

RVTN – Sentinel
Respiratory Virus Transmission Network

Protocol

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1 Summary of Protocol Changes

Protocol Version: 1
Protocol Date: July 19, 2021
Summary of changes: N/A

Protocol Version: 2
Protocol Date: November 19, 2021
Summary of Changes:

- Added FDA as Sponsor
- Updated target enrollment from 900 to 1050 households
- Added COVID-like symptoms as qualifying symptoms for identification of index cases and for characterization of clinical manifestations of infection, added wheezing, chest tightness/chest pain, abdominal pain, diarrhea, vomiting
- Addition of Columbia University as an enrollment site
- Clarification of optional follow-up encounters/visits at 12 weeks after enrollment to collect information on persistence of symptoms
- Updated narrative to clarify expansion of recommendations for vaccination of young children

2 Protocol Summary

The US Advisory Committee on Immunization Practices (ACIP) recommends annual influenza vaccination for those 6 months old or older and SARS-CoV-2 vaccination for subjects age 5 years or older. While prior influenza vaccine effectiveness (VE) studies have evaluated prevention of disease in different healthcare settings, the impact of these vaccines in preventing transmission of infection remains unknown. Moreover, the new SARS-CoV-2 vaccines have been approved for use based on demonstrated efficacy against symptomatic disease but their effectiveness against transmission of infection is unclear. Understanding whether recommended vaccines are effective in preventing infection among exposed individuals or reducing the chance of passing the infections to others in close contact is of great public health interest, but this is currently unknown.

Households, where individuals share common areas and usually interact in close proximity provide an optimal venue to study viral transmission. Case-ascertained designs, where household members are enrolled and observed after a first household member is known to be infected, provides efficient opportunities to assess the impact of vaccination on viral transmission. To maximize efficiency and generalizability of findings, multi-center studies are warranted.

The goal of this public health surveillance study is to conduct a multi-center evaluation of the effectiveness of influenza and SARS-CoV-2 vaccines for preventing transmission of infections in households.

3 Background

Households provide excellent environments for influenza, SARS-CoV-2, and other respiratory viruses to transmit, because close contacts among household members are common and the household environment is generally considered 'safe' by household members. Indeed, much of our understanding of influenza transmission, its patterns and timing, comes from household-based studies because the household provides a strategic setting to track influenza infections among close contacts of cases. Early household transmission studies led by CDC, the Marshfield Research Clinic Institute and VUMC investigators have provided important data on the transmission of SARS-CoV-2 within US households.^{1,2} Although vaccines are recommended for prevention of influenza and SARS-CoV-2 related disease, the effectiveness of vaccines to prevent transmission is unclear. While our Nashville, TN site, together with the Marshfield Research Clinic Institute (Marshfield, WI) have been conducting seasonal surveillance as part of the FluTES and FluTES-C household transmission studies, enrollment of sufficient number of households requires surveillance through multiple seasons. Moreover, viral activity is highly variable as demonstrated by the recent spread of the Delta variant, and findings from two sites may not be directly applicable to other areas. Rapid assessments of patterns of infections and viral transmission, how these patterns are affected by available vaccines or treatments, virus types, duration and type of contacts, and other factors, are necessary for public health and vaccination policy recommendations. Therefore, CDC and FDA are sponsoring a new network of US sites to conduct a multi-center evaluation of the effectiveness of influenza and SARS-CoV-2 vaccines for preventing transmission of infections in households. VUMC will serve as a site and the Data and Laboratory Coordinating Center. Sites will implement a standardized intensive case-ascertained design with daily collection of data and specimens to determine the effectiveness of vaccination on reducing transmission of viral infections within households. Because of the pandemic and as required by CDC and FDA, findings from these activities will be shared with these public health agencies in a timely manner, to inform public health decision making and vaccination policies

4 Study objectives

The objectives of this study are to:

- a. Estimate attack rates of SARS-CoV-2 and influenza virus infection among household contacts
- b. Estimate attack rates of SARS-CoV-2 and influenza virus infection among household contacts of vaccinated and unvaccinated index cases to estimate the impact of vaccination on transmission
- c. Estimate attack rates of SARS-CoV-2 and influenza virus infection among vaccinated and unvaccinated household contacts to estimate the impact of vaccination on the risk of infection and disease manifestations
- d. Identify individual-level and household-level factors associated with increased or decreased risk of SARS-CoV-2 and influenza virus infection and transmission in households

5 Definitions of common terms

Household: ≥ 2 people who routinely sleep (slept in the household about half the nights in the last month) in a shared living space, regardless of their relationship to one another; excluding correctional facilities, long-term care facilities, boarding schools, hostels, dormitories, or other similar institutionalized/congregate settings

Index case: the first household member with laboratory-confirmed SARS-CoV-2 or influenza virus infection identified in a household during a defined period of time

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 has slept in the household for at least 1 night in the period since 1 day prior to illness onset or positive test date in the index case

Acute respiratory illness/COVID-like symptoms: fever/feverish, cough, sore throat, shortness of breath, fatigue, muscle or body aches, headache, new loss/change of taste/smell, or congestion/runny nose, wheezing, chest tightness/chest pain, abdominal pain, diarrhea, vomiting, of no more than 5 days duration

Asymptomatic infection: evidence of laboratory-confirmed SARS-CoV-2 or influenza virus infection without the presence of symptoms.

Secondary attack rate: the proportion of household contacts who were not ill/infected at the time of illness onset/infection in the SARS-CoV-2 or influenza index case who subsequently become infected

6 Study design

This will be a case-ascertained transmission study with active observation of a cohort of household members who are exposed to a household member with laboratory-confirmed SARS-CoV-2 or influenza virus infection (index case). Each study household will be eligible when the first individual with acute SARS-CoV-2 or influenza infection (index case) is identified. Once the index case and his/her household contacts have been identified and enrolled, they will be followed for 10 consecutive days to identify new virus infections among household members. Follow-up will include interviews/questionnaires on day 1, self-collection of an acute blood specimen on day 1 or 2, daily data collection from all participating household members (days 1–10), daily respiratory specimen self-collection from all participating household members (days 1–10), a series of remote video/telephone or in-person visits during the follow-up period, and optional collection of data and a blood specimen ~4–6 and ~12 weeks after enrollment.

7 Selection of study subjects

7.1 Inclusion criteria

7.1.1 Index cases

An index case is eligible for inclusion if s/he:

- has laboratory-confirmed SARS-CoV-2 or influenza virus infection by either rapid diagnostic assay or RT-PCR AND
- has acute respiratory illness/COVID-like symptoms* with onset no more than 5 days prior to presentation at the recruiting/testing clinic/site or reports being asymptomatic on the testing date AND
- lives, and has plans to live in his/her household for the follow-up period AND
- is not hospitalized and has not been hospitalized since the date of illness onset

*this does not include symptoms with known presumed cause e.g. transient general symptoms post vaccination

7.1.2 Household contacts

A household contact is eligible for inclusion if s/he:

- 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 at least 1 night in the period from 1 day prior to illness onset or positive test date in the index case through the current date AND
- lives and has plans to live in the household for the follow-up period

7.1.3 Households

A household is eligible for inclusion if:

- At least 1 eligible household member, other than the index case, enrolls in the study AND
- there is at least 1 eligible household member who was not ill on the day of illness onset in the index case (or the date the index case was tested, in the instance of an asymptomatic index case)

7.2 Exclusion criteria

7.2.1 Index cases

An eligible 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/COVID-like symptoms, or tested positive for SARS-CoV-2 or influenza in the 7 days before or on the date of the index case illness onset or testing date

7.2.2 Household contacts

There are no exclusion criteria for household members

7.2.3 Households

An eligible household will be excluded from the study if:

- seven (7) or more days have elapsed between illness onset in the index case and the enrollment encounter. The enrollment encounter must occur within 0-6 days after the index case's illness onset or the date the index case was tested if asymptomatic OR
- more than a third (33%) of household contacts do not intend to enroll (for example, in a 2-3 member household all household contacts must participate; in households with 4-6 members, only 1-2 contact may decline to participate to remain eligible; and in households with 7-9 members, only 2-3 contacts may decline to participate to remain eligible)

8 Study procedures

8.1 Period of study enrollment

Enrollment will begin as soon as IRB review and approvals have been completed. Enrollment will continue until either the site enrolls the target number of households or in consultation with CDC. The target enrollment number is up to 1,050 index cases and their households; however, the study may choose to modify the target number in consultation with CDC as long as funds are available.

8.2 Identification of index cases

Index cases will be identified through SARS-CoV-2 or influenza testing sites, outpatient medical clinics, such as primary healthcare clinics, urgent care clinics, walk-in clinics, emergency departments, or telephone hotlines used as patient triage. Other strategies to identify and recruit index cases may also be used, including leveraging connections with state, county, or local health departments, connections with occupational health clinics, or other entities providing SARS-CoV-2 or influenza testing. Advertising at testing centers, healthcare facilities and through social media for eligibility screening could be considered as well.

Patients who test positive for SARS-CoV-2 or influenza are the primary patients of interest for identification of index cases. A screening log should be kept that collects information on potentially eligible index cases and whether they

meet inclusion/exclusion criteria. This log should be collected in such a way that allows comparison of eligible subjects who were and were not enrolled in the study. The log may include de-identified information on age group, race/ethnicity, and COVID-19 and influenza vaccination status.

8.3 *Recruitment*

Once a potential index case has been identified as having an acute SARS-CoV-2 or influenza illness, study staff will communicate with the case (or case's parent/guardian, in the instance of a minor) and try to initiate the enrollment process as soon as possible. Study staff will explain the purpose and activities of the study, answer questions, obtain consent (below) and/or screen the potential index case for study eligibility according to approved local procedures. If the case meets eligibility criteria and the case (or parent/guardian) indicates that the household members and household are likely eligible, then a member of the household should be identified who will be the primary point of contact (household POC) for study-related communications and who will be responsible for scheduling follow-up activities. Primary and alternate points of communication with household members will be recorded to help coordinate study activities throughout follow-up.

Other members of the index case's household will be recruited into the study during the first interaction(s). At that time, study staff will explain the purpose and activities of the study, answer questions, obtain consent (below) and/or screen each household member for study eligibility. Recruitment activities should align with the local regulations and accepted procedures.

8.4 *Informed consent*

Study staff will review study requirements with the index case and each eligible household member and obtain and document consent, and assent for children as applicable. As part of this consent process, study staff will also request permission, which could be through verbal consent or a release of information form, to access medical records to obtain data related to medical history, medication use, and vaccination history for each participant.

8.5 *Scheduling follow-up study visits*

Study staff will coordinate with the household contact to schedule follow-up visits/encounters that can occur in-person, by remote video or over the phone during the 10-day follow-up period. The first follow-up visit/encounter(s) may also include a video/phone call and should be scheduled on the date the household is recruited (or soon thereafter) to deliver the study collection kit and to instruct the participants on study activities. All subsequent follow-up visits/encounters can be scheduled during recruitment or the first visit or during follow-up.

8.6 *Scheduled follow-up visits*

Index cases and household members will be followed from enrollment date to assess symptoms of acute respiratory illness/COVID-like symptoms, detect respiratory viruses in self-collected nasal swabs, and to assess risk factors for respiratory virus transmission and infection. The period of follow-up is 10 days starting with a first visit on enrollment date. The first visit should occur no later than 6 days after illness onset in the index case (or no later than 6 days after the index case was tested if the index case was asymptomatic). A study kit with supplies will be dropped off at or delivered to the residence of the index case and his/her household members at an agreed upon time, on enrollment date or soon thereafter.

Follow-up visits/encounters every ~3-4 days may occur during follow-up. These visits/encounters can be performed in person, through email, paper or electronic surveys via email or text messages, phone calls or other means of communications. Additionally, additional follow-up visits/encounters to collect data/sera for the detection of virus-specific antibodies may be scheduled ~4-6 after enrollment and ~12 weeks after enrollment to explore the influence of vaccination on the persistence of symptoms related to viral infections. Shipment of study materials from the households to the research sites may be considered in lieu of household visits. The duration of follow-up and intervals between household visits/encounters may be flexible to accommodate participant and site preferences, and intercurrent weekends and/or holidays.

Possible activities during follow-up interactions are listed below.

8.6.1 *First "visit"*

After household enrollment, the first visit/encounter will be scheduled with the household POC as soon as possible. The appropriate format will depend on the site regulations and preferences and could change during the course of the

project. The first visit/encounter should occur when all (or the majority) of potentially eligible household members and the index case are available and can be present, as applicable.

The following activities will occur during the first “visit”/encounter:

- 1) Further explain the activities of the study
- 2) Interview or collect information from the household POC, or other knowledgeable member of the household, to gain details about the household composition and household exposures
- 3) Interview or collect information from each enrolled household member, including the index case, to collect information on demographics, self-reported high-risk conditions, vaccination history, possible individual exposures, and prior and current symptoms
- 4) Interview or collect information from each enrolled household member, including the index case, about patterns of interaction with other enrolled and non-enrolled household members, including duration and type of interaction
- 5) Explain and demonstrate proper entries in the daily diaries
- 6) Explain proper self-collection/guardian-collection of nasal swabs and samples for serology, correct labelling of samples with pre-made labels/identification of labeled materials, and storage of samples. Households will have access to videos on self-swabbing and self-collection of samples for serologic testing.
- 7) If respiratory specimens are being collected, instruct all enrolled household members on self-collection/guardian-collection of nasal swabs, labeling of the samples, and storing the samples.
- 8) If specimens for serology are collected, instruct all household members on self-collection/guardian-collection of samples, labeling of the samples, and storing the samples.
- 9) If the visit occurs in-person, obtain a staff-collected nasal swab and/or sample for serology from each enrolled household member, including the index case as appropriate. Study staff could also help and/or supervise self-collection of specimens. If the visit occurs remotely, schedule follow-up visits to pick-up collected forms and/or samples from the household during the follow-up period as appropriate.

Study staff should also explain that each member of the household (including the index case) should seek medical care for any illness as they would have had they not be enrolled in the study. This study is observational and is not meant to replace appropriate medical care and should not preclude outpatient medical visits, hospitalization, or medical prescriptions. Study staff should not provide medical advice.

The date and time of the remaining follow-up visit(s) should be arranged at the first follow-up visit, if possible and if not arranged during recruitment. Study staff should also leave study contact information with the household POC in case there are questions or concerns between scheduled visits. Study staff should conduct visits/encounters according to the site-specific regulations and safety procedures.

8.6.2 Follow-up activities that occur between scheduled visits

Between scheduled visits each enrolled participant (index cases and household members) will be asked to complete a daily diary. The diaries should be filled in each day at approximately the same time of the day. In addition, each enrolled participant (index cases and household members) will self-collect nasal swabs on a daily basis. Participants can collect the nasal swabs themselves or have another member of their household collect the swab for them; for example, parents/guardians or the household POC may help collect nasal swabs from children. For consistency, participants will be encouraged to fill the diary information and self-collect their samples at the end of each day, during evenings hours if possible. If a participant forgets to fill/miss a diary, the participant can still complete the information at a later date indicating the appropriate date(s) for each diary.

8.6.3 Respiratory specimen collection

Each enrolled index case and household member will self-collect an anterior nasal swab on each day of the 10-day follow-up period. The swab will be self-collected regardless of whether the individual has acute respiratory illness/COVID-like signs or symptoms.

Depending on a site’s resources, preferences or recommended infection prevention and control practices, supplies for respiratory specimen collections can be provided to or collected from the household members in a variety of ways,

including but not limited to, delivered to the household via courier, delivered through the mail, provided at time of enrollment, collected from a location convenient for the participants, or delivered at the participants' household.

8.6.4 Scheduled "visits"/encounters

Additional visits/encounters will be scheduled at approximately ~3-4 day intervals during follow-up. The following activities can occur during these visits:

- 1) Assess completeness of daily diaries, interview or collect information from appropriate household members to obtain information on any missing or incomplete details on diary entries, and collect all diaries for data entry
- 2) Confirm the number of swabs collected from each participant during the follow-up period, thus far, and ensure that swabs are collected and labelled appropriately
- 3) Collect or help collect nasal swabs and/or samples for serologic testing (if the visit occurs in-person and a scheduled specimen has not been already collected)
- 4) Gather collected specimens for transport to the study laboratory. Visits to pick-up collected samples will require advanced coordination of appropriate times with the household members.
- 5) Review process of swab collection and diary entry if there are questions in the household.
- 6) Review the household composition to see if changes have occurred. If there have been changes, an interview should be conducted to indicate the new household composition

8.6.5 Final "visit"/encounter

A final visit should be scheduled approximately 10 days after the first visit. The following activities can occur during the final visit:

- 1) Review the household composition to see if changes have occurred. If there have been changes, an interview should be conducted to indicate the new household composition
- 2) Interview or collect information from each enrolled household member (including the index case) about medical care sought and influenza or coronavirus testing that occurred during follow-up
- 3) Assess symptoms in each enrolled participant (e.g., if a diary entry for the current day has not already been filled) and collect a nasal swab (e.g., if the visit occurs in-person and a specimen has not been already collected for that date)
- 4) Assess completeness of daily diaries, interview appropriate household members to obtain information on any missing or incomplete details on diary entries, and collect all diaries for data entry
- 5) Confirm the number of swabs collected from each participant during the follow-up period and ensure that swabs are labelled appropriately
- 6) Gather collected respiratory specimens for transport to the study laboratory. Visits to pick-up collected samples will require advanced coordination of appropriate times with the household.
- 7) Interview or collect information from each enrolled household member and the index case about patterns of interaction with other enrolled and non-enrolled household members (including the index case), including duration and type of interaction

8.6.6 Blood collection for serology

Blood collection for serology is an additional activity that would support understanding whether household members are susceptible to infection and support assessments of SARS-CoV-2 or influenza infection risk in household members. Participants will be asked to self-collect blood samples for serology at the beginning of follow-up (day 1 or 2) and in the convalescent phase (approximately ~4–6 weeks after the household is enrolled). This will be done through finger prick sampling, and collection in dried blood spot cards or a similar dried blood collection device.

Additional blood collections may be considered for certain participants e.g., vaccination failures from whom blood samples may be gathered through venipuncture. When these participants are identified, they will be invited for a venipuncture blood collection. The final blood collection volume (e.g., 10 mL for adults) for those optional collections may vary depending on participants age and preference. This optional collection should occur as soon as

possible and within 5 days following disease onset. Sites will determine the eligibility criteria and additional details for blood draws, in consultation with CDC and local regulations. If blood is collected from participants in-person during the acute phase of illness, for example through a household visit or participant visit to a site location, this collection will follow local clinical guidelines for patient contacts. Residual recent clinical blood specimens may be obtained by the research team, if available.

9 Data collection

9.1 *Screening log*

A screening log will be created to collect information on potentially eligible index cases. The log will include the age, sex, and available race/ethnicity and COVID-19 vaccination information status of the potential participant and whether they meet inclusion/exclusion criteria. This log should be collected in such a way that data analysis can be done to compare index cases who were and were not enrolled in the study. Furthermore, available aggregated summaries of tested participants at study sites, including age, race/ethnicity data when available, vaccination status, would be compiled throughout the duration of the study to characterize and monitor the representativeness of the enrolled participants.

9.2 *Enrollment questionnaire*

Each consenting household member and the index case, or his/her parent/guardian, will be interviewed or asked to provide information on participant demographics, recent exposures, presence of high-risk conditions, prior and current symptoms, COVID-19 vaccination, prior and current influenza vaccination status, household characteristics, and interactions with other enrolled and non-enrolled household members and people outside the home, and other social or medical history, such as other vaccination history, deemed appropriate by the sites. Interaction questions will include duration as well as type of interaction (e.g., physical or not). Participants may also be asked about prior and current use of COVID-19 or influenza antivirals or other medications or interventions pertinent to treatment of respiratory virus infections. The household POC will be also asked about household characteristics, including but not limited to household composition, socioeconomic information, age and sex details of enrolled and non-enrolled household members as well as household exposures.

9.3 *Daily diary*

Each consenting participant (index cases and household members; or the household POC/parent/guardian on behalf of children) will complete daily questionnaires regarding presence or absence of specific symptoms and whether the participant slept in the household, had a nasal swab collected, used antivirals or other medications or interventions (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 members. These diaries will characterize occurrences since the day of enrollment through the end of follow-up, approximately 10 days after enrollment. In addition, retrospective 'baseline' daily diaries will be collected at enrollment to characterize these data elements for all participants starting on the day prior to the index case disease onset/testing date through the date prior to enrollment.

9.4 *Final visit questionnaire*

This questionnaire may include re-assessing patterns of interactions with other enrolled and non-enrolled household members (including duration as well as type of interaction), medical care sought and clinical respiratory virus testing that occurred during follow-up, and any changes to the household characteristics and exposures. For optional additional follow-up encounters (~3-4 weeks and ~12 weeks after enrollment), assessments will include history of recent infections post enrollment, additional vaccination changes, healthcare utilization and persistence of signs/symptoms.

9.5 *Vaccination history and vaccination verification*

All enrolled participants will be asked about current and prior season influenza vaccination, COVID-19 vaccination, as well as other relevant vaccinations, using the screening and/or enrollment questionnaires as appropriate. Sites should gather data (for each dose, if applicable) about date or approximate date of vaccination, location of vaccination, and manufacturer or type of vaccination in order to determine vaccination status. When asking about date of vaccination, sites can ask for an exact or best estimated date, whether the vaccine was given 14 or more days before illness onset, or both. All sites will also attempt to determine location of vaccination to help with the

vaccination verification process. In addition to asking for vaccination status at enrollment, each site will query their health system's medical record system, the state immunization registry or equivalent resource, or other vaccine providers (e.g., primary care providers, retail stores, and pharmacies) to obtain current and past season influenza and/or SARS-CoV-2 vaccination data for all participants regardless of self-reported vaccination status. For SARS-CoV-2 vaccination verification, participants may be asked to provide image(s) of their vaccination record card(s). Past season influenza and SARS-CoV-2 vaccination data will include for as many records as are available in the electronic medical record and other aforementioned sources of vaccination data. A signed release of information form may be obtained from participating individuals to facilitate the retrieval of records from providers, non-traditional providers, vaccination registries or other sources.

10 Participant compensation

Household members may receive compensation for their participation in the study. This will be a single household compensation and not an individual level compensation. Final compensation may vary according to site preferences, but references are provided here. Households that completed the requested data and specimen collections (including self-collected samples for serology testing) may receive up to \$200 at the end of the ~10-day follow-up in the form of a gift card or check or an equivalent compensation approach depending on site preference. Households that were not able to collect samples for serology testing may receive up to \$150 at the end of the ~10-day follow-up. Households that participate in the subsequent household follow-up encounters with collection of data and self-collected specimens for serology testing (~4-6 weeks after enrollment) may receive up to an additional \$50 (per household), and \$25 with subsequent collection of data on persistent symptoms (~12 weeks after enrollment). Individual participants who provide blood samples through venipuncture (e.g., those known to be breakthrough cases) may receive a compensation of up to \$50. Sites may require personal information (i.e. social security number) as part of institutional tax reporting requirements.

10.1 Medical record review

Available medical records of enrolled index cases and household contacts may be accessed to verify or determine risk factors for complications of respiratory virus infections, vaccination status, antivirals and other relevant medications taken for an acute SARS-CoV-2 or influenza illness, and any medical visits that may have occurred during the follow-up period and up to 30 days after enrollment. To collect information on medical visits/encounters that occurred up to 30 days after enrollment, sites may access medical records and/or may contact the participants with a post-follow-up phone or electronic survey.

11 Laboratory methods

11.1 Detection and characterization of novel coronaviruses and influenza viruses

11.1.1 For screened index cases

Index cases will be identified among people presenting to clinics or testing sites. Study sites may request that specimens used for initial SARS-CoV-2 or influenza testing 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.

11.1.2 For detecting respiratory virus infection during follow-up

Swabs collected during follow-up will be tested for respiratory viruses such as SARS-CoV-2 or influenza virus infection using molecular methods such as TMA or RT-PCR. Specimens will be considered positive based on current guidance by CDC or FDA based on testing methods used. Specimens may need to be sent to CDC, or a CDC-designated laboratory, for additional testing.

11.1.3 For detecting respiratory virus infection using serology

Blood specimens collected at the initial study visit and/or during follow-up will be tested for antibodies against respiratory viruses such as SARS-CoV-2 or influenza virus.

11.1.4 For sequencing detected respiratory viruses

Detected viruses will be further characterized by genetic sequencing. This information will be used to monitor the evolution of circulating viral strains and variants (e.g., Alpha, Delta SARS-CoV-2 variants) during the duration of the project and explore potential differences in transmission patterns. Samples with positive detections will be selected according to criteria defined in consultation with CDC and the central and sequencing laboratories. Selected samples will be sent to the Loring Laboratory at University of Michigan for viral sequencing.

11.2 Proficiency testing for detection of respiratory viruses

Each laboratory conducting testing for the study will demonstrate proficiency to detect respiratory viruses such as SARS-CoV-2 or influenza viruses (or antibodies specific to these viruses). Sites laboratories can use proficiency testing from other study protocols that include detection of SARS-CoV-2 or influenza viruses, or antibodies, to demonstrate proficiency. If a laboratory has been deemed proficient by CDC or other accreditation agencies, because of repeated successful completion of proficiency panels in the recent past, then that will also suffice. Additional proficiency testing may be required if necessary.

11.3 Specimen storage, transport, and shipping

Nasal swab specimens collected at the initial screening or during follow-up should be placed in transport media and stored according to best-practices, which will be outlined by standard operating procedures written and distributed prior to beginning study enrollment. The transport media used should preserve influenza and SARS-CoV-2 viral RNA as well as genetic material from other respiratory viruses. The exact specifications for the use of the nasal swabs and transport media will be worked out with each site, in consultation with subject matter experts.

Participant-collected blood specimens that are stored in the home prior to sending to the laboratory, should be stored according to best practices, which will be outlined by standard operating procedures written prior to beginning study enrollment. Blood specimens that are collected by a staff member will also be stored, handled, and transported using best practices for infection control and to ensure the quality of the specimen for later testing.

Collected specimens will be shipped from the participating sites to the central laboratory for testing. At least 4 aliquots of respiratory specimens may be obtained at the central laboratory from each original, as volume allows. CDC or other subject matter experts should be consulted to ensure that the volume of transport media and volume of each aliquot is sufficient for the study objective and possible future objectives.

Specimen aliquots may be sent to CDC or other laboratories for further antigenic or genetic characterization or 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.

11.4 Additional testing

Additional testing may be conducted on the collected nasal swabs or blood specimens to address the study objectives, including, but not limited to, viral sequencing, viral loads quantification/quantitative PCR, antibody titers, or testing for other respiratory pathogens.

12 Data analysis

The proposed design and characterization of infection and vaccination status for index cases and household contacts will allow us to compute at least 3 different VE estimates, briefly described here. The most commonly reported VE against *Susceptibility* will be derived from comparing the secondary attack rates (SAR) from vaccinated[v] household contacts and SAR from unvaccinated[u] household contacts. VE against *Infectiousness* will be derived from comparing SAR from household contacts who live with a vaccinated index case vs SAR from household contacts who live with an unvaccinated index case. Finally, the *Total* VE will be derived from comparing the SAR from vaccinated household contacts who live with a vaccinated index case vs SAR from unvaccinated household contacts who live with an unvaccinated index case. VE will be calculated following the general equation $1 - (\text{SAR}_v / \text{SAR}_u)$ and modified according to the corresponding VE estimates outlined above and expressed in percentages.³

In an initial analysis, descriptive statistics and unadjusted SAR will be calculated by dividing the number of new influenza and SARS-CoV-2 laboratory confirmed infections by the number of subjects considered at risk, as previously reported.² Estimates will be presented stratified by sociodemographic characteristics and by index versus household contact status. The next step will be inferring serial and generation intervals based on the data, while

acknowledging the traditional reliance on the presence of symptoms and the recognized presence of asymptomatic and pauci-symptomatic infections among household members.⁴⁻⁶ This information will be used to inform the identification of the most likely index case in each household and identify potential co-primary infections. This method primarily relies on integrating out over all possible routes of transmission within households to identify the most likely route. Furthermore, a household transmission model adapted from Cauchemez et al.⁷ and Van Boven et al.⁸ will be used to estimate within household transmission SAR acknowledging the role of each of the household members. The daily assessments of symptoms and laboratory-confirmed infections will be used to inform and estimate those transmission rates. Household final size outbreak distributions will be estimated and used as a sensitivity analysis towards the timing of the observed household clinical and laboratory data.^{9,10}

As recommended by Cauchemez et al.^{4,7} and Van Boven et al.⁸, we will examine relevant household transmission model assumptions including the assumption of independence between households, and the possibility of introduction of secondary infections from outside the household. As an alternative modelling approach and sensitivity analysis, we will revisit a previously constructed transmission simulation model¹¹ which will be adjusted towards the measured household mixing (two-level mixing model) based on described contacts and interactions among household members. This project analytical plan and its execution will benefit from the expertise of network investigators and an ongoing collaboration with Dr. Niel Hens, an expert from Hasselt University, Belgium and his team.

This plan outline will be flexible to accommodate the anticipated introduction of new vaccine formulations and changes and expansions in vaccine recommendations. A similar approach will be used for influenza SAR and VE estimations, though the ascertainment of serial intervals may be more straightforward. Separate from the outcome of viral infection for the main VE assessments, we will also evaluate the influence of vaccination on shedding duration. Given the uncertainty about duration of protection derived from vaccination, analyses will have built-in stratifications based on time since vaccination. These analytical plans will be completed in coordination with CDC.

12.1 Subgroup analyses

These assessments will include estimates by age group, presence of immunosuppressive conditions, recency of vaccination, vaccine type, virus variant, vaccination preference, evidence of previous infection and other relevant factors. Of special interest will be estimates for pediatric index cases, virus variants, and the influence of time since vaccination for index cases and household contacts on vaccine effectiveness.

12.2 Detectable VE based on projected sample size

We plan to enroll 1050 households across our network, encompassing ~4200 subjects (1050 index cases and ~3150 household contacts). We will focus the subsequent calculations on SARS-CoV-2 VE for prevention of infection among household contacts; similar calculations would apply for influenza VE estimates. Anticipating a vaccination coverage of ~25% among household contacts, we are planning a study with ~788 vaccinated and ~2362 unvaccinated household contacts. Prior data from our household transmission study indicate that the unadjusted risk of infection among unvaccinated household contacts is 0.53.² Using this as reference, we would be able to detect a VE of 11% or higher, with power of 0.8. The Type I error probability associated with the test of the null hypothesis that this relative risk equals 1 is 0.05. This study will have high power to detect small VE and enable study of subgroups.

13 Quality assurance

13.1 Quality of screening, enrollment

Each site will establish a set of quality assurance procedures to ensure reliability of screening, enrollment, and follow-up practices, as well as data collection. These procedures include but are not limited to periodic second review of screening laboratory tests, double data entry or review of data entry, and developing and applying data cleaning and consistency rules. Some of these quality assurance procedures should be implemented on an on-going basis throughout study enrollment (e.g., reliability of screening laboratory tests, data entry review) whereas others can be conducted after enrollment ends.

13.2 Quality of self-collected specimens

Each study site will establish quality assurance procedures to ensure reliability of collection and storage of collected specimens. These procedures will be informed by regular review of processes for collection, handling, storage and shipping of study specimens.

14 Data management

To ensure uniform and consistent data collection among network sites, the central coordinating site will develop a central REDCap database that includes agreed-upon data elements to be collected through records reviews, participant interviews/interactions, surveys and other study data collection methods. Data will be collected by study sites into a secured central REDCap database and stored behind secure institutional firewalls.

15 Data sharing and use

The study will be guided by a Steering Committee comprised of up to 2 representatives from each site and 2 from CDC. The goal of the Steering Committee is to guide the network, so it produces high quality work and is optimally productive. Roles of the committee include guiding the data collection and data management, analytic processes and projects, deciding project priorities, facilitating equitable distribution of publications, and resolving disputes.

Data and associated documentation from this study will be available only under a data use agreement developed by the steering committee and that provides for (1) a commitment to using the data only for research purposes and not to identify any individual participant; (2) a commitment to securing the data using appropriate information technology; and (3) commitments for destruction, return, or retention of data as stipulated by the steering committee.

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

16 Regulatory and Ethical Considerations

16.1 *Protection of human subjects*

The coordinating site will submit the study protocol and necessary forms/instruments to the single Institutional Review Board (sIRB) for review and approval. Study sites may need to submit materials to their local IRB if requested or required to. The sIRB and CDC will request a reliance upon the single IRB for human subjects' review of the study protocol. Should there be modifications to the study, each site may be responsible for updating their local IRB approval should that be necessary. CDC's Human Research Protection Office would receive copies of agreements, initial approvals, amendments and incidents as well as annual approvals and renewals as applicable.

16.2 *Return of research results*

Sites may decide to share laboratory testing results conducted for this research study with participants, but research test results will not be a part of the medical record. Available test results that may be distributed require stating the research nature of the test(s) and distribution can be allowed approximately 3-6 weeks after enrollment to avoid potential interference with medical care. Participants will not be notified of specific research reports or findings of this study.

16.3 *Collection and Storage of Health Information*

During this project, personnel will obtain health information from participant interview, surrogate interviews, surveys, and medical records (including vaccination history) review. This will include personal information, including date of birth and date of disease onset, test(s), vaccinations and healthcare encounters. Study information will be entered by personnel at each site into a central REDCap electronic database maintained at Vanderbilt University Medical Center.

REDCap is a web-based data entry program accessible via an Internet connection. REDCap contains customizable data entry forms for data collection as well as an audit trail for tracking all activity within the system. REDCap is a secure web application for building and managing online surveys and databases. While REDCap can be used to collect virtually any type of data (including 21 CFR Part 11, FISMA, and HIPAA-compliant environments), it is specifically geared to support online or offline data capture for research studies and operations. REDCap employs several layers of security, including authentication of end-users, automatic user logout after 30 minutes of inactivity, a time-stamped audit trail, encrypted web-based information transmission, and firewall protection of uploaded documents. Additional information on REDCap is available at: www.project-redcap.org. The central database will include the minimal personal identifiers required to perform study activities outlined above and to enable communication with the study team and data gathering during follow-up. 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. In

preparation for analyses, limited datasets will be prepared by the Data Coordinating center and transferred to CDC using research identification numbers and a subset of identifiers such as geographical area location (e.g., zip code area or census tract) and date elements. All analyses will be conducted by the study research team using analytical datasets that do not contain PHI information or using limited datasets that may include relevant dates, site and location variables.

The primary risk of collection and storage of health information is inadvertent disclosure of this information. Inadvertent disclosure of health information will be minimized by using only professionals trained in responsible conduct of research and use of the REDCap system for data collection and storage. All personnel will receive appropriate training and certification in protection of subjects at their institutions, before accessing the project REDCap systems.

16.4 *Collection and Storage of Biological Specimens*

All collected samples will be labeled with unique research study numbers (without PHI information). These numbers allow linkage to epidemiologic data collected from study participants. Collected labelled samples will be shipped to Vanderbilt University Medical Center or CDC, where they will undergo analysis and long-term storage.

17 Additional research initiatives

Additional research activities can be proposed by study sites. Specific details about the additional activities should be shared, before implementation, with CDC and the study Steering Committee for consideration to adopt into the common protocol.

18 References

1. Rolfes MA, Grijalva CG, Zhu Y, et al. Implications of Shortened Quarantine Among Household Contacts of Index Patients with Confirmed SARS-CoV-2 Infection - Tennessee and Wisconsin, April-September 2020. *MMWR Morb Mortal Wkly Rep* 2021;69:1633-7.
2. Grijalva CG, Rolfes MA, Zhu Y, et al. Transmission of SARS-COV-2 Infections in Households - Tennessee and Wisconsin, April-September 2020. *MMWR Morb Mortal Wkly Rep* 2020;69:1631-4.
3. Halloran ME, Longini IM, Struchiner CJ. Household-based studies. *Design and Analysis of Vaccine Studies: Springer*; 2010:205-34.
4. Cauchemez S, Carrat F, Viboud C, Valleron AJ, Boelle PY. A Bayesian MCMC approach to study transmission of influenza: application to household longitudinal data. *Stat Med* 2004;23:3469-87.
5. Ganyani T, Kremer C, Chen D, et al. Estimating the generation interval for coronavirus disease (COVID-19) based on symptom onset data, March 2020. *Euro Surveill* 2020;25.
6. Torneri A, Libin P, Vanderlocht J, Vandamme AM, Neyts J, Hens N. A prospect on the use of antiviral drugs to control local outbreaks of COVID-19. *BMC Med* 2020;18:191.
7. Cauchemez S, Donnelly CA, Reed C, et al. Household transmission of 2009 pandemic influenza A (H1N1) virus in the United States. *N Engl J Med* 2009;361:2619-27.
8. van Boven M, Donker T, van der Lubben M, et al. Transmission of novel influenza A(H1N1) in households with post-exposure antiviral prophylaxis. *PLoS One* 2010;5:e11442.
9. Ludwig, D. (1975) Final Size Distributions for Epidemics. *Mathematical Biosciences*, 23, 33-46. [https://doi.org/10.1016/0025-5564\(75\)90119-4](https://doi.org/10.1016/0025-5564(75)90119-4).
10. Longini IM, Jr., Koopman JS. Household and community transmission parameters from final distributions of infections in households. *Biometrics* 1982;38:115-26.
11. Torneri A, Libin P, Scalia Tomba G, Faes C, Wood JG, Hens N. On realized serial and generation intervals given control measures: The COVID-19 pandemic case. *PLoS computational biology* 2021;17:e1008892.