US Influenza Vaccine Effectiveness Network Protocol for Influenza and Other Respiratory Viruses (including COVID-19)

Background

Influenza is an important cause of morbidity, mortality, and healthcare burden across all age groups. Because influenza viruses are constantly changing and vaccines are reformulated every year, annual estimates of the effectiveness of influenza vaccines in preventing influenza infection and its associated complications are needed in order to evaluate the protection provided by annual, nationwide vaccination programs. Estimating influenza vaccine effectiveness (VE) as soon as possible after the start of a seasonal influenza epidemic or pandemic and monitoring it over time are important to guide vaccination policies for influenza control. Estimation of vaccine effectiveness depends upon accurate assessment of vaccination status, laboratory-confirmed disease outcomes, timing of illness and vaccination, and assessment of other factors that may affect vaccine use and immune response to vaccination. Moreover, a number of potential modifiers of vaccine response and vaccine effectiveness have been identified, including individual factors (age, prior vaccination), environmental factors (exposure to cigarette smoke), viral (influenza type and subtype) and infectious disease factors. This protocol describes methods to identify and control for a variety of potential confounders in analysis.

In the setting of community transmission of coronavirus disease 2019 (COVID-19), enrollment of persons with acute respiratory illnesses for influenza vaccine effectiveness studies may identify persons with COVID-19 and contribute to the public health response to the COVID-19 pandemic, including evaluation of the effectiveness of licensed COVID-19 vaccines against medically attended acute respiratory illness and COVID-like illness. This Influenza Vaccine Effectiveness Network protocol has been updated to include testing for SARS-CoV-2, coordination with local public health authorities for reporting, changes to patient enrollment and specimen collection procedures, and documentation of COVID-19 vaccination for estimates of COVID-19 VE.

Participating institutions will coordinate enrollment of patients of all ages (including infants) with acute respiratory illness (ARI), and testing for influenza and other respiratory viruses (including SARS-CoV-2) may include standardized reverse-transcription polymerase chain reaction (RT-PCR) assay or other molecular assays. Participating sites will contribute data to CDC to estimate VE using a test-negative study design. Influenza and COVID-19 VE estimates will be used to inform and assess the public health impact of influenza and COVID-19 vaccination programs on the prevention of medically attended influenza- and COVID-19 associated illness. In addition, this network will allow comparison of VE data for specific vaccine types available in the US and describe the epidemiology of respiratory illness, including COVID-19.

Additionally, influenza vaccine effectiveness during recent seasons has been lower than expected given level of antigenic match between vaccine and circulating influenza viruses. Lower than expected vaccine effectiveness has been observed with both A(H1N1)pdm09 and A(H3N2) viruses and may be related to antigenic changes in egg-grown influenza vaccine viruses. Examination of the immune response to influenza and SARS-CoV-2 infection among vaccinated and unvaccinated individuals may identify reasons for vaccine failure. The US Flu VE Network presents a unique platform to investigate immune responses to acute infection among patients with laboratory-confirmed infection with influenza or other respiratory viruses, including SARS-CoV-2, enrolled in a consented study. This protocol includes collection of serum specimens and peripheral blood mononuclear cells (PBMC) during acute- and convalescent phases of illness from patients with confirmed infection with influenza or other respiratory viruses, including SARS-CoV-2, to fill a critical gap in immunologic data produced by CDC's Influenza Division and Division of Viral Diseases, and to develop this capacity for use during the COVID-19 pandemic, as well as in a pandemic of influenza or other respiratory viruses. Sera and PBMCs collected from vaccine failures will provide valuable information on the causes for failure and how to improve vaccine effectiveness.

Objectives

The goal of the US Influenza Vaccine Effectiveness Network is to establish a sustainable network of US institutions to obtain data from ambulatory settings in order to provide: 1) accurate estimates of seasonal influenza vaccine and COVID-19 vaccine effectiveness to prevent medically attended influenza and COVID-19 among the US population; and 2) describe the epidemiology of acute respiratory illness due to influenza and other respiratory viruses, including SARS-CoV-2.

The primary objectives of this study are to enroll outpatients with acute respiratory illness (ARI) or symptoms associated with acute COVID-19 meeting a standard case definition, confirm infection with influenza and other respiratory viruses, including SARS-CoV-2, using standardized RT-PCR assays, and estimate influenza and COVID-19 VE using a test-negative study design. Specifically, the study aims to provide annual estimates of influenza vaccine effectiveness, as well as estimates of COVID-19 VE, and estimate and compare VE for specific vaccine types licensed in the US, if feasible.

Secondary objectives of the study include estimating the incidence of outpatient visits or healthcare consultations (including telemedicine) due to laboratory-confirmed influenza or other respiratory viral illnesses, including COVID-19 (or providing data to improve current methods to estimate incidence) and serving as an emergency response resource during the COVID-19 pandemic and in the event of a pandemic due to novel influenza virus or other respiratory virus.

The objective of the substudy is to investigate immune responses to infection with influenza or other respiratory viruses, including SARS-CoV-2, in children and adults and factors associated with breakthrough infection or vaccine failure. It specifically aims to collect acute- and convalescent-phase serum and/or PBMC specimens, as well as respiratory specimens for virus characterization and genetic

sequencing, from patients infected with influenza, SARS-CoV-2 or other respiratory viruses to measure (i) antibody titers against the infecting virus, including measures of immune responses to vaccination or natural infection, and (ii) cell mediated immune responses to infection with influenza and other respiratory viruses, including SARS-CoV-2.

This protocol for the 2020-2021 influenza season and COVID-19 activity presents the study components that are common across the US Influenza Vaccine Effectiveness Network study sites, and thus is referred to as the "core/common protocol."

Study Design and Methods

Overview

This study will use a prospective test-negative case-control design to estimate the effectiveness of licensed influenza vaccines and COVID-19 vaccines against medically attended influenza in the US. We will perform active case-finding for persons with acute respiratory illness or symptoms associated with COVID-19 in participating outpatient settings. Eligible participants are patients of any age, including infants, with acute respiratory illness of ≤10 days duration. Identification of potentially eligible patients will occur by review of chief complaints on daily clinic schedules. Potentially eligible patients will be approached or reason/s for appointment from electronic appointment logs will be reviewed and screened for eligibility under a standard case definition. Interested, eligible patients will provide informed consent for themselves; parents of patients <18 years will provide informed consent for their children and HIPAA authorization will be obtained from patients who may be eligible and interested in participating after approach and screening. Enrolled patients will complete an interview, permit collection of a respiratory specimen, and provide authorization for access to medical records to collect clinical, demographic, health status, and vaccination information. In addition, clinical personnel or research staff will collect respiratory specimens for this study (mid-turbinate/nasal and throat swabs) or clinical staff will obtain an aliquot of respiratory specimens collected for clinical testing to be used for this protocol (nasopharyngeal, mid-turbinate/nasal and throat swabs). Alternatively, participants may receive a specimen collection kit to collect their own respiratory specimen (mid-turbinate or nasal swabs) for testing. Influenza cases are patients who test positive for influenza by molecular assays and controls are those who test negative for influenza by RT-PCR. COVID-19 cases are patients who test positive for SARS-CoV-2 infection using molecular assays and controls are those who test negative for SARS-CoV-2 infection by RT-PCR. During periods of co-circulation, enrolled patients will be tested for both COVID-19 and influenza using molecular assays, and test-negative controls will be patients who test negative for both influenza and SARS-CoV-2. Influenza and COVID-19 vaccination status is reported by the patient and documented by review of medical records, state immunization registry records, vaccination cards and information from vaccination providers. Influenza vaccine effectiveness is estimated using multivariable logistic regression with influenza case status as the outcome and influenza vaccination status as the main exposure. COVID-19 VE will be estimated using the same approach.

Analyses of the clinical characteristics of patients with medically attended acute respiratory illness (MAARI) will be repeated at regular intervals to identify changes in clinical presentation of COVID-19, as well as changes in proportions of patients with MAARI due to SARS-CoV-2 infection. Incidence estimates will be extrapolated from the percentage of enrolled MAARI patients who test positive for SARS-CoV-2 to all MAARI patients from a defined source population.

Source population and settings

Study sites may identify eligible patients at ambulatory care centers such as pediatric, family medicine, internal medicine, or urgent care outpatient clinics or emergency medicine centers. Normal clinic operations may be severely disrupted during widespread COVID-19 activity, and sites will determine settings for patient identification and enrollment procedures based on the local situation. Sites may additionally identify eligible patients from telemedicine/medical advice systems.

For purposes of estimating the population-based incidence of influenza or other respiratory illness, including COVID-19, each site will estimate a defined source population in which a subset of eligible patients will be identified, according to six age group (6 tiers: 0 months to <2 years, 2 to <5 years, 5 to ≤17 years, 18 to ≤49 years, 50 to ≤64 years, 65 to ≤79, and 80+years), sex, and race. Sites may enroll patients from outside the defined source population, but incidence calculations will be based on participants from within the defined source population.

Each site will describe a process to estimate the number of patients infected with influenza or other respiratory viruses, including SARS-CoV-2, in the source population (over a given period of time) based on the number of positive enrollees in the study (e.g., using zip codes, county of residence, or health plan membership) and an estimate of the number or proportion of study-eligible patients that were missed (i.e., not enrolled).

Pre-enrollment surveillance and initiation of study enrollment

Each site will use laboratory-confirmed evidence of local circulation of influenza and other respiratory viruses, including SARS-CoV-2, to monitor local respiratory virus activity during enrollment. Each site will begin limited pre-season enrollments when there is evidence of local influenza or SARS-CoV-2 circulation. Sites may begin pre-season enrollment earlier, if desired and feasible.

Full local enrollment will be triggered by two consecutive weeks of increasing detection of influenza viruses by RT-PCR assays conducted as part of pre-season surveillance, or at the discretion of the site PI if local circulation and surveillance sample positivity rate is sufficiently high. Increasing detection will be based on the week-to-week increase in the total number of influenza positive specimens and the proportion that is influenza positive among those tested. During periods of SARS-CoV-2 circulation,

enrollment of persons in groups targeted for COVID-19 vaccination may be prioritized to contribute to estimates of COVID-19 VE.

Enrollment will continue for at least ten weeks at each site. The end of the enrollment period will be defined by the lack of laboratory-confirmed influenza cases for at least one week, or for as long as possible based on funding if influenza and other respiratory virus activity, including COVID-19, is ongoing.

Inclusion criteria

All patients seeking care for a new acute respiratory illness of ≤10 days duration with cough, fever or loss of taste or smell will be eligible for enrollment. Some sites may enroll patients from a defined source population based on healthcare plan membership and/or geographic area of residence. Participants' consent to enroll and at least one specimen collection is required for inclusion.

Exclusion criteria

- Illness duration of >10 days at the time of respiratory specimen collection, measured from the date of the first symptom of the current acute illness. Individuals may be enrolled if respiratory specimens are collected from illness day 0 (onset date) through day 10.

- Inability to provide informed consent in English

Residents of long-term care facilities who meet inclusion criteria may be enrolled. Enrolled subjects are eligible for re-enrollment at a subsequent visit for an illness meeting inclusion criteria; data from re-enrolled patients will only be considered in analyses if 14 or more days have elapsed since the date of previous enrollment.

Participant identification (screening)

Sites may use a variety of methods to screen for patients with symptoms meeting inclusion criteria, including fever or feverishness, cough, or loss of taste or smell. Patients with acute respiratory illness (ARI) who are not approached during a clinical encounter or who sought care via telehealth may be identified on the following day using electronic diagnosis codes entered by providers or protocols utilized by telehealth staff to address chief complaints of interest. Some of these individuals will be contacted by phone and screened for eligibility (duration of illness and symptoms). Eligible and consenting individuals may be asked to provide a respiratory specimen, either self-collected, collected by a parent/guardian, or collected by clinical or research personnel, with instructions to deliver or send specimens to designated laboratories. The number of individuals recruited by this method ("remote" or "next day enrollment") will vary daily based on volume and staff availability.

Data recorded for all subjects on screening log. Each site will generate summary tables of patients approached for screening and those who refused.

Similarly, sites will track tallies on the number of (1) patients who were approached, but refused to be screened, (2) patients who were screened but ineligible for enrollment, and (3) patients who were eligible but refused enrollment. This will be provided at the end of the season rather than on the weekly Dashboard. Reasons for ineligibility and/or refusal may not be recorded.

There are no predetermined enrollment locations. Sites decide enrollment and allocation of staff based on their experience and how most effectively to meet sample size overall as well as within each age group.

Approach and enrollment

Each weekday, study staff will create a log of potentially eligible patients identified per the site's screening method to be approached for enrollment. The goal is to approach all potentially eligible patients. Approach will include a short verbal request to speak with the patient/parent and confirm the presence of cough, fever or loss of taste or smell and date of illness onset within the previous 10 days.

Enrolled subjects are eligible for re-enrollment at any subsequent clinical visit (no minimum time interval between outpatient visits is required). However, as noted above, re-enrolled patient data will only be considered in analyses if 14 or more days have elapsed since the date of previous enrollment.

All sites may offer an incentive for enrollment and completion of follow-up questionnaire.

Sites may include information for eligible participants regarding optional participation in a substudy of immune response to infection with influenza or other respiratory virus, including SARS-CoV-2. Eligible patients will be informed of the procedures for testing for influenza and other respiratory viruses, including SARS-CoV-2, and blood collection. An acute phase blood specimen, PBMC and/or sera, may be collected from all eligible patients who consent to participate in the immunologic substudy or from those who test positive once the result of the test is known (draw 1). A convalescent phase blood specimen will be collected within a target range of 21–42 days, but no later than 56 days, after illness onset (draw 2). Participants who consent to participate in the substudy of immune response to infection with influenza or other respiratory viruses, including SARS-CoV-2, may receive an additional amount as an incentive for providing each blood specimen.

All sites will maintain a dashboard beginning with the pre-season surveillance/enrollment period. During pre-season surveillance/enrollment, the following information will be recorded: Total number of specimens, number of laboratory-confirmed Influenza A specimens positive, number of laboratory-confirmed Influenza B specimens positive, and number of untyped or pending specimens.

Once full enrollment begins, the following information will be recorded in the Dashboard: Number approached, number enrolled, number Influenza A positive, number Influenza B positive, number untyped or pending influenza testing, number positive for SARS-CoV-2, and number influenza-negative and SARS-CoV-2 negative controls. For both influenza and COVID-19 cases and controls, the following will be recorded: Number vaccinated, number not vaccinated, and number of unknown vaccination status. Dashboard vaccination status may rely on patient self-report.

All sites will submit dashboard information bi-weekly to CDC, with a one week delay in data. Each biweekly period will run Sunday through Saturday.

Consent process

Sites will use informed written or verbal consent/assent for study enrollment as determined by local IRB requirements. Consent forms will include language that will allow for release of medical records, if necessary. Each site will assure that the consent/assent language includes necessary provisions for archiving residual clinical and research specimens at the participating sites and/or CDC. Participants will be informed of testing for SARS-CoV-2 and other respiratory viruses, and will be informed of study procedures for reporting SARS-CoV-2 positive results to public health authorities (e.g., local/state health departments), and public health authorities may follow up with the subject for further actions per appropriate guidelines. In addition, individual surveillance sites may also elect to reveal testing results to the study subject or his/her doctor in select circumstances as detailed in their consent forms according to individual site institutional requirements.
At selected sites, an additional informed written or verbal consent process will be included for eligible patients who wish to be enrolled in the immunologic substudy of immune responses to infection with influenza or other respiratory viruses, including SARS-CoV-2. Eligible patients who consent to enrollment in the VE study but do not consent to enroll in the immunologic substudy will be included only in the VE study.

Enrollment interview

After providing informed consent, each participant or his/her parent will be interviewed to collect information on patient demographics, household characteristics, symptoms, influenza and COVID-19 vaccination status, general health status, and smoking history or exposure. Those sites with immediate access to vaccination data from the medical record or vaccination card may obtain date of vaccination and vaccine product from these sources rather than self-report. Those sites asking about date of vaccination can ask for an exact (or best estimate) date, whether the vaccine was given 14 or more days before illness onset, or both. Sites may attempt to determine location of vaccination, whether at the time of enrollment or from a subsequent medical record/state registry query and/or follow up telephone consultation. All sites will provide lot number and manufacturer information for documented influenza vaccination, if recorded. All sites will provide information on length of membership in health system, either from self-report or from a tabulation of electronic medical records (EMRs). Sites may include additional questions (e.g. insurance status and self-reported asthma).

Specimen Collection

Residual clinical specimens may be obtained for this evaluation. Clinical specimens may include nasopharyngeal, mid-turbinate, nasal and throat swabs; nasopharyngeal and mid-turbinate specimens are preferred over nasal specimens, but nasal specimens may be used if collected for clinical purposes. Clinical specimens may be stored in separate vials with universal transport media (UTM) or combined in one vial per patient and time-point. If a clinical specimen has been collected, staff may determine if an aliquot is available for testing for this protocol, in which case collection of additional respiratory specimens may not be required.

Specimens collected by US Flu VE Network staff for this evaluation may include mid-turbinate/nasal (participants aged <2 years) and mid-turbinate/nasal and throat swabs (participants aged ≥2 years). These specimens may be collected by staff at the time of enrollment and combined in a single vial of universal transport media (UTM) or separated into separate vials. Participants can still be included if they withdraw consent for the second swab. Collected respiratory specimens may be stored and transported at refrigerator temperatures (2-10°C) until processed and tested for influenza and other respiratory viruses, including SARS-CoV-2 (described in subsequent sections).

Mid-turbinate or nasal specimens may also be collected by the patient following informed consent. Written instruction or instructional videos may be used to guide self-collection of mid-turbinate or nasal swabs. Parents or guardians may collect mid-turbinate/nasal swabs on infants and young children. Self-collection of respiratory specimens for this study will depend on local determination of the feasibility of staff or clinically collected swabs and the availability of delivery and return of self-collected swabbing kits.

Self-collected swabs may be collected at additional time points after enrollment for confirmation/validation of SARS-CoV-2 diagnostic testing and to follow-up SARS-CoV-2-positive patients for duration of infection.

For participants who consent to enrollment in the immunologic substudy, additional respiratory specimens may be required for conducting rapid influenza or SARS-CoV-2 tests to screen patients for influenza or SARS-CoV-2 infection. Rapid influenza or SARS-CoV-2 testing, if used, will follow manufacturers' instructions and will be performed by research staff. Sites may use any FDA-approved influenza or SARS-CoV-2 test to determine substudy eligibility. Results of any rapid testing, if performed, will be shared with the participant.

For study sites that will collect acute phase blood specimens from all patients who consent to participate in the immunologic substudy, blood specimens may be collected at the time of study enrollment or residual clinical specimens may be obtained for use in this study. For study sites that will collect acute phase blood specimens only from patients who consent to participate in the immunologic substudy and test positive for influenza or COVID-19, participants will be asked to provide an acute-

phase blood specimen as soon as possible after test results are available, no later than 7 days after illness onset. For participants who test positive for influenza or other respiratory viruses, including SARS-CoV-2, collection of convalescent blood specimen will be scheduled within a target range of 21 to 42 days, but no more than 56 days, after illness onset, and participants may receive at least one appointment reminder prior to the date by their preferred method of communication and follow-up attempts to reschedule missed appointments for convalescent blood. Acute and convalescent blood will be processed for sera and/or PBMCs, aliquoted, and stored at VE network laboratories until shipped to CDC for immunologic assays (Appendix E and F).

Handling and storage of respiratory and blood specimens

Respiratory specimens may be divided into three or more aliquots, with a system for tracking inventory of aliquots as coordinated with CDC: one aliquot for influenza and other respiratory virus testing, including SARS-CoV-2, one aliquot for possible additional testing by a designated public health laboratory or CDC, and one aliquot with any remaining specimen for possible further testing, evaluation, and/or storage. This latter specimen can be stored at the site or sent to CDC and stored through the biorepository. The volume of aliquots obtained from original clinical specimens may be limited by the volume or type of clinical specimen. When volume is insufficient to provide three 1 mL aliquots as described above, obtaining two 800 µL to 1 mL aliquots for testing at the site and for shipment to CDC are to be prioritized. If feasible and available, sites may obtain any type of residual clinical specimens from participants for antigenic characterization, sequencing, and/or other characterization of influenza or other respiratory viruses, including SARAS-CoV-2.

Personal Protective Equipment for Staff

Guidance for use of personal protective equipment for staff enrolling patients and collecting specimens will follow CDC guidance current at the time of enrollment.

Follow Up Survey

All participants will have an opportunity to complete a follow up survey between 7 and 14 days after enrollment; additional follow-up with participants may be needed for surveillance. The follow up survey will be administered via telephone, text-based or online. Sites may provide reminders to complete the survey, either by telephone or email. Sites may choose to prioritize these reminders for who enrollees who test positive for influenza or other respiratory viruses, including SARS-CoV-2. All sites will ask questions on duration of illness, antiviral medication, medical encounters after enrollment, frequency of vaccination, and intent to vaccinate in future years. Additionally, adults aged ≥18 years may be asked questions on employment and parents/guardians of those subjects <18 years of age may be asked about school attendance and social distancing measures. Those ≥65 years may be asked questions about activities of daily living.

A subset of participants at sites participating in the long term follow up survey will have an opportunity to complete an additional survey between 8 and 12 weeks after illness onset/enrollment. Participants in the survey should include approximately equal numbers of subjects with a positive RT-PCR test for SARS-CoV-2 (cases) and subjects with negative RT-PCR tests for SARS-CoV-2 (controls). The controls should be enrolled from within the same time-period as the cases. Controls will be excluded from this survey if they test RT-PCR positive for SARS-CoV-2 in the intervening time between enrollment and follow up. Sites are encouraged (but not required) to collect an optional convalescent blood sample from controls. The results of antibody testing will be used in secondary analyses to address potential case misclassification based on RT-PCR. Participants in this follow up may overlap with participants in the immunologic study, but it is preferred that some of the controls be RT-PCR negative for both SARS-CoV-2 and influenza. This follow up survey will be administered via telephone, text or online with direct entry into REDCap. The survey will assess measures of global health, fatigue, physical function and dyspnea using validated, standardized instruments from the PROMIS® network.

Documentation of influenza and COVID-19 vaccination status

In addition to asking vaccination status at enrollment, each site will query their health system's medical record system and the state immunization registry to obtain current and past season influenza vaccination data and COVID-19 vaccination for all participants regardless of self-reported vaccination status. Past season influenza vaccination data will include for as many records as are available in the EMR. The following data elements for vaccination verification will be collected for each dose if provided: Date of vaccination, product name, manufacturer, lot number, route of administration, valence, dose level, and source of information.

Determination of plausible self-reported vaccination status

A standard algorithm will be used to determine vaccination status using a combination of all available vaccination data. For all sites, report of vaccination (with date) from an electronic information system/immunization registry (EIR) or vaccination cardwill be considered a valid vaccination. Participants who report no vaccination at enrollment and who do not have EIR evidence of vaccination will be considered unvaccinated. For participants aged ≥9 years at enrollment who report vaccination and do not have EIR or vaccination card evidence of current vaccination, we will take several steps to determine plausibility of a self-reported vaccination if necessary. To be considered a plausible self-report, a participant must report a date/estimated date ≥14 days prior to illness onset. Second, location of vaccination must be outside the site's health system, not captured by EMR (as determined by site investigators). Participants reporting receipt <14 days prior to illness onset or unable to provide a date/estimated date of vaccination will be excluded from any vaccine effectiveness analyses using plausible self-report as the primary exposure due to indeterminate vaccination status. Participants reporting vaccine receipt ≥14 days prior to illness onset from a provider within the site's health system or a location determined by a site representative to likely be captured by the EMR will be excluded from any vaccine effectiveness analyses using plausible self-report as the primary exposure due to

indeterminate vaccination status. Any participants with evidence of vaccination after illness onset (either by EIR or self/parent report) will be considered unvaccinated at time of enrollment.

Medical Record Extraction

Each site will collect patient height, weight, age, and sex from the EMR and/or self-report.

All sites will query the medical record of all enrollees to gather specific data elements to classify underlying health conditions, as well as patient outcomes.

Each site will collect ICD10 codes that correspond to all medical encounters from all enrollees during the 12 months preceding enrollment.

Additionally, all sites will provide CPT codes for chest and sinus x-rays, discharge diagnoses for hospitalization data, and hospitalization with a MAARI code occurring within 90 days after enrollment. The minimum data elements to be collected include subject identification, date of admission (for hospitalizations), and relevant ICD10 or CPT codes.

All sites will provide ICD10 codes associated with the enrollment visit and any subsequent outpatient visits in the 14 days after the enrollment visit. Any clinical diagnostic testing (and results of testing if feasible) for influenza, COVID-19 or Group A streptococcus done at the enrollment visit will also be included.

In addition to diagnosis codes, all sites will provide data on prescription practices as described below:

Assessment of antiviral treatment

For each participant, all sites will provide information on the name, prescription date, and dispensed dates (where possible) for all antiviral medications prescribed at enrollment and the subsequent 7 days. These data elements may be collected by electronic query.

Assessment of antibiotic treatment

For each participant, all sites will collect information on name, prescription date, and dispensed dates (where possible) for antibiotic medications prescribed at enrollment and the subsequent 7 days for relevant medications listed in HEDIS 2019.

Quality assurance

Each site will establish a set of quality assurance procedures to ensure reliability of screening and enrollment practices and information capture. These procedures include but are not limited to periodic second review of chief complaint lists, double data entry or review of data entry, developing and applying data cleaning and consistency rules, and comparing the number of patients identified by

screening as potentially eligible with other sources. Some of these quality assurance procedures should be implemented on an on-going basis throughout study enrollment (e.g., data entry review) whereas others can be conducted after seasonal enrollment ends.

Assessment of Vaccine Effectiveness

Case/control Classification. The results of the research RT-PCR test will be used to classify enrollees. Enrollees testing positive for influenza or COVID-19 will be classified as cases, respectively, and enrollees testing negative classified as controls (See "Detection of Influenza and SARS-CoV-2 Viruses").

Defining vaccination status. Enrollees will be considered vaccinated if they received ≥1 dose of current season influenza or licensed COVID-19 vaccine ≥14 days prior to illness onset, which will be determined by plausible self-report. Those vaccinated 0–13 days prior to illness onset will be excluded from analyses. Vaccinated persons for whom two doses are recommended, including children aged <9 years and persons receiving some licensed COVID-19 vaccines, will be further classified as either fully or partially vaccinated depending on number of doses they have received. We will use current guidance from the ACIP on number and combination of doses needed to be considered fully vaccinated.

Defining high-risk status. A person will be defined as having a high-risk condition if he/she had ≥1 ICD10 code of interest [APPENDIX B] in the EMR in either the outpatient or inpatient setting during the 12 months preceding enrollment. Codes will be further aggregated by the data manager into the following categories: cardiac diseases, cerebrovascular diseases, pulmonary diseases, renal diseases, diabetes, artery/arterioles/capillary diseases, endocrine disorders, vein/lymphatic vessel/lymph node diseases, hemoglobinopathies, immunosuppressive disorders, liver diseases, long-term medication use, malignancies, other metabolic diseases, morbid obesity, and neurological/musculoskeletal conditions. Codes that make up these categories can be found in the data dictionary.

Analytic approach. VE will be estimated using multivariate logistic regression with influenza or COVID-19 status as the outcome and vaccination status as the main predictor with estimated VE = (1 – *adjusted odds ratio*) x 100. The model for estimating VE will include patient characteristics and other characteristics of interest or those that may confound the relationship between vaccination and laboratory confirmed illness . A fully adjusted model will control for all factors (age, sex, site, race/Hispanic ethnicity, interval from onset to enrollment, high-risk status, and calendar time). A parsimonious model will control for a minimum of age, site, high-risk status, and calendar time. Additional variables will be assessed using a forward selection procedure and will be retained in the model if their addition to the minimally adjusted model changes the odds ratio by ≥5%. Data collected for this study are intended to be pooled across sites. Participants aged ≥24 months who do not provide paired nasal and throat specimens may be still included in the analyses with one specimen.

Laboratory Procedures

Detection of influenza and SARS-CoV-2 viruses

Respiratory specimens will be tested for influenza A and B and SARS-CoV-2 using CDC singleplex or multiplex RT-PCR assays (Appendix A). Influenza A subtype and B lineage will be determined for influenza positive specimens using the CDC A subtyping and B-genotyping RT-PCR assays. Specimens with an RT-PCR CT value <40 will be considered positive. RNase P CT values will also be monitored for specimen quality control. Specimens with co-infections, unsubtypable (negative result on subtyping assay), or inconclusive subtyping (e.g. only one H1N1 target positive) RT-PCR results will be sent to CDC for confirmation testing. Specimens with unrepeatable (CT ≥ 40 upon repeat testing may be sent to CDC at discretion of the sites. If an unsubtypable specimen has influenza A/B CT value of ≤30, or a SARS-CoV-2 result indicating infection with a variant virus, sites will ship specimen to CDC immediately. Unsubtypables/inconclusives with higher CT values, co-infections, or unrepeatables can be shipped together at the end of the enrollment period or in bulk mid-season if necessary. Specific shipment address for unrepeatable, co-infection, inconclusive, or unsubtypable influenza specimens is as follows:

WHO Collaborating Center for the Surveillance, Epidemiology, and Control of Influenza
Centers for Disease Control and Prevention
Influenza Division, G-16
1600 Clifton Road
Atlanta, GA 30329
404-639-1657

Specimens with unrepeatable, co-infection, inconclusive, or unsubtypable results sent to CDC for further testing will be assigned final determinations as follows:

InfA	H3	pdm InfA	pdmH1	B	RP	Result
+	+	-	-	-	+/-	A/H3
+	-	+	+	-	+/-	A/H1pdm
-	-	-	-	+	+/-	B
+	+	+	+	-	+/-	Co-infection (H1/H3)
+	+	-	-	+	+/-	Co-infection (H3/B)
+	-	+	+	+	+/-	Co-infection (H1/B)
+		+			+/-	Inconclusive (high Cts)
+			+		+/-	Inconclusive (high Cts)
	+	+			+/-	Inconclusive (high Cts)
	+				+/-	Inconclusive (high Cts)

Surveillance specimens

Antigenic characterization and sequencing may be performed by CDC or a designated laboratory on influenza and SARS-CoV-2 positive specimens from each site. For influenza positive specimens, each site will ship 2 0.5 mL aliquots of positive specimens with Inf A/B CT value ≤30 at pre-determined intervals to the CDC. Specific shipment address for influenza positive specimens to CDC is as follows:

John Barnes
CDC Influenza Division
1600 Clifton Road
Building 23 Room 12-440
Atlanta, GA 30329
fzq9@cdc.gov
404.639.2434

Timelines and procedures for specimen shipment will be established early in the season via discussions on the bi-weekly laboratory calls.

Proficiency testing

Each site will demonstrate proficiency by completing proficiency panels when provided by CDC. Additional proficiency testing may be required if necessary. More information regarding laboratory protocol and procedures can be found in Appendix A.

Specimens for Immunologic assessment

Each site will send acute and convalescent serum and/or PBMC specimens to CDC in two shipments, one mid-season and one end of season shipment. Please view Appendices E (sera) and F (PBMC) for more information.

Data Management, Transfer, and Security

Data will be collected locally at the sites and stored behind secure institutional firewalls. 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. Partial de-identification of data will be conducted by the sites, and a limited dataset will be transferred to CDC using research identification numbers. Data privacy will be maintained according to local IRB protocols.

To ensure uniform and consistent data collection among network sites, CDC will provide data dictionaries and data collection forms/surveys. Data dictionaries will be created based on agreed-upon data elements to be collected through electronic medical records and enrollment interview. Study sites may decide to collect additional and optional pieces of information, and if they make the CDC aware of

such additions early in the form development process, these elements can be added to customized site forms.

All sites are expected to use the secure FTP site set up by CDC for data transfer (upload, download, etc.).

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.

Study Governance

The study will be guided by a Steering Committee comprised of up to two representatives from each site and two from CDC for a total of up to 12 members. The goal of the Steering Committee is to steer or guide the network so it produces high quality work and is optimally productive. Roles of the Steering Committee include guiding the analytic processes and projects, deciding project priority, facilitating equitable distribution of publications, and resolving disputes.

Role of US Flu VE Network during the COVID-19 Pandemic

The US Flu VE Network research institutions serve as an emergency response resource during the COVID-19 pandemic to assess VE to prevent medically attended influenza and COVID-19, as well as to describe the epidemiology of acute respiratory illness due to influenza and other respiratory viruses, including SARS-CoV-2. The studies conducted as part of this response may differ from US Flu VE Network's normal seasonal influenza VE study activities. Additional funding would be made available to support these activities, and amended study protocols would be submitted for IRB approval as required.

Regulatory and Ethical Considerations

Protection of human subjects

Each site will submit study protocols and any amendments and associated forms and instruments to their local IRB for review and approval. Each site will submit to their IRB the appropriate site-specific consent forms for the study. For each site, CDC will request a reliance upon the local IRB for human subjects' review of the study protocol. Each site is responsible for updating their local IRB approval annually.

Return of results

Results of COVID-19 and influenza testing may be returned to the study participant, healthcare provider or public health authority as requiredPublic health authorities may follow up with the subject for further actions per appropriate guidelines. In addition, individual surveillance sites may also elect to reveal testing results to the study subject or his/her doctor in select circumstances as detailed in their consent forms according to individual site institutional requirements.

Compliance with Office of Management and Budget (OMB) Paperwork Reduction Act (PRA)

The US Centers for Disease Control and Prevention, National Center for Infectious Diseases (CDC/NCIRD) has determined the information collection activities conducted under this project qualify for the NCVIA - conferred PRA waiver as they come under the activities authorized under the NCVIA at section 2102(a)(7) of the Public Health Services Act (42 U.S.C 300aa-2(a)(7). The CDC Office of General Counsel agrees with CDC/NCIRD's determination that the information collection activities conducted under this project qualify for the NCVIA-conferred Paperwork Reduction Act waiver. Each site is responsible for obtaining the necessary OMB PRA waiver or demonstrating compliance with the OMB PRA if additional documentation beyond the CDC-approved waiver is required by the site.

Appendix A.

Laboratory procedures

Information for Clinicians on Influenza Virus Testing | CDC

https://www.internationalreagentresource.org/

CDC 2019-Novel Coronavirus (2019-nCoV) Real-Time RT-PCR Diagnostic Panel

CDC's Diagnostic Test for COVID-19 Only and Supplies | CDC

Real-time RT-PCR Primers and Probes for COVID-19 | CDC

CDC Influenza SARS-CoV-2 (Flu SC2) Multiplex Assay

CDC's Diagnostic Multiplex Assay for Flu and COVID-19 at Public Health Laboratories and Supplies | CDC

Appendix B

High Risk Codes

Condition Category	ICD10	Description
Hypertension	I10*	Essential (primary) hypertension
Cerebrovascular diseases	I60*	Nontraumatic subarachnoid hemorrhage
Cerebrovascular diseases	I61*	Nontraumatic intracerebral hemorrhage
Cerebrovascular diseases	I62*	Other and unspecified nontraumatic intracranial hemorrhage
Cerebrovascular diseases	I63*	Cerebral infarction
Cerebrovascular diseases	I68*	Cerebrovascular disorders in diseases classified elsewhere
Cerebrovascular diseases	I69*	Sequelae of cerebrovascular disease
Chronic Cardiac Diseases	A52.0*	Cardiovascular syphilis
Chronic Cardiac Diseases	I01*	Rheumatic fever with heart involvement
Chronic Cardiac Diseases	I02*	Rheumatic chorea
Chronic Cardiac Diseases	I05*	Rheumatic mitral valve diseases
Chronic Cardiac Diseases	I06*	Rheumatic aortic valve diseases
Chronic Cardiac Diseases	I07*	Rheumatic tricuspid valve diseases
Chronic Cardiac Diseases	I08*	Multiple valve diseases
Chronic Cardiac Diseases	I09*	Other rheumatic heart diseases
Chronic Cardiac Diseases	I11*	Hypertensive heart disease
Chronic Cardiac Diseases	I13*	Hypertensive heart and chronic kidney disease
Chronic Cardiac Diseases	I20*	Angina pectoris
Chronic Cardiac Diseases	I21*	ST elevation (STEMI) and non-ST elevation (NSTEMI) myocardial infarction
Chronic Cardiac Diseases	I22*	Subsequent ST elevation (STEMI) and non-ST elevation (NSTEMI) myocardial infarction
Chronic Cardiac Diseases	I23*	Certain current complications following ST elevation (STEMI) and non-ST elevation (NSTEMI) myocardialinfarction (within the 28 day period)
Chronic Cardiac Diseases	I24*	Other acute ischemic heart diseases
Chronic Cardiac Diseases	I25*	Chronic ischemic heart disease
Chronic Cardiac Diseases	I26*	Pulmonary embolism
Chronic Cardiac Diseases	I27*	Other pulmonary heart diseases
Chronic Cardiac Diseases	I28*	Other diseases of pulmonary vessels
Chronic Cardiac Diseases	I31*	Other diseases of pericardium
Chronic Cardiac Diseases	I33*	Acute and subacute endocarditis
Chronic Cardiac Diseases	I34*	Nonrheumatic mitral valve disorders
Chronic Cardiac Diseases	I35*	Nonrheumatic aortic valve disorders
Chronic Cardiac Diseases	I36*	Nonrheumatic tricuspid valve disorders
Chronic Cardiac Diseases	I37*	Nonrheumatic pulmonary valve disorders
Chronic Cardiac Diseases	I38*	Endocarditis, valve unspecified
Chronic Cardiac Diseases	I39*	Endocarditis and heart valve disorders in diseases classified elsewhere
Chronic Cardiac Diseases	I40*	Acute myocarditis
Chronic Cardiac Diseases	I41*	Myocarditis in diseases classified elsewhere

Chronic Cardiac Diseases	I42*	Cardiomyopathy
Chronic Cardiac Diseases	I43*	Cardiomyopathy in diseases classified elsewhere
Chronic Cardiac Diseases	I44*	Atrioventricular and left bundle-branch block
Chronic Cardiac Diseases	I46*	Cardiac arrest
Chronic Cardiac Diseases	I48*	Atrial fibrillation and flutter
Chronic Cardiac Diseases	I50*	Heart failure
Chronic Cardiac Diseases	I51*	Complications and ill-defined descriptions of heart disease
Chronic Cardiac Diseases	I52*	Other heart disorders in diseases classified elsewhere
Chronic Cardiac diseases	I97.0*	Postcardiotomy syndrome
Chronic Cardiac diseases	I97.1*	Other postprocedural cardiac functional disturbances
Chronic Cardiac Diseases	M31*	Other necrotizing vasculopathies
Chronic Cardiac Diseases	Q20*	Congenital malformations of cardiac chambers and connections
Chronic Cardiac Diseases	Q21*	Congenital malformations of cardiac septa
Chronic Cardiac Diseases	Q22*	Congenital malformations of pulmonary and tricuspid valves
Chronic Cardiac Diseases	Q23*	Congenital malformations of aortic and mitral valves
Chronic Cardiac Diseases	Q24*	Other congenital malformations of heart
Chronic Cardiac Diseases	Q25*	Congenital malformations of great arteries
Chronic Cardiac Diseases	Q26*	Congenital malformations of great veins
Chronic Cardiac Diseases	Q27.0	Congenital absence and hypoplasia of umbilical artery
Chronic Cardiac Diseases	Q27.3	Arteriovenous malformations (peripheral)
Chronic Cardiac Diseases	Q27.4	Congenital phlebectasia
Chronic Cardiac Diseases	Q27.8	Other specified congenital malformations of peripheral vascular system
Chronic Cardiac Diseases	Q27.9	Congenital malformation of peripheral vascular system
Chronic Cardiac Diseases	Q28*	Other congenital malformations of circulatory system
Chronic Cardiac diseases	Q89.3*	Situs inversus
Chronic Cardiac diseases	R00.1*	Bradycardia, unspecified
Chronic Cardiac Diseases	Z94.1*	Heart transplant status
Chronic Cardiac Diseases	Z95*	Presence of cardiac and vascular implants and grafts
Chronic Cardiac Diseases	Z98.61*	Coronary angioplasty status
Chronic pulmonary diseases	A15*	Respiratory tuberculosis
Chronic pulmonary diseases	A31.0*	Pulmonary mycobacterial infection
Chronic pulmonary diseases	B39*	Histoplasmosis
Chronic pulmonary diseases	B40*	Blastomycosis
Chronic pulmonary diseases	B41*	Paracoccidioimycosis
Chronic pulmonary diseases	B44*	Aspergillosis
Chronic pulmonary diseases	B45*	Cryptococcosis
Chronic pulmonary diseases	B46.0*	Pulmonary mucormycosis
Chronic pulmonary diseases	D86.0*	Sarcoidosis of lung
Chronic pulmonary diseases	E84*	Cystic fibrosis
Chronic pulmonary diseases	E88.01*	Alpha-1-antitrypsin deficiency

Chronic pulmonary diseases	J18.2*	Hypostatic pneumonia, unspecified organism
Chronic pulmonary diseases	J41*	Simple and mucopurulent chronic bronchitis
Chronic pulmonary diseases	J42*	Unspecified chronic bronchitis
Chronic pulmonary diseases	J43*	Emphysema
Chronic pulmonary diseases	J44*	Other chronic obstructive pulmonary disease
Chronic pulmonary diseases (Asthma)	J45*	Asthma
Chronic pulmonary diseases	J47*	Bronchiectasis
Chronic pulmonary diseases	J60*	Coalworker's pneumoconiosis
Chronic pulmonary diseases	J61*	Pneumoconiosis due to asbestos and other mineral fibers
Chronic pulmonary diseases	J62*	Pneumoconiosis due to dust containing silica
Chronic pulmonary diseases	J63*	Pneumoconiosis due to other inorganic dusts
Chronic pulmonary diseases	J64*	Unspecified pneumoconiosis
Chronic pulmonary diseases	J65*	Pneumoconiosis associated with tuberculosis
Chronic pulmonary diseases	J66*	Airway disease due to specific organic dust
Chronic pulmonary diseases	J67*	Hypersensitivity pneumonitis due to organic dust
Chronic pulmonary diseases	J68*	Respiratory conditions due to inhalation of chemicals, gases, fumes and vapors
Chronic pulmonary diseases	J69*	Pneumonitis due to solids and liquids
Chronic pulmonary diseases	J70*	Respiratory conditions due to other external agents
Chronic pulmonary diseases	J80*	Acute respiratory distress syndrome
Chronic pulmonary diseases	J81*	Pulmonary edema
Chronic pulmonary diseases	J82*	Pulmonary eosinophilia, not elsewhere classified
Chronic pulmonary diseases	J84*	Other interstitial pulmonary diseases
Chronic pulmonary diseases	J85*	Abscess of lung and mediastinum
Chronic pulmonary diseases	J86*	Pyothorax
Chronic pulmonary diseases	J95.0*	Tracheostomy complications
Chronic pulmonary diseases	J96*	Respiratory failure, not elsewhere classified
Chronic pulmonary diseases	J98.1*	Pulmonary collapse
Chronic pulmonary diseases	J99*	Respiratory disorders in diseases classified elsewhere
Chronic pulmonary diseases	P25*	Interstitial emphysema and related conditions originating in the perinatal period
Chronic pulmonary diseases	P26*	Pulmonary hemorrhage originiating in perinatal period
Chronic pulmonary diseases	P27*	Chronic respiratory disease originating in the perinatal period
Chronic pulmonary diseases	P28*	Other respiratory conditions originating in perinatal period
Chronic pulmonary diseases	Q33*	Congenital malformations of lung
Chronic pulmonary diseases	T86.3*	Complications of heart-lung transplant
Chronic pulmonary diseases	T86.8*	Complications of lung transplant
Chronic pulmonary diseases	Z94.2*	Lung transplant status
Chronic renal disease	I12*	Hypertensive chronic kidney disease
Chronic renal disease	N01*	Rapidly progressive nephritic syndrome
Chronic renal disease	N02*	Recurrent and persistent hematuria
Chronic renal disease	N03*	Chronic nephritic syndrome

Chronic renal disease	N04*	Nephrotic syndrome
Chronic renal disease	N05*	Unspecified nephritic syndrome
Chronic renal disease	N06*	Isolated proteinuria with specified morphological lesion
Chronic renal disease	N07*	Hereditary nephropathy, not elsewhere defined
Chronic renal disease	N08*	Glomerular disorders in diseases classified elsewhere
Chronic renal disease	N11*	Chronic tubulo-interstitial nephritis
Chronic renal disease	N14*	Drug- and heavy-metal-induced tubulo-interstitial and tubular conditions
Chronic renal disease	N15*	Other renal tubulo-interstitial diseases
Chronic renal disease	N16*	Renal tubulo-interstitial disorders in diseases classified elsewhere
Chronic renal disease	N17*	Acute kidney failure
Chronic renal disease	N18*	Chronic kidney disease
Chronic renal disease	N25*	Disorders resulting from impaired renal tubular function
Chronic renal disease	N26*	Unspecified contracted kidney
Chronic renal disease	N28*	Other disorders of kidney and ureter, not elsewhere classified
Chronic renal disease	Q27.1	Congenital renal artery stenosis
Chronic renal disease	Q27.2	Other congenital malformations of renal artery
Chronic renal disease	Q60*	Renal agenesis and other reduction defects of kidney
Chronic renal disease	Z49*	Encounter for care involving renal dialysis
Chronic renal disease	Z91.15*	Patient's noncompliance with renal dialysis
Chronic renal disease	Z94.0*	Kidney transplant status
Chronic renal disease	Z99.2*	Dependence on renal dialysis
Diabetes Mellitus	E08*	Diabetes mellitus due to underlying condition
Diabetes Mellitus	E09*	Drug or chemical induced diabetes mellitus
Diabetes Mellitus	E10*	Type 1 diabetes mellitus
Diabetes Mellitus	E11*	Type 2 diabetes mellitus
Diabetes Mellitus	E13*	Other specified diabetes mellitus
Diabetes Mellitus	O24*	Diabetes mellitus in pregnancy, childbirth, and the puerperium
Diseases of arteries, arterioles, and capillaries	I71*	Aortic aneurysm and dissection
Diseases of arteries, arterioles, and capillaries	I72*	Other aneurysm
Diseases of arteries, arterioles, and capillaries	I73*	Other peripheral vascular diseases
Diseases of arteries, arterioles, and capillaries	I74*	Arterial embolism and thrombosis
Diseases of arteries, arterioles, and capillaries	I75*	Atheroembolism
Diseases of arteries, arterioles, and capillaries	I76*	Septic arterial embolism
Diseases of arteries, arterioles, and capillaries	I79*	Disorders of arteries, arterioles and capillaries in diseases classified elsewhere
Endocrine disorders	E00*	Congenital iodine-deficiency syndrome
Endocrine disorders	E01*	Iodine-deficiency related thyroid disorders and allied conditions
Endocrine disorders	E03*	Other hypothyroidism
Endocrine disorders	E05*	Thyrotoxicosis [hyperthyroidism]

Endocrine disorders	E06*	Thyroiditis
Endocrine disorders	E15*	Other disorders of glucose regulation and pancreatic internal secretion
Endocrine disorders	E16*	Other disorders of pancreatic internal secretion
Endocrine disorders	E20*	Hypoparathyroidism
Endocrine disorders	E21*	Hyperparathyroidism and other disorders of parathyroid gland
Endocrine disorders	E22*	Hyperfunction of pituitary gland
Endocrine disorders	E23*	Hypofunction and other disorders of the pituitary gland
Endocrine disorders	E24*	Cushing's syndrome
Endocrine disorders	E25*	Adrenogenital disorders
Endocrine disorders	E26*	Hyperaldosteronism
Endocrine disorders	E27*	Other disorders of adrenal gland
Endocrine disorders	E28*	Ovarian dysfunction
Endocrine disorders	E29*	Testicular dysfunction
Endocrine disorders	E31*	Polyglandular dysfunction
Endocrine disorders	E32*	Diseases of thymus
Endocrine disorders	E34*	Other endocrine disorders
Hemoglobinopathies	D55*	Anemia due to enzyme disorders
Hemoglobinopathies	D56.0*	Alpha thalassemia
Hemoglobinopathies	D56.1*	Beta thalassemia
Hemoglobinopathies	D56.2*	Delta-beta thalassemia
Hemoglobinopathies	D56.4*	Hereditary persistence of fetal hemoglobin [HPFH]
Hemoglobinopathies	D56.5*	Hemoglobin E-beta thalassemia
Hemoglobinopathies	D56.9*	Thalassemia, unspecified
Hemoglobinopathies	D57.0*	Hb-SS disease with crisis
Hemoglobinopathies	D57.1*	Sickle-cell disease without crisis
Hemoglobinopathies	D57.2*	Sickle-cell/Hb-C disease
Hemoglobinopathies	D57.4*	Sickle-cell thalassemia
Hemoglobinopathies	D57.8*	Other sickle-cell disorders
Hemoglobinopathies	D58*	Other hereditary hemolytic anemias
Hemoglobinopathies	D59*	Acquired hemolytic anemia
Hemoglobinopathies	D60*	Acquired pure red cell aplasia [erythroblastopenia]
Hemoglobinopathies	D61*	Other aplastic anemias and other bone marrow failure syndromes
Hemoglobinopathies	D64.0*	Hereditary sideroblastic anemia
Hemoglobinopathies	D64.1*	Secondary sideroblastic anemia due to disease
Hemoglobinopathies	D64.2*	Secondary sideroblastic anemia due to drugs and toxins
Hemoglobinopathies	D64.3*	Other sideroblastic anemias
Hemoglobinopathies	D64.4*	Congenital dyserythropoietic anemia
Hemoglobinopathies	D64.8*	Other specified anemias
Hemoglobinopathies	D65*	Disseminated intravascular coagulation [defibrination syndrome]
Hemoglobinopathies	D66*	Hereditary factor VIII deficiency

Hemoglobinopathies	D67*	Hereditary factor IX deficiency
Hemoglobinopathies	D68*	Other coagulation defects
Immunosuppressive disorders	B20*	Human immunodificiency virus (HIV) disease
Immunosuppressive disorders	B59*	Pneumocystosis
Immunosuppressive disorders	B97.3*	Retrovirus as the cause of diseases classified elsewhere
Immunosuppressive disorders	D47.Z1*	Post-transplant lymphoproliferative disorder (PTLD)
Immunosuppressive disorders	D70*	Neutropenia (including agranulocytosis)
Immunosuppressive disorders	D71*	Functional disorders of polymorphonuclear neutrophils
Immunosuppressive disorders	D72*	Other disorders of white blood cells
Immunosuppressive disorders	D73*	Diseases of spleen
Immunosuppressive disorders	D76*	Other specified diseases with participation of lymphoreticular and reticulohistiocytic tissue
Immunosuppressive disorders	D80*	Immunodeficiency with predominantly antibody defects
Immunosuppressive disorders	D81*	Combined immunodeficiencies
Immunosuppressive disorders	D82*	Immunodeficiency associated with other major defects
Immunosuppressive disorders	D83*	Common variable immunodeficiency
Immunosuppressive disorders	D84*	Other immunodeficiencies
Immunosuppressive disorders	D89*	Other disorders involving the immune mechanism, not elsewhere classified
Immunosuppressive disorders	M05*	Rheumatoid arthritis with rheumatoid factor
Immunosuppressive disorders	M06*	Other rheumatoid arthritis
Immunosuppressive disorders	M07*	Enteropathic arthropathies
Immunosuppressive disorders	M08*	Juvenile arthritis
Immunosuppressive disorders	M30*	Polyarteritis nodosa and related conditions
Immunosuppressive disorders	M31*	Other necrotizing vasculopathies
Immunosuppressive disorders	M32*	Systemic lupus erythematosus (SLE)
Immunosuppressive disorders	M33*	Dermatopolymyositis
Immunosuppressive disorders	M34*	Systemic sclerosis [scleroderma]
Immunosuppressive disorders	M35.0*	Sicca syndrome [Sjögren]
Immunosuppressive disorders	M35.9*	Systemic involvement of connective tissue, unspecified
Immunosuppressive disorders	Q89.0*	Congenital absence and malformations of spleen
Immunosuppressive disorders	T45.1X1	Poisoning by antineoplastic and immunosuppressive drugs, accidental(unintentional)
Immunosuppressive disorders	Z21*	Asymptomatic human immunodeficiency virus [HIV] infection status
Immunosuppressive disorders	Z48.2*	Encounter for aftercare following organ transplant
Immunosuppressive disorders	Z51.0*	Encounter for antineoplastic radiation therapy
Immunosuppressive disorders	Z51.1*	Encounter for antineoplastic chemotherapy and immunotherapy
Immunosuppressive disorders	Z94*	Transplanted organ and tissue status
Liver diseases	B18*	Chronic viral hepatitis
Liver diseases	K70*	Alcoholic liver disease
Liver diseases	K71*	Toxic liver disease
Liver diseases	K72*	Hepatic failure, not elsewhere classified
Liver diseases	K73*	Chronic hepatitis, not elsewhere classified

Liver diseases	K74*	Fibrosis and cirrhosis of liver
Liver diseases	K75*	Other inflammatory liver diseases
Liver diseases	K76*	Other diseases of liver
Liver diseases	K77*	Liver disorders in diseases classified elsewhere
Liver diseases	I81*	Portal vein thrombosis
Liver diseases	I85*	Esophageal varices
Long-term medication use	Z79.5*	Long term (current) use of steroids
Long-term medication use	Z79.82*	Long term (current) use of aspirin (*will only be used for those <19 years of age)
Malignancy	C00*	Malignant neoplasm of lip
Malignancy	C01*	Malignant neoplasm of base of tongue
Malignancy	C02*	Malignant neoplasm of other and unspecified parts of tongue
Malignancy	C03*	Malignant neoplasm of gum
Malignancy	C04*	Malignant neoplasm of floor of mouth
Malignancy	C05*	Malignant neoplasm of palate
Malignancy	C06*	Malignant neoplasm of other and unspecified parts of mouth
Malignancy	C07*	Malignant neoplasm of parotid gland
Malignancy	C08*	Malignant neoplasm of other and unspecified major salivary glands
Malignancy	C09*	Malignant neoplasm of tonsil
Malignancy	C10*	Malignant neoplasm of oropharynx
Malignancy	C11*	Malignant neoplasm of nasopharynx
Malignancy	C12*	Malignant neoplasm of pyriform sinus
Malignancy	C13*	Malignant neoplasm of hypopharynx
Malignancy	C14*	Malignant neoplasm of other and ill-defined sites in the lip, oral cavity and pharynx
Malignancy	C15*	Malignant neoplasm of esophagus
Malignancy	C16*	Malignant neoplasm of stomach
Malignancy	C17*	Malignant neoplasm of small intestine
Malignancy	C18*	Malignant neoplasm of colon
Malignancy	C19*	Malignant neoplasm of rectosigmoid junction
Malignancy	C20*	Malignant neoplasm of rectum
Malignancy	C21*	Malignant neoplasm of anus and anal canal
Malignancy	C22*	Malignant neoplasm of liver and intrahepatic bile ducts
Malignancy	C23*	Malignant neoplasm of gallbladder
Malignancy	C24*	Malignant neoplasm of other and unspecified parts of biliary tract
Malignancy	C25*	Malignant neoplasm of pancreas
Malignancy	C26*	Malignant neoplasm of other and ill-defined digestive organs
Malignancy	C30*	Malignant neoplasm of nasal cavity and middle ear
Malignancy	C31*	Malignant neoplasm of accessory sinuses
Malignancy	C32*	Malignant neoplasm of larynx
Malignancy	C33*	Malignant neoplasm of trachea
Malignancy	C34*	Malignant neoplasm of bronchus and lung

Malignancy	C37*	Malignant neoplasm of thymus
Malignancy	C38*	Malignant neoplasm of heart, mediastinum and pleura
Malignancy	C39*	Malignant neoplasm of other and ill-defined sites in the respiratory system and intrathoracic organs
Malignancy	C40*	Malignant neoplasm of bone and articular cartilage of limbs
Malignancy	C41*	Malignant neoplasm of bone and articular cartilage of other and unspecified sites
Malignancy	C43*	Malignant melanoma of skin
Malignancy	C44*	Other and unspecified malignant neoplasm of skin
Malignancy	C45*	Mesothelioma
Malignancy	C46*	Kaposi's sarcoma
Malignancy	C47*	Malignant neoplasm of peripheral nerves and autonomic nervous system
Malignancy	C48*	Malignant neoplasm of retroperitoneum and peritoneum
Malignancy	C49*	Malignant neoplasm of other connective and soft tissue
Malignancy	C4A*	Merkel cell carcinoma
Malignancy	C50*	Malignant neoplasms of breast
Malignancy	C51*	Malignant neoplasm of vulva
Malignancy	C52*	Malignant neoplasm of vagina
Malignancy	C53*	Malignant neoplasm of cervix uteri
Malignancy	C54*	Malignant neoplasm of corpus uteri
Malignancy	C55*	Malignant neoplasm of uterus, part unspecified
Malignancy	C56*	Malignant neoplasm of ovary
Malignancy	C57*	Malignant neoplasm of other and unspecified female genital organs
Malignancy	C58*	Malignant neoplasm of placenta
Malignancy	C60*	Malignant neoplasm of penis
Malignancy	C61*	Malignant neoplasm of prostate
Malignancy	C62*	Malignant neoplasm of testis
Malignancy	C63*	Malignant neoplasm of other and unspecified male genital organs
Malignancy	C64*	Malignant neoplasm of kidney, except renal pelvis
Malignancy	C65*	Malignant neoplasm of renal pelvis
Malignancy	C66*	Malignant neoplasm of ureter
Malignancy	C67*	Malignant neoplasm of bladder
Malignancy	C68*	Malignant neoplasm of other and unspecified urinary organs
Malignancy	C69*	Malignant neoplasm of eye and adnexa
Malignancy	C70*	Malignant neoplasm of meninges
Malignancy	C71*	Malignant neoplasm of brain
Malignancy	C72*	Malignant neoplasm of spinal cord, cranial nerves and other parts of central nervous system
Malignancy	C73*	Malignant neoplasm of thyroid gland
Malignancy	C74*	Malignant neoplasm of adrenal gland
Malignancy	C75*	Malignant neoplasm of other endocrine glands and related structures
Malignancy	C76*	Malignant neoplasm of other and ill-defined sites

Malignancy	C77*	Secondary and unspecified malignant neoplasm of lymph nodes
Malignancy	C78*	Secondary malignant neoplasm of respiratory and digestive organs
Malignancy	C79*	Secondary malignant neoplasm of other and unspecified sites
Malignancy	C7A*	Malignant neuroendocrine tumors
Malignancy	C7B*	Secondary neuroendocrine tumors
Malignancy	C80*	Malignant neoplasm without specification of site
Malignancy	C81*	Hodgkin lymphoma
Malignancy	C82*	Follicular lymphoma
Malignancy	C83*	Non-follicular lymphoma
Malignancy	C84*	Mature T/NK-cell lymphomas
Malignancy	C85*	Other specified and unspecified types of non-Hodgkin lymphoma
Malignancy	C86*	Other specified types of T/NK-cell lymphoma
Malignancy	C88*	Malignant immunoproliferative diseases and certain other B-cell lymphomas
Malignancy	C90*	Multiple myeloma and malignant plasma cell neoplasms
Malignancy	C91*	Lymphoid leukemia
Malignancy	C92*	Myeloid leukemia
Malignancy	C93*	Monocytic leukemia
Malignancy	C94*	Other leukemias of specified cell type
Malignancy	C95*	Leukemia of unspecified cell type
Malignancy	C96*	Other and unspecified malignant neoplasms of lymphoid, hematopoietic and related tissue
Malignancy	D03*	Melanoma in situ
Malignancy	D46*	Myelodyplastic syndromes
Malignancy	Z85*	Personal history of malignant neoplasm
Metabolic diseases (not diabetes)	E70*	Disorders of aromatic amino-acid metabolism
Metabolic diseases (not diabetes)	E71*	Disorders of branched-chain amino-acid metabolism and fatty-acid metabolism
Metabolic diseases (not diabetes)	E72*	Other disorders of amino-acid metabolism
Metabolic diseases (not diabetes)	E74*	Other disorders of carbohydrate metabolism
Metabolic diseases (not diabetes)	E75.2*	Other sphingolipidosis
Metabolic diseases (not diabetes)	E76*	Disorders of glycosaminoglycan metabolism
Metabolic diseases (not diabetes)	E77*	Disorders of glycoprotein metabolism
Metabolic diseases (not diabetes)	E78*	Disorders of lipoprotein metabolism and other lipidemias
Metabolic diseases (not diabetes)	E79*	Disorders of purine and pyrimidine metabolism
Metabolic diseases (not diabetes)	E80*	Disorders of porphyrin and bilirubin metabolism
Metabolic diseases (not diabetes)	E83*	Disorders of mineral metabolism
Metabolic diseases (not diabetes)	E85*	Amyloidosis
Metabolic diseases (not diabetes)	E88*	Other and unspecified metabolic disorders
Metabolic diseases (not diabetes)	E89.1*	Postprocedural hypoinsulinemia
Metabolic diseases (not diabetes)	E89.6*	Postprocedural adrenocortical (-medullary) hypofunction
Morbid Obesity	E66.01*	Morbid (severe) obesity due to excess calories
Morbid Obesity	E66.2*	Morbid obesity with alveolar hypoventilation (pickwickian syndrome)

Morbid Obesity	Z68.4*	Body mass index (BMI) 40 or greater, adult
Neurological/musculoskeletal	H49.81*	Kearns-Sayre syndrome
Neurological/Musculoskeletal	M12.0*	Chronic postrheumatic arthropathy [Jaccoud]
Neurological/Musculoskeletal	M36.0*	Dermato(poly)myositis in neoplastic disease
Neurological/Musculoskeletal	A17.0*	Tuberculoisis meningitis
Neurological/Musculoskeletal	E75.02*	Tay-Sachs disease
Neurological/Musculoskeletal	E75.19*	Other gangliosidosis
Neurological/Musculoskeletal	E75.4*	Neuronal ceroid lipofuscinosis
Neurological/Musculoskeletal	F01*	Vascular dementia
Neurological/Musculoskeletal	F02*	Dementia in other diseases classified elsewhere
Neurological/Musculoskeletal	F03*	Unspecified dementia
Neurological/Musculoskeletal	F71*	Moderate intellectual disabilities
Neurological/Musculoskeletal	F72*	Severe intellectual disabilities
Neurological/Musculoskeletal	F73*	Profound intellectual disabilities
Neurological/Musculoskeletal	F84.2*	Rett's syndrome
Neurological/Musculoskeletal	G10*	Huntington's disease
Neurological/Musculoskeletal	G11*	Hereditary ataxia
Neurological/Musculoskeletal	G12*	Spinal muscular atrophy and related syndromes
Neurological/Musculoskeletal	G13*	Systemic atrophies primarily affecting central nervous system in diseases classified elsewhere
Neurological/Musculoskeletal	G14*	Postpolio syndrome
Neurological/Musculoskeletal	G20*	Parkinson's disease
Neurological/Musculoskeletal	G21*	Secondary parkinsonism
Neurological/Musculoskeletal	G23*	Other degenerative diseases of basal ganglia
Neurological/Musculoskeletal	G24*	Dystonia
Neurological/Musculoskeletal	G25*	Other extrapyramidal and movement disorders
Neurological/Musculoskeletal	G26*	Extrapyramidal and movement disorders in diseases classified elsewhere
Neurological/Musculoskeletal	G30*	Alzheimer's disease
Neurological/Musculoskeletal	G31*	Other degenerative diseases of nervous system, not elsewhere classified
Neurological/Musculoskeletal	G32*	Other degenerative disorders of nervous system in diseases classified elsewhere
Neurological/Musculoskeletal	G35*	Multiple sclerosis
Neurological/Musculoskeletal	G36*	Other acute disseminated demyelination
Neurological/Musculoskeletal	G37*	Other demyelinating diseases of central nervous system
Neurological/Musculoskeletal	G40*	Epilepsy and recurrent seizures
Neurological/Musculoskeletal	G45*	Transient cerebral ischemic attacks and related syndromes
Neurological/Musculoskeletal	G46*	Vascular syndromes of brain in cerebrovascular diseases
Neurological/Musculoskeletal	G60*	Hereditary and idiopathic neuropathy
Neurological/Musculoskeletal	G61*	Inflammatory polyneuropathy
Neurological/Musculoskeletal	G62*	Other and unspecified polyneuropathies
Neurological/Musculoskeletal	G63*	Polyneuropathy in diseases classified elsewhere
Neurological/Musculoskeletal	G64*	Other disorders of peripheral nervous system

Neurological/Musculoskeletal	G70*	Myasthenia gravis and other myoneural disorders
Neurological/Musculoskeletal	G71*	Primary disorders of muscles
Neurological/Musculoskeletal	G73*	Disorders of myoneural junction and muscle in diseases classified elsewhere
Neurological/Musculoskeletal	G80*	Cerebral palsy
Neurological/Musculoskeletal	G81*	Hemiplegia and hemiparesis
Neurological/Musculoskeletal	G82*	Paraplegia (paraperesis) and quadriplegia (quadriparesis)
Neurological/Musculoskeletal	G83*	Other paralytic syndromes
Neurological/Musculoskeletal	G90.3*	Multi-system degeneration of the autonomic nervous system
Neurological/Musculoskeletal	G91*	Hydrocephalus
Neurological/Musculoskeletal	G93*	Other disorders of brain
Neurological/Musculoskeletal	G94*	Other disorders of brain in diseases classified elsewhere
Neurological/Musculoskeletal	G95*	Other and unspecified diseases of spinal cord
Neurological/Musculoskeletal	G99.2*	Myelopathy in diseases classified elsewhere
Neurological/Musculoskeletal	P91*	Other disturbances of cerebral status of newborn
Neurological/Musculoskeletal	Q00*	Anencephaly and similar malformations
Neurological/Musculoskeletal	Q01*	Encephalocele
Neurological/Musculoskeletal	Q02*	Microcephaly
Neurological/Musculoskeletal	Q03*	Congenital hydrocephalus
Neurological/Musculoskeletal	Q04*	Other congenital malformations of brain
Neurological/Musculoskeletal	Q05*	Spina bifida
Neurological/Musculoskeletal	Q06*	Other congenital malformations of the spinal cord
Neurological/Musculoskeletal	Q07*	Other congenital malformations of nervous system
Neurological/Musculoskeletal	Q76*	Congenital malformations of spine and bony thorax
Neurological/Musculoskeletal	Q77*	Osteochondrodysplasia with defects of growth of tubular bones and spine
Neurological/Musculoskeletal	Q78*	Other osteochondrodysplasias
Neurological/Musculoskeletal	Q79*	Congenital malformations of musculoskeletal system, not elsewhere classified
Neurological/Musculoskeletal	Q85*	Phakomatoses, not elsewhere classified
Neurological/Musculoskeletal	Q87.4*	Marfan's syndrome
Neurological/Musculoskeletal	Q90*	Down syndrome
Neurological/Musculoskeletal	Q91*	Trisomy 18 and Trisomy 13
Neurological/Musculoskeletal	Q92*	Other trisomies and partial trisomies of the autosomes, not elsewhere classified
Neurological/Musculoskeletal	Q93*	Monosomies and deletions from the autosomes, not elsewhere classified
Neurological/Musculoskeletal	Q96*	Turner's syndrome
Neurological/Musculoskeletal	R41*	Other symptoms and signs involving cognitivie functions and awareness
Neurological/Musculoskeletal	R53.2*	Functional quadriplegia
Neurological/Musculoskeletal	R54*	Age-related physical debility/frailty
Perinatal	P05*	Disorders of newborn related to slow fetal growth and fetal malnutrition
Perinatal	P07*	Disorders of newborn related to short gestation and low birth weight, not elsewhere classified
Charlson score – Peripheral vascular disease	K55.1*	Chronic vascular disorders of intestine

Charlson score – Peripheral vascular disease	K55.8*	Other vascular disorders of intestine
Charlson score – Peripheral vascular disease	K55.9*	Vascular disorder of intestine, unspecified
Charlson score – Peripheral vascular disease	I70*	Atherosclerosis
Charlson score – Peripheral vascular disease	I77*	Other disorders of arteries and arterioles
Charlson score – Peripheral vascular disease	Z95.8*	Presence of other cardiac and vascular implants and grafts
Charlson score – Peripheral vascular disease	Z95.9*	Presence of cardiac and vascular implant and graft, unspecified
Charlson score – Cerebrovascular disease	I64*	*Code may not exist in US version of ICD10
Charlson score – Cerebrovascular disease	I65*	Occlusion and stenosis of precerebral arteries, not resulting in cerebral infarction
Charlson score – Cerebrovascular disease	I66*	Occlusion and stenosis of cerebral arteries, not resulting in cerebral infarction
Charlson score – Cerebrovascular disease	I67*	Other cerebrovascular diseases
Charlson score – Cerebrovascular disease	H34.0*	Transient retinal artery occlusion
Charlson score – Dementia	F00*	*Code may not exist in US version of ICD10
Charlson score - Dementia	F05.1*	*Code may not exist in US version of ICD10
Charlson score – Chronic pulmonary disease	J40*	Bronchitis, not specified as acute or chronic
Charlson score – Chronic pulmonary disease	J46*	*Code may not exist in US version of ICD10
Charlson score – Chronic pulmonary disease	M35.1*	Other overlap syndromes
Charlson score – Chronic pulmonary disease	M35.3*	Polymyalgia rheumatica
Charlson score – Peptic ulcer disease	K25*	Gastric ulcer
Charlson score – Peptic ulcer disease	K26*	Duodenal ulcer
Charlson score – Peptic ulcer disease	K27*	Peptic ulcer, site unspecified
Charlson score – Peptic ulcer disease	K28*	Gastrojejunal ulcer
Charlson score – Mild liver disease	Z94.4*	Liver transplant status
Charlson score – Diabetes	E12*	*Code may not exist in US version of ICD10
Charlson score – Diabetes	E14*	*Code may not exist in US version of ICD10
Charlson score – Paraplegia	G04.1*	Tropical spastic paraplegia
Charlson score – Renal disease	N19*	Unspecified kidney failure
Charlson score – Malignancy	C97*	*Code may not exist in US version of ICD10
Charlson score – Moderate or severe liver disease	I86.4*	Gastric varices
Charlson score – Moderate or severe liver disease	I98.2*	*Code may not exist in US version of ICD10
Charlson score – Moderate or severe liver disease	K79.9*	*Code may not exist in US version of ICD10
Charlson score – HIV/AIDS	B21*	*Code may not exist in US version of ICD10
Charlson score – HIV/AIDS	B22*	*Code may not exist in US version of ICD10
Charlson score – HIV/AIDS	B24*	*Code may not exist in US version of ICD10
Charlson score – Congestive Heart Failure	P29.0*	Neonatal cardiac failure

Appendix C

MAARI Codes

Code Group	ICD10	Condition
Acute respiratory infections	J00	Acute nasopharyngitis [common cold]
Acute respiratory infections	J01.*	Acute sinusitis
Acute respiratory infections	J02.*	Acute pharyngitis
Acute respiratory infections	J03.*	Acute tonsillitis
Acute respiratory infections	J04.*	Acute laryngitis and tracheitis
Acute respiratory infections	J05.*	Acute obstructive laryngitis [croup] and epiglottitis
Acute respiratory infections	J06.*	Acute upper respiratory infections of multiple and unspecified sites
Acute respiratory infections	J20.*	Acute bronchitis
Acute respiratory infections	J21.*	Acute bronchiolitis
Acute respiratory infections	J22.*	Unspecified acute lower respiratory infection
Acute respiratory infections	B97.4*	Respiratory syncytial virus as the cause of diseases classified elsewhere
Chronic obstructive pulmonary disease and allied conditions	J40.*	Bronchitis, not specified as acute or chronic
Chronic obstructive pulmonary disease and allied conditions	J41.*	Simple and mucopurulent chronic bronchitis
Chronic obstructive pulmonary disease and allied conditions	J42.*	Unspecified chronic bronchitis
Chronic obstructive pulmonary disease and allied conditions	J44.*	Other chronic obstructive pulmonary disease
Chronic obstructive pulmonary disease and allied conditions	J45.*	Asthma
Chronic obstructive pulmonary disease and allied conditions	J43.*	Emphysema
Diseases of ear and mastoid process	H66.0*	Acute suppurative otitis media
Diseases of ear and mastoid process	H66.4*	Suppurative otitis media, unspecified
Diseases of ear and mastoid process	H66.9*	Otitis media, unspecified
Diseases of ear and mastoid process	H67.*	Otitis media in diseases classified elsewhere
Dyspnea and respiratory abnormalities	R06.2	Wheezing
General symptoms	R50.9	Fever, unspecified
General symptoms	R50.81*	Fever presenting with conditions classified elsewhere
General symptoms	R53.81*	Other malaise
General symptoms	R53.83*	Other fatigue
General symptoms	R68.83	Chills (without fever)
Pneumonia and influenza	A37.01	Whooping cough due to Bordetella pertussis with pneumonia
Pneumonia and influenza	A37.11	Whooping cough due to Bordetella parapertussis with pneumonia
Pneumonia and influenza	A37.81	Whooping cough due to other Bordetella species with pneumonia
Pneumonia and influenza	A37.91	Whooping cough, unspecified species with pneumonia
Pneumonia and influenza	B25.0	Cytomegaloviral pneumonitis
Pneumonia and influenza	J09.*	Influenza due to certain identified influenza viruses
Pneumonia and influenza	J10.*	Influenza due to other identified influenza virus
Pneumonia and influenza	J11.*	Influenza due to unidentified influenza virus
Pneumonia and influenza	J12.*	Viral pneumonia, not elsewhere classified

Pneumonia and influenza	J13.*	Pneumonia due to Streptococcus pneumoniae
Pneumonia and influenza	J14.*	Pneumonia due to Hemophilus influenzae
Pneumonia and influenza	J15.*	Bacterial pneumonia, not elsewhere classified
Pneumonia and influenza	J16.*	Pneumonia due to other infectious organisms, not elsewhere classified
Pneumonia and influenza	J17.*	Pneumonia in diseases classified elsewhere
Pneumonia and influenza	J18.*	Pneumonia, unspecified organism
Symptoms involving respiratory system and other chest symptoms	R05	Cough
Symptoms involving respiratory system and other chest symptoms	R06.00*	Dyspnea unspecified
Symptoms involving respiratory system and other chest symptoms	R06.02*	Shortness of breath
Symptoms involving respiratory system and other chest symptoms	R06.1*	Stridor
Symptoms involving respiratory system and other chest symptoms	R06.82*	Tachypnea, not elsewhere classified
Other diseases of upper respiratory tract	J39.8*	Other specified diseases of upper respiratory tract
Other diseases of upper respiratory tract	J39.9*	Disease of upper respiratory tract, unspecified
COVID-19	B34.2	Coronavirus infection, unspecified
COVID-19	J12.89	Pneumonia due to Wuhan coronavirus
COVID-19	B97.29*	Other coronavirus as the cause of diseases classified elsewhere
COVID-19	R68.89	Suspected Wuhan coronavirus infection, but also “Other general symptoms and signs”
COVID-19	Z20.828	Exposure to Wuhan coronavirus
COVID-19	Z03.818*	COVID-19 Test ordered/pending and clinically unsure
COVID-19	U07.1*	Patients clinically suspected to have COVID-19 illness or asymptomatic COVID-19 test-positive patients

Appendix D

Antiviral NDC Numbers

NDC	Proprietary Name	Non-Proprietary Name	Company Name
42291-664	Oseltamivir Phosphate	Oseltamivir	Avkare, Inc.
42291-666	Oseltamivir Phosphate	Oseltamivir	Avkare, Inc.
47781-468	Oseltamivir Phosphate	Oseltamivir Phosphate	Alvogen Inc.
47781-469	Oseltamivir Phosphate	Oseltamivir Phosphate	Alvogen Inc.
47781-470	Oseltamivir Phosphate	Oseltamivir Phosphate	Alvogen Inc.
53217-280	Oseltamivir Phosphate	Oseltamivir Phosphate	Aidarex Pharmaceuticals Llc
68071-3105	Oseltamivir Phosphate	Oseltamivir Phosphate	Nucare Pharmaceuticals, Inc.
68071-3385	Oseltamivir Phosphate	Oseltamivir Phosphate	Nucare Pharmaceuticals,inc.
69238-1264	Oseltamivir Phosphate	Oseltamivir	Amneal Pharmaceuticals Llc
69238-1265	Oseltamivir Phosphate	Oseltamivir	Amneal Pharmaceuticals Llc
69238-1266	Oseltamivir Phosphate	Oseltamivir	Amneal Pharmaceuticals Llc
70710-1008	Oseltamivir Phosphate	Oseltamivir Phosphate	Zydus Pharmaceuticals Inc.
70710-1009	Oseltamivir Phosphate	Oseltamivir Phosphate	Zydus Pharmaceuticals Inc.
70710-1010	Oseltamivir Phosphate	Oseltamivir Phosphate	Zydus Pharmaceuticals Inc.
0004-0800	Tamiflu	Oseltamivir Phosphate	Genentech, Inc.
0004-0801	Tamiflu	Oseltamivir Phosphate	Genentech, Inc.
0004-0802	Tamiflu	Oseltamivir Phosphate	Genentech, Inc.
0004-0822	Tamiflu	Oseltamivir Phosphate	Genentech, Inc.
42254-001	Tamiflu	Oseltamivir Phosphate	Rebel Distributors Corp
42254-092	Tamiflu	Oseltamivir Phosphate	Rebel Distributors Corp
52125-307	Tamiflu	Oseltamivir Phosphate	Remedyrepack Inc.
54868-4476	Tamiflu	Oseltamivir Phosphate	Physicians Total Care, Inc.
54868-6083	Tamiflu	Oseltamivir Phosphate	Physicians Total Care, Inc.
54868-6315	Tamiflu	Oseltamivir Phosphate	Physicians Total Care, Inc.
55045-2759	Tamiflu	Oseltamivir Phosphate	Dispensing Solutions, Inc.
55045-3198	Tamiflu	Oseltamivir Phosphate	Dispensing Solutions, Inc.
61364-181	Rapivab	Peramivir	Biocsl Inc.
0173-0681	Relenza	Zanamivir	Glaxosmithkline
54868-4377	Relenza	Zanamivir	Physicians Total Care, Inc.
68258-3030	Relenza	Zanamivir	Dispensing Solutions, Inc.
50242-828-02	Xofluza	Baloxavir Marboxil	Genentech, Inc.
50242-828-04	Xofluza	Baloxavir Marboxil	Genentech, Inc.
50242-860-01	Xofluza	Baloxavir Marboxil	Genentech, Inc.
50242-860-02	Xofluza	Baloxavir Marboxil	Genentech, Inc.

Appendix E

Human Sera Collection Guidelines for Influenza Serology

Influenza Division
Centers for Disease Control and Prevention

Collection Details

1. For influenza serology using human sera, we suggest collecting the following volumes of whole blood:

Category	Age of blood donor	Volume of blood to collect*
Pediatric	Less than 3 years old	5.0 ml (≥1.5ml)
Children	3 through 11 years old	5-10.0 ml (≥3ml)
Teens, adults, and elderly	12 years and older	≥10.0 ml (≥3ml)

Sera may be tested in multiple assays and potentially with multiple viruses.

*In general, while the above volumes are preferred, smaller volumes can be accepted, if the situation does not allow for the collection of these amounts, e.g. for infants and young children. Collect 2 x 10mL tubes of blood.

2. Use tubes designated for the collection of serum, not plasma. We suggest the use of vacutainer tubes. The following vacutainer tubes are acceptable:

a. glass red top vacutainer tubes
b. plastic red top vacutainer tubes with clot activator
c. plastic gold top serum separator tubes (SST) with clot activator and gel

3. For testing of serum samples in influenza serology assays, it is very important to minimize hemolysis. Hemolyzed serum often has a negative impact on the cells in the influenza microneutralization assays. To minimize hemolysis, the use of a butterfly needle connected to a vacutainer tube is recommended for blood collection (Barnaby DP et al., 2016; Wollowitz A et al., 2013). The butterfly needle is a safe one-way system with blood being delivered into sealed vacutainer with a consistent pressure flow. The only source of possible hemolysis with this system is if the needle in the vein scrapes against vein wall and blood cells break up as they enter the needle bore. However, if butterfly needles are not available, the use of a needle that connects directly to the vacutainer tube is acceptable as an alternative.

Sera Collection and Storage Recommendations

1. Depends on the types of serum collection tubes used, follow manufacturer's instructions for the serum collection. In general, immediately after blood collection, gently invert the tubes several times to reach a proper mix. Do not shake the tubes. Vigorous mixing may cause foaming or hemolysis. Insufficient mixing or delayed mixing in serum tubes may result in delayed clotting. Collected blood should be stored at 4°C immediately. This can be done by placing the sample on ice, in a 4°C refrigerator, or in a cooler with cold packs.

2. Allow the blood to fully clot (minimum 30 min -1 hour depending on the tubes used). It is recommended that clotted blood be centrifuged immediately to separate from serum. Depends on the types of tubes used, follow manufacture's recommendations for centrifugation speed. For example, BD vacutainer SST tubes can be centrifuged at 1100 to 1300g for 10 minutes in swing-head units or 15 minutes in fixed angle centrifugation units (balance the tubes in the centrifuge). After centrifugation, transfer the serum to a clean tube, the clotted blood may be discarded.

Note: after the blood fully clots, it is recommended that blood be centrifuged immediately (within 2 hours) to separate clotted blood from serum. Only in rare scenarios if centrifugation is not immediately available at the site of the blood collection, blood may be stored at 4°C for up to 18 hours (though less ideal) prior to centrifugation.

3. Serum should be aliquoted into smaller volumes in labeled tubes to avoid repeated freeze-thaw. After aliquoting, serum samples should be immediately stored frozen at -20°C or colder. Aliquots can be prepared at either 1mL or 2 mL sizes depending on the site's storage capacity. At least 3 aliquots per specimen should be prepared.

Note: Sera can be stored at 4C for no more than 24 hours if not able to aliquot and freeze immediately.

Questions regarding the sera collection for influenza serology can be addressed to:
Dr. Min Levine
Influenza Division
Centers for Disease Control and Prevention
Email: MLevine@cdc.gov
Office: 404-639-3504

Shipping Guidelines
All shipments should be made via overnight carrier, to ensure delivery within 24 hours of shipment. All serum shipments should be packed with sufficient dry ice to ensure that samples remain frozen for a minimum of 48 hours after shipment. Send serum samples to:

CDC - Influenza Serology
Attn: Dr. Min Levine / Ms. Lauren Horner
Bldg. 23, Room 8451
1600 Clifton Road, NE
Atlanta, GA 30329
Phone: 404-639-3504/404-639-4130

Send shipping questions and tracking info to: MLevine@cdc.gov/ lyz9@cdc.gov.

References:

Barnaby DP et al. Generalizability and Effectiveness of Butterfly Phlebotomy in Reducing Hemolysis. Acad Emerg Med. 2016 Feb;23(2):204-7. 2016 Jan 14.

Wollowitz A et al. Use of butterfly needles to draw blood is independently associated with marked reduction in hemolysis compared to intravenous catheter. Acad Emerg Med. 2013 Nov;20(11):1151-5.

Appendix F

BD Vaccutainer® CPT Tube-based PBMC Isolation and Cryopreservation Protocol

Influenza Division
Centers for Disease Control and Prevention

For CMI studies, we suggest collecting the following volumes of whole blood.

Category	Age of blood donor	Volume of blood to collect*
Pediatric	Less than 3 years old	5.0 ml
Children	3 through 11 years old	5-10.0 ml (≥5ml)
Teens, adults, and elderly	12 years and older	≥10.0 ml (≥5ml)

Reagents and Materials:

- Sterile PBS without calcium and magnesium (ThermoFisher, Cat#10010023)
- Fetal Bovine Serum, heat inactivated (FBS, GE Healthcare, Cat #SH30070.03HI)
- Dimethyl Sulfoxide (DMSO, Sigma, Cat #D2650)
- ViaStain™ AOPI Staining Solution (Nexcelom, Cat# CS2-0106-5ml)
- Trypan Blue
- 50 ml conical centrifuge tubes (Fisher Scientific, Cat #14-959-49A2098)
- BD Vacutainer® CPT™ tube (BD Bioscience, Cat #362761)
- Cryovial, (Nalgene labware, Cat #5000-0020)
- Mr. Frosty (Nalgene Labware, Cat, #5100-0001)
- Cardboard Cryo freezer boxes (Fisher Scientific, Cat #03-395-464)
- INCYTO C-Chip disposable hemocytometer (Fisher Scientific, Cat# DHCN015)
- 10 ml pipettes
- Sharps disposable container

Equipment:

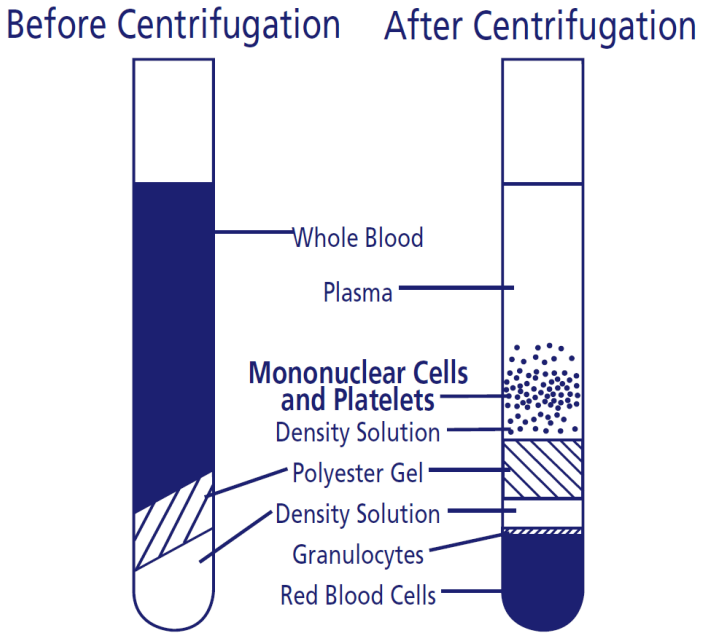
- Centrifuge with swing-out bucket rotor (Sorvall Legend RT)
- Biosafety cabinet (BSC)
- -80°C and liquid nitrogen freezer

Important notes:

1. All work needs to be performed under the biosafety cabinet using sterile technique.
2. Process the blood the same day it is collected: collect on the morning and process afternoon.
3. After collection keep and process samples at room temperature.

Procedure:

1. Prepare freezing medium: 90% FBS, 10% DMSO. Keep at 4^0C. The freezing medium can be kept at 4^0C for a week.
2. Remix the blood sample immediately prior to centrifugation by gently inverting the tube 8 to 10 times.
3. Centrifuge the blood sample in CPT tubes at 1600g for 15 min at ROOM TEMPERATURE (acceleration 9, Deceleration 1, keep the brake OFF).
   BALANCE THE BUCKETS.
   USE BUCKET LIDS.
   DO NOT CENTRIFUGE CPT TUBE OVER 2000g AS IT MAY CAUSE TUBE BREAKAGE.
4. After centrifugation you should be able to see the following layers and it is normal to see some red cells in or above the gel plug of the CPT tube after centrifugation in some donors. Collection of cells immediately following centrifugation will yield best results.



5. Carefully open the CPT tube, remove the upper plasma layer by pipetting. DO NOT DISTURB the mononuclear cell layer.
6. Using a 10ml pipette, gently collect the PBMCs from the interface and transfer to a clean 50ml conical tube. Avoid vigorous pipetting that would disintegrate the gel plug itself. Combine PBMC layers from 3-6 CPT tubes into one 50ml tube.
7. Add 1X PBS to bring the volume up to 50ml and mix cells by inverting tubes 3-5 times.
8. Centrifuge at 1500rpm for 10 min at RT. Keep the break ON. Pour off the supernatant without disturbing the pellet.
9. Re-suspend cell pellet by gently tapping tube with index finger. Add 50ml PBS and mix cells by inverting tubes 3-5 times; take 20µl aliquot for cell count.

10. Count viable and dead cells by of the following methods. Calculate total number of cells and viability.

    a. Count Trypan Blue-treated cells suspension with hemocytometer under the microscopy.
       - Mix 20µl cell suspension with 20µl of 0.4% Trypan blue.
       - Fill INCYTO C-Chip hemocytometer chamber with 10µl of the mix and allow suspension to settle for at least 10 sec before counting.
       - Count live cells in the four large corner squares. Include cells that touch either the top line or left vertical perimeter line of any corner square. Do not count any cells that touch either the bottom line or right vertical perimeter line of any corner square.
       - Use the formula below to calculate the cell number per ml:
         Viable cells/ml = [(corner 1+corner 2+corner 3+corner 4)/4] $x10^4$ x2/ml

    b. Count using Nexcelom Cellometer after staining cells with AOPI.
       - Mix 20µl cell suspension with 20µl of AOPI.
       - Fill chamber with 20µl of the mix and allow suspension to settle for at least 10 sec before counting.

11. Centrifuge at 1500rpm for 10min at RT. Keep the break ON. Discard the supernatant without disturbing the pellet.
12. Re-suspend the cell pellets by tapping the tube with your finger until no clumps are visible.
13. After re-suspending the cell pellet by tapping, slowly re-suspend cells at 0.5-1.0 $x10^7$ cells/mL in freezing medium by adding drop-by-drop of the solution over several minutes. To mix the cells, gently pipette up and down.
14. Slowly dispense 1 mL cell suspension per cryovial.
15. Label cryovial with the following information:
    - Subject number
    - Study name
    - Visit number(v1,v2, v3) or day post vaccination (d0 , d7, d28)
    - Date cells were frozen
    - Number of cells
16. Place the cryovials in a “Mr. Frosty” container and place immediately at -80^0C to allow for a slow freeze. Cells/cryovials should be kept at a minimum of 24 hours and a maximum of 72 hours at -80^0C.
17. Transfer the cryovial for long term storage into liquid nitrogen tank.

Questions regarding the PBMC collection and documentation can be addressed to:

Dr. Weiping Cao/ Ms. Rita Mishina
Influenza Division
Centers for Disease Control and Prevention
Email: jgz9@cdc.gov or vvn6@cdc.gov
Phone: 404-639-5443 or 404-639-4125

Shipping Guidelines

All shipments should be made via overnight carrier, to ensure delivery within 24 hours of shipment. All PBMC shipments should be coordinated with Dr. Weiping Cao / Ms. Margharita Mishina who will provide shipper to send PBMC in liquid nitrogen. The PBMC samples in liquid N2 shipper should be sent to

Centers for Disease Control Influenza Division
Attn: Dr. Weiping Cao / Ms. Margarita Mishina
Bldg. 17, Room 5230
1600 Clifton Road, NE
Atlanta, GA 30329
Phone: 404-639-5443/404-639-4125

Send shipping questions and tracking info to: Dr. Weiping Ca0o (jgz9@cdc.gov)/ Margarita Mishina (vvn6@cdc.gov).