness from SARS-CoV-2 virus among vaccinated and unvaccinated individuals.

11.5 Return of results

Study results for the index case will be part of the medical record at the national laboratories. The laboratories involved in testing specimens from household contacts will be required to report positive

laboratory testing results and specified demographic information to the local public health department. Westat will work with national laboratories to obtain SARS-CoV-2 test results and provide them to all consented study participants in a timely manner.