Protocol

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

Protocol for: Thompson MG, Stenehjem E, Grannis S, et al. Effectiveness of Covid-19 vaccines in ambulatory and inpatient care settings. N Engl J Med. DOI: 10.1056/NEJMoa2110362

This supplement contains the following items:

1. Original protocol, final protocol, summary of changes.

2. Original statistical analysis plan, final statistical analysis plan, summary of changes

Initial Protocol

Virtual Network: Investigating the Risk of Influenza-Associated Outcomes and Influenza Vaccine Effectiveness Using Integrated Medical and Public Health Records (VISION) with COVID-19 related addendum

Centers for Disease Control and Prevention

& Westat

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1.0 Study Summary

1.1 Title of Study

Investigating the Risk of Influenza-Associated Outcomes and Influenza Vaccine Effectiveness Using Integrated Medical and Public Health Records

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1.3 Protocol Rationale

This project will create new collaborations among multiple health systems to pilot and understand the use and limitations of existing medical, laboratory, pharmaceutical, and vaccination records for conducting research on influenza. Once established, the network of collaborating sites can address gaps in our understanding of the risk of severe influenza virus infection, its complications, and the effectiveness of influenza vaccination. Furthermore, the joint information captured across the participating sites will enable us to explore and understand how the risk of influenza and the effectiveness of influenza vaccination may differ among people of different ages and among those with underlying medical conditions.

The COVID-19 associated addendum to this protocol (see Appendix G) will extend the current network and associated research data platform (RDP) to capture the data needed to both

retrospectively and prospectively examine some of the most difficult-to-study populations, who may experience some of the most extreme outcomes associated with COVID-19. This addendum will apply our established “virtual network” approach and refine our current methodology to address multiple research questions regarding severe SARS-CoV-2-associated outcomes among high-risk groups to better understand the disease burden of SARS-COV-2 infection, its complications and the trajectory of illness in those with severe COVID-19 illness. Furthermore, building on the current influenza platform, the joint information captured across the participating sites will enable us to explore and understand the impact that circulating SARS-CoV-2 might have on influenza illness and associated vaccination coverage.

1.4 Protocol Objectives

Network objectives

We aim to develop a multi-site collaboration to better utilize existing medical and public health records to address key research questions for influenza prevention and control. We will build retrospective cohorts of individuals, identify individuals within the cohorts that are at high risk of influenza complications, determine whether individuals within the cohorts have been vaccinated for influenza, and enumerate laboratory-confirmed influenza-associated events. This effort consists of primary objectives centered on assessing the appropriateness of cohort definitions, assessing validity and biases present in extracted data, and analyzing the data to answer key initial research questions. After these primary goals are met, a set of secondary objectives will be addressed with a deeper level of data collection or analysis. Funding of data collection or analysis for these secondary objectives will depend on resources and may involve single study sites or combinations of some but not necessarily all participating sites.

For the COVID-19 related study addendum, we will leverage the existing network and data collection platform to extract existing medical and public health records to address key research questions about the incidence of COVID illness and its complications among high risk individuals, utilizing medical, laboratory, pharmacy, and vaccination records. We will build prospective cohorts of individuals, identify individuals within the cohorts that are at high risk of complications related to SARS-CoV-2 infection, and enumerate clinical signs and symptoms, severe outcomes, and the care trajectory associated with COVID-19 among those individuals most at risk for severe outcomes.

Analytic objectives

We aim to determine the validity of and biases generated from different definitions used to construct retrospective cohorts from EHR data, determine the validity of these data on influenza vaccination for the current season and prior seasons, and explore the frequency and patterns of testing for influenza and other respiratory viruses among inpatients and outpatients, and evaluate biases that may come from using information from clinician-driven testing in epidemiologic studies. We will then build upon the information gained in the first objectives to measure incidence of health outcomes related to influenza and estimate the effectiveness of current season influenza vaccination in preventing severe influenza-associated outcomes (e.g. hospitalization, intensive care unit admission) by age groups, influenza type/subtype, and high-risk conditions.

1.5 Methods Summary

To fulfill the network aims each site will construct patient cohorts based on care seeking and if possible health insurance enrollment criteria and extract select demographic, health system utilization, medical, laboratory, pharmaceutical, and vaccination records from electronic health

records for each retrospective study period. Study periods are defined by influenza seasons. Each site will determine the number of years for which they will contribute data, or the period of time in which records are robust enough for cohort identification, beginning as early as the 2010/11 influenza season.

Retrospective cohorts will be defined among individuals within the health system who would visit an outpatient provider or would be hospitalized within the health system if s/he had an influenza virus infection that required hospitalization. A cohort will be defined for each influenza season during the retrospective surveillance period. Influenza season will be broadly defined from September 1 of a year through May 31 of the following year. For analysis, influenza seasons can be more narrowly defined by the frequency of influenza positive test results within the health system. Separate pediatric and adult cohorts will be defined.

For each individual in each of the cohorts, information will be extracted from medical and public health records. Each site will contribute individual-level, but limited, data for the primary analytic objectives. For assessing risk of influenza-associated outcomes, we expect to calculate rates of influenza-positive respiratory hospitalizations among persons at risk of influenza during the season. We intend to calculate rates stratified by age group, high risk underlying conditions, current season vaccination status, current and prior season vaccination status, and other stratifications as suggested by the collaborating network. We will further estimate influenza vaccine effectiveness against influenza-associated respiratory hospitalization and other associated outcomes, both overall and stratified by high-risk conditions. Possible further analytic objectives may be pursued given resources and successful completion of the primary objectives.

2.0 Abbreviations

ARI – Acute respiratory illness

CDC – Centers for Disease Control and Prevention

CPT – Common procedural terminology

EHR – Electronic health record

HIPAA - Health Insurance Portability and Accountability Act

ICD – International Classification of Diseases

ICU – Intensive care unit

RSV – Respiratory syncytial virus

RT-PCR – Reverse transcription polymerase chain reaction

VE – Vaccine effectiveness

3.0 Background Information

Annual influenza vaccination remains the best way to protect against influenza virus infection and associated complications. Each year, the Centers for Disease Control and Prevention (CDC) engages in surveillance and research activities dedicated to estimating the burden of influenza and the effectiveness of seasonal influenza vaccination. While the existing surveillance and research networks are large, encompassing catchment areas of millions or enrolling many thousands of patients with respiratory illness each year, they are not designed to capture the incidence of influenza or the effect of influenza vaccination among people at high-risk of complications nor for rare, yet severe outcomes. Other respiratory viruses also circulate in the United States during the influenza season and sporadically cause widespread illness, contributing to the number of hospitalizations and intensive care unit (ICU) admissions during the winter months in the United States.

This network of health systems is being developed to pilot and understand limitations in the use of existing medical, laboratory, pharmaceutical, and vaccination records for conducting research on complications of influenza and other respiratory virus infections and influenza vaccine effectiveness (VE) against complications of influenza. Ultimately, the network will be able to estimate and further understand the risk of severe outcomes associated with influenza and other respiratory viruses in the general population and among those at high risk of complications. Furthermore, this network can be leveraged to help us understand how seasonal influenza vaccination mitigates several influenza complications.

3.1 Scientific Background

Burden of influenza

Influenza continues to be of global public health importance due to the burden of influenza disease across age groups and among individuals with chronic conditions who are at high risk for severe influenza-related outcomes. Annually in the United States, influenza viruses result in millions of illnesses, hundreds of thousands of hospitalizations, and tens of thousands of deaths.[1 2]

While all people are susceptible to influenza virus infection, young children, older adults, and people with underlying medical conditions are particularly vulnerable and account for the majority of influenza-associated morbidity and mortality each year.[3 4] Routine surveillance for hospitalizations with laboratory-confirmed influenza conducted in the United States show that 82–94% of adults and 34–59% of children hospitalized with influenza each season have an underlying medical condition.[5] In fact, across the seasons, people with underlying conditions account for >90% of flu-hospitalizations.[6] A recent population-based study in Auckland, New Zealand, found increased influenza-related hospitalizations among individuals with chronic

medical conditions including congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), coronary artery disease (CAD), and end-stage renal disease (ESRD) among others.[7] [8] Aside from this study in New Zealand, there are limited data on the actual incidence of severe influenza-related events among those at highest risk.

Influenza vaccine effectiveness to prevent severe influenza

Influenza vaccination is the most important public health strategy to prevent influenza illness and vaccination is recommended annually for all people aged 6 months or older in the United States.[9] However, influenza VE varies from season to season, and across different age and risk groups.[10] A growing body of research points to the effectiveness of influenza vaccination in preventing influenza-associated hospitalizations and other severe outcomes, such as admission to the ICU and in-hospital death.[11] [12] [13] [14] [15] While these studies have begun to explore the benefits of vaccination in reducing the risk of influenza-related severe outcomes, with some studies suggesting that the vaccine is more effective in reducing severe disease than reducing infection[16], the data are largely inconclusive as most are insufficiently powered or not designed to examine and stratify VE by high-risk groups, including children, older adults and those with chronic conditions.

Of the recent studies, Thompson, et al., examined hospitalized adults over multiple influenza seasons found that influenza vaccination decreased influenza-related hospitalizations by 37%, and reduced ICU admission for influenza-related complications by 82%.[17] Analysis of influenza-positive hospitalized adults in the United States also suggests 37% reduction in odds of ICU admission among those vaccinated for influenza.[18] Similarly, studies have shown that influenza vaccination can decrease children's risk of admission to the pediatric intensive care unit by as much as 74% [19] and influenza-associated mortality by 65%.[20] Studies of influenza VE

among those at high risk for influenza-associated complications are rare, with the exception being pregnant women for whom several studies have demonstrated effectiveness of influenza vaccination against influenza infection during pregnancy and in the neonate.[21] [22] [23]

Burden of other respiratory viruses

Respiratory viruses, such as respiratory syncytial virus (RSV), adenoviruses, rhinoviruses, enteroviruses, parainfluenza viruses, and coronaviruses, commonly circulate in the United States and contribute to the, so-called, "cold and flu" season. RSV is a common cause of lower respiratory tract infection in young children and the elderly, resulting in substantial numbers of hospitalizations in the United States and globally.[24] More recently in late 2019 and early 2020, the emergence of a novel coronavirus (SARS-CoV-2) resulted in a pandemic. This collaborative network is uniquely poised to address questions about the occurrence and severity of numerous respiratory viruses, including newly emerging viruses.

3.2 Rationale and Justification

Each year CDC communicates with the public about the burden of influenza and the importance of influenza vaccination and other prevention and control measures. People get vaccinated for influenza in part because they perceive the risk of influenza to the health of themselves and their family to be high and they perceive that the influenza vaccine is effective. Part of CDC's mission is, then, to empower people by using information and data to protect themselves and their family from influenza.

This mission drives the need to measure the incidence of severe health outcomes related to influenza in a variety of groups, including among pediatric and adult age groups, and by high-risk conditions. Furthermore, it is imperative to understand the effectiveness of influenza vaccination against rare, but severe, complications of influenza in the general population and

also among people with underlying medical conditions. These data are essential to supporting the communication messages that CDC and other public health entities rely on to keep people safe from influenza each year.

To effectively estimate the full burden of severe influenza and address these needs, annual retrospective cohorts of individuals will be constructed from a network of large health systems. Within each cohort, individuals can be linked with their vaccination records and their clinical data can be queried to estimate the incidence of outcomes of interest, including influenza-related hospitalizations and outpatient visits. Building each cohort from clinically available data within health systems that integrate, or link, medical records across an individual's medical encounters will enable the analysis to be stratified by underlying medical conditions. Furthermore, joining multiple health systems together will provide the statistical power to investigate less common underlying conditions or clinical outcomes, like ICU admission.

3.3 Expected Benefits

There are no direct benefits to patients whose data contribute to this study. There may be future indirect benefits to the populations of the participating health systems, especially those with risk factors for severe illness from influenza. For example, information from this study may allow for the examination of less common underlying conditions, which to date, have been difficult to examine with statistical precision. These data may influence vaccination strategies for high risk groups which may improve future outcomes for children, elderly adults, and others with high risk conditions. In addition, understanding factors that put individuals at higher risk for influenza-associated hospitalization may help in developing and improving prevention and treatment guidelines.

4.0 Study Objectives

We aim to develop a multi-site collaboration to better utilize existing medical and public health records to address key research questions for influenza prevention and control. We will build retrospective cohorts of individuals, identify individuals within the cohorts that are at high risk of influenza complications, determine whether individuals within the cohorts have been vaccinated for influenza, and enumerate laboratory-confirmed influenza-associated events. This effort consists of primary objectives centered on methodological goals and initial research questions.

4.1 Primary Objectives

1. Assess the validity and biases associated with defining the source population based on care-seeking.
    - Compare characteristics of the different cohorts, as defined above, assessing differences in the demographics, the frequency of underlying high-risk conditions, and the frequency of respiratory hospitalizations during influenza season.
2. Assess internal and external validity of influenza vaccination data for current and prior seasons.
    - Internal validity:
        - Assess the accuracy of the derived vaccine status variable in relation to a manual review of records on a subset of the cohort.
        - Describe the contributions to the overall conclusion about vaccination status by various sources from which vaccination data were obtained.
        - Describe the consistency of vaccination data that are available by data source, including date of vaccination, vaccine type, vaccine route, vaccine

lot number, setting in which vaccine was administered, number of doses of vaccine (children <9 years).

- Describe completeness of vaccination data (e.g. date of vaccination, type of vaccine, lot number) by data source for the current season and prior seasons.

- External validity:
  - Compare vaccine coverage and data completeness to values reported from other studies with active enrollment / prospective data collection.

3. Assess biases associated with clinical testing for influenza and other respiratory viruses and whether they differ in the inpatient versus outpatient setting:
   - Assess the accuracy of the extracted test dates, types, and results in relation to a manual review of records on a subset of the cohort.
   - Estimate proportion of cohort enrollees tested for influenza and other respiratory viruses during the influenza season.
   - Describe types of influenza and other respiratory virus tests performed on cohort enrollees by pediatric and adult age groups and how test types vary by setting.
   - Estimate the proportion of respiratory hospitalizations tested for influenza during the influenza season and factors associated with influenza testing in the inpatient setting including age, high-risk conditions, current season influenza vaccination status, ICU stay, timing of encounter within season, diagnoses codes.
   - Estimate the proportion of outpatient visits for acute respiratory illness (ARI) that were tested for influenza and factors associated with influenza testing in the outpatient setting including age, high-risk conditions, current season influenza

vaccination status, visit type, timing of encounter within influenza season, diagnoses codes.

4. Measure the incidence of health outcomes related to influenza by pediatric and adult age groups as outlined below. The incidence of these outcomes will be assessed by age groups, demographic characteristics, influenza type/subtype, and high-risk conditions:
    - Laboratory confirmed influenza-associated respiratory hospitalizations.
    - ICU admission among persons with laboratory-confirmed influenza-associated respiratory hospitalizations.
    - Invasive mechanical ventilation use among persons with laboratory-confirmed influenza-associated respiratory hospitalizations.
    - In-hospital death among persons with laboratory-confirmed influenza-associated respiratory hospitalizations.
    - Laboratory-confirmed influenza among persons with outpatient visits for acute respiratory illness.
5. Estimate the effectiveness of current season influenza vaccine in preventing the below outcomes by age groups, influenza type/subtype, and high-risk conditions:
    - Laboratory confirmed influenza-associated respiratory hospitalizations (all ages).
    - ICU admission among persons with laboratory-confirmed influenza associated respiratory hospitalizations (all ages).
    - Laboratory-confirmed influenza among persons with outpatient visits for acute respiratory illness (pediatrics; adults if outpatient influenza testing permits).

Appendix A presents the main outcomes, exposures, and modifiers of interest for the primary and secondary study objectives. Appendix B provides the data dictionary of analytic variables needed to meet these objectives.

4.2 Secondary Objectives

After these primary goals are met, a set of secondary objectives will be addressed with a deeper level of data collection or analysis. Funding of data collection or analysis for these secondary objectives will depend on resources and may involve single study sites or combinations of some but not necessarily all participating sites.

- Assess feasibility of defining underlying high risk conditions using a combination of ICD codes, medications, and laboratory data.
- Assess whether specific forms of immunosuppression or use of immunosuppressive medications may increase the risk of severe influenza-associated outcomes and/or reduce influenza VE.
- Among children, examine the association between the number and timing of priming doses with the VE against outcomes of interest in subsequent seasons.
- Examine the association between prior season vaccinations on current season VE.
- Determine measures of disease severity at hospital admission using data on signs and symptoms, vital signs and lab findings and assess their impact on measures of VE.
- Measure the incidence of secondary outcomes following influenza-related hospitalization, including hospital readmissions, rehabilitation and long-term care, post-discharge death.
- Collect data prospectively during an ongoing influenza season to produce within-season estimates of influenza VE.

5.0 Methods

5.1 Study Design

All sites will define retrospective seasonal cohorts of adults and children, which are intended to include all individuals within the health system who would be hospitalized or seek outpatient care within that health system if they had an influenza virus infection that required hospitalization. Among all individuals in the retrospective cohort, medical, laboratory, and vaccination records will be extracted to assess the primary study objectives.

The influenza season will be defined as the time between September 1 of a year and May 31 of the subsequent year. For example, the 2015–2016 influenza season begins on September 1, 2015 and ends after May 31, 2016. Each study site will determine the number of previous influenza seasons (considering seasons between 2010/11 and 2018/19) for which their site will contribute data, depending on the availability and quality of electronic health record (EHR) data in their health system. Adult and pediatric cohorts will be analytically defined for each influenza season for which a site contributes data. Cohorts will be followed up for the duration of each influenza season to meet the primary objectives.

Figures 1 and 2 display the high-level study design for the primary hospitalization and outpatient outcomes, respectively.

Figure 1. High-level study design for hospitalization outcomes

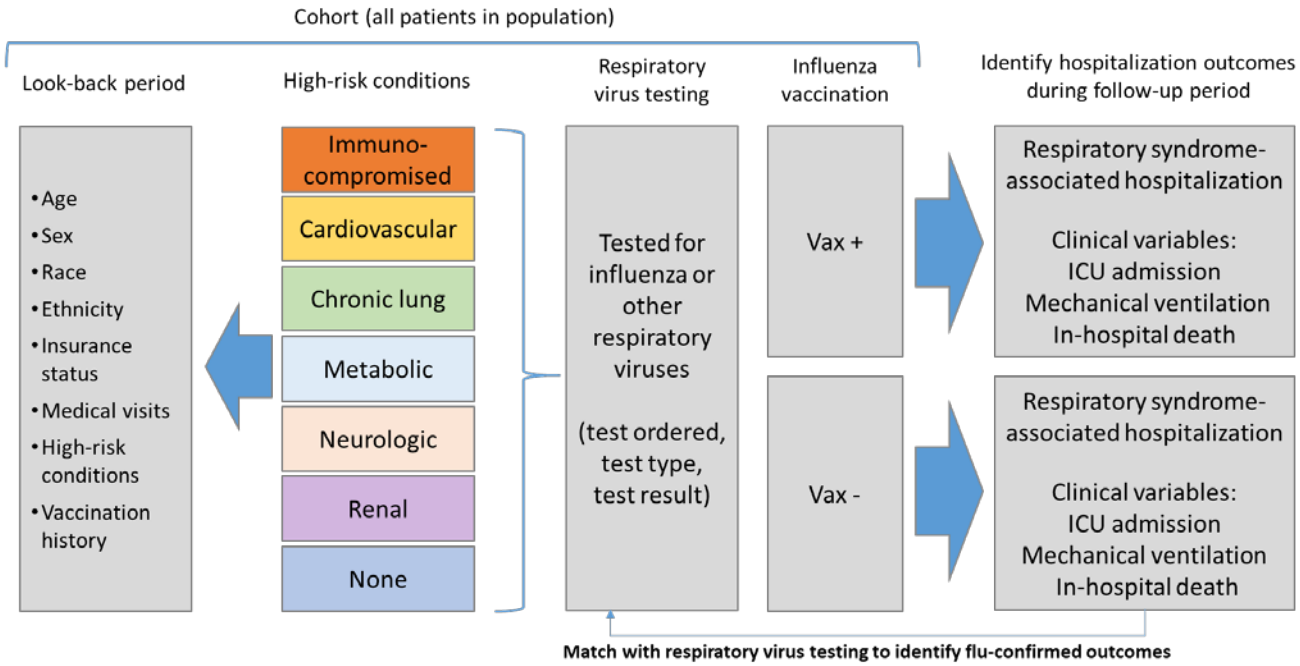
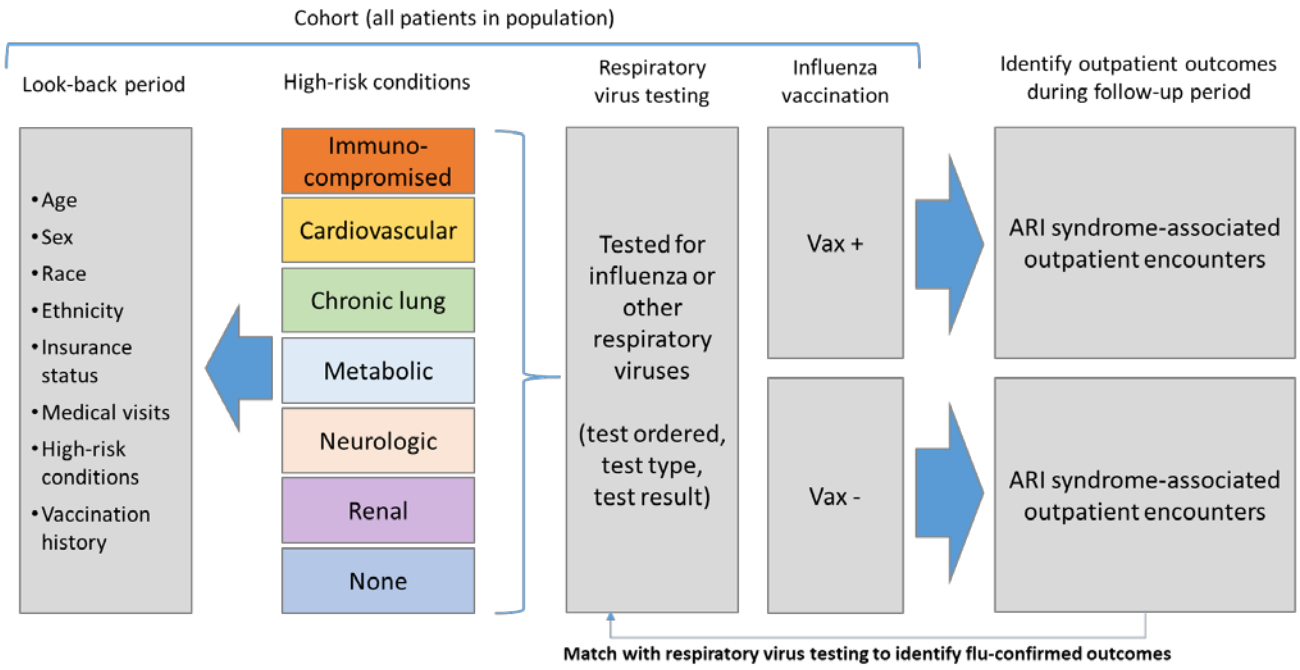


Figure 2. High-level study design for outpatient outcomes



5.2 Participant Eligibility

Eligible individuals in each seasonal cohort will be those who can and would seek care for influenza at a healthcare facility within the network. Inclusion in the cohorts will be defined by each site based on enrollment information within the health system, allowing for ≤ 30 day administrative gaps, and care being sought within the system in the 12 months prior to the start of the influenza season. Individuals born in the 12 months prior to the start of the influenza season will be eligible for the cohorts as long as other inclusion criteria are met and no exclusion criteria are met.

Inclusion criteria

Several different inclusion criteria are possible and will be assessed in the first primary objective. Individuals will be included if they reside in the catchment area or are active members in the health system's insurance plan and then will be evaluated against each of the following criteria.

1) Any individual who is otherwise eligible and had a telephone-based care visit, an ambulatory encounter, an urgent care encounter, an emergency department encounter, or an inpatient encounter with the health system in the 12 months prior to the start of influenza season. Ambulatory encounters include office-based visits to a primary care practice office (including but not limited to general pediatrics, general internal medicine, med-peds, obstetrics/gynecology, or general family medicine), or office-based visits to a medical specialty office (including but not limited to cardiology clinic, diabetes clinic, rehabilitation clinic, gastrointestinal specialist, etc.).

2) Any individual who is otherwise eligible and had an ambulatory encounter (to a primary care practice office or a medical specialty office) or an inpatient encounter with the health system in the 12 months prior to the start of influenza season.
3) Any individual who is otherwise eligible and had an ambulatory encounter with the health system in the 12 months prior to the start of influenza season.
4) Any individual who is otherwise eligible and had an encounter to a primary care practice office with the health system in the 12 months prior to the start of influenza season. General practice encounters include office-based visits to a general pediatrics, general internal medicine, med-peds, obstetrics/gynecology, or general family medicine clinic.
5) **[For closed health systems only]** For health systems where individuals can have an active membership in the health system, an additional inclusion criterion will be considered. The inclusion criteria will be any individual who was an active member in the health system for the period of 12 months before the start of influenza season (or was born and became a member during the 12 months prior to the start of or during the influenza season) and were active members until the end of influenza season, death, or disenrollment, whichever occurred first.

For a single season, such as the 2017/18 season, the cohorts defined by the different inclusion criteria will be assessed in terms of the number, the demographic characteristics, the frequency of subsequent medical care, and the frequency of respiratory hospitalizations among cohort members (Appendix C). The definition of "medical care" to use will be determined by joint consensus among the collaborating sites prior to extracting data for the interim and final datasets.

Exclusion criteria

Individuals will be excluded from the seasonal cohorts if they are not active members of the health system or they resided outside of the catchment area of the health system for the entire 12-month period before the start of influenza season. Active membership can be determined based on enrollment in the health system. Catchment area may be known or approximated based on prior studies or other surveillance activities that the health system is engaged in. Catchment area can also be determined starting first with the counties surrounding the hospitals and then be further refined using information on county of residence, selecting the counties that unique patients most frequently live in.

5.3 Observation Time during Influenza Season

For the primary objective of estimating the incidence of influenza-associated respiratory hospitalizations and ARI outpatient encounters, the person-time at risk for the underlying cohort will be needed. Person-time at risk for influenza will be calculated for all individuals in the seasonal retrospective cohorts. Observation time for a given season will start on the day that influenza season begins, September 1 of each year. For the same season, observation time will end on the day of death, disenrollment, move away from the catchment area, or the end of the influenza season (May 31), whichever occurs first. The total observation time, person-time, is then the difference between the start and end of observation. For analyses, observation time may be restricted to a shorter period of time when influenza viruses are known to be circulating in the communities surrounding the collaborating sites. Final determination for analysis will be made by group consensus.

5.4 Exposures of Interest

Vaccination status

Within each annual retrospective cohort, an individual will be considered vaccinated for influenza if there is documented evidence of influenza vaccination and evidence that the vaccination was administered at least two weeks prior to an influenza-associated respiratory hospitalization (or influenza-associated ARI outpatient visit).

In order to assess influenza vaccination status, multiple sources will be queried, as available, including EHR, state/local vaccine registries, all-payer claims or other billing databases. For each available source, data will be provided on date of vaccination, type of vaccine administered, vaccination route, location of vaccination, vaccine lot number and number of vaccine doses (for children <9 years of age). Vaccination records will be considered as evidence of vaccination if there is at least a partial date (month and year). Children (aged <9 years) will be considered fully vaccinated for the current season if they received two doses, at least one month apart, during the current season or if they received one dose of the current season's vaccine and had at least two doses in prior seasons.

Network sites will provide information on number of sources queried for vaccine data and completeness of data by vaccine source. Because each site is querying multiple sources, a hierarchy of sources will be established for each site or through joint consensus with collaborating partners. For vaccination data extracted from EHRs, sites will provide information on how vaccination data was pulled (for example, though use of CPT or other codes).

For a subset of patients (number to be determined by joint consensus by the collaborating partners), accuracy of extracted vaccination data will be verified through manual review of source data (i.e. medical chart review).

Influenza and other respiratory virus testing

Data on all influenza and other respiratory virus test results will be extracted for all members of the cohort during the surveillance period. For each test result, sites will provide data on encounter type associated with the lab test, diagnoses (based on ICD code) associated with encounter during which testing occurred, date of specimen collection, type of test performed and test result. Network sites will provide information on how laboratory testing data was pulled (for example, through use of CPT or other procedure codes or from laboratory databases). For a subset of patients (number to be determined by joint consensus by the collaborating partners), accuracy of extracted laboratory data will be verified through manual review of source data (i.e. medical chart review or review of laboratory databases). Respiratory viruses for which data will be collected, in addition to influenza, include respiratory syncytial virus, adenovirus, parainfluenza virus, human metapneumovirus, rhinovirus, enterovirus, coronaviruses, and other viruses, including novel viruses.

High risk conditions

For the primary objectives, high risk conditions will be defined using ICD diagnosis codes. A patient with at least 1 inpatient encounter or at least 1 outpatient encounter with a high-risk ICD diagnosis code (see Appendix D) recorded in the 12 months prior to the current influenza season will be considered as having a high-risk condition. The following high-risk conditions will be defined:

- Chronic lung disease;
    - Asthma;
    - COPD;
    - Pulmonary tuberculosis
    - Endemic mycoses

- Chronic metabolic disease;
    - Diabetes mellitus;
- Blood disorders;
- Cardiovascular disease;
    - Coronary artery disease;
    - Heart failure;
    - Congenital heart disease;
- Neuromuscular disorder;
- Neurologic disorder;
- Immunocompromised condition;
    - Solid organ malignancy;
    - Hematologic malignancy;
    - Solid organ transplant;
    - Hematopoietic stem cell transplant;
- Chronic renal disease;
- Gastrointestinal/liver disease;
- Rheumatologic/Autoimmune condition.

Additional underlying conditions, including, but not limited to, pregnancy, sickle cell disease, hypertension, obesity, and cystic fibrosis have also been associated with increased risk of severe influenza or COVID-19 disease and thus might be further defined and explored in the network.

Data on healthcare utilization

Healthcare utilization is an important data element to consider for the primary objectives. The use of healthcare directly informs the definition of each of the seasonal cohorts and also is

known to be associated with subsequent care for influenza and other respiratory virus infections as well as the propensity for seasonal influenza vaccination. Healthcare utilization will be captured using data on the number of telemedicine encounters, office-based encounters, and inpatient hospital admissions, for any reason, that occurred prior to the start of influenza season, during the influenza, and, for those who remain in the cohort, after the end of influenza season.

To better understand healthcare utilization patterns in the cohort, among vaccinated individuals, and among those with respiratory-associated inpatient or outpatient visits, several different categories of healthcare encounters will be enumerated in the 12 months before, during, and 12 months after each influenza season.

- Primary care encounters include office-based visits that occurred in a general pediatric, general internal medicine, med-peds, general family medicine, or obstetrics/gynecology practice.
- Telemedicine/telehealth encounters include any call for a clinical consultation
- Medical specialty care encounters include office-based visits that occurred in a practice for cardiology clinic, diabetes clinic, rehabilitation clinic, gastrointestinal specialist, etc. Excluded visits are those that are for laboratory only, imaging only, or nurse only.
- Urgent care encounters.
- Emergency department encounters include visits to the emergency department that did not result in an inpatient admission.
- Inpatient hospital admissions include admissions to an inpatient ward or an observation unit.

Vaccine Type	Age group
SARS-COV-2	All ages (as licensed and available)

Data on other exposures of interest

Individual level data will be extracted and provided on:

- Patient age as of the start date of the observation period,
- Sex
- Race and ethnicity
- Date of enrollment in the membership health plan or date of first qualifying healthcare encounter in the 12 months prior to influenza season (the encounter that included the individual into the cohort)
- Primary, secondary, tertiary and quaternary insurance type

5.5 Outcomes of Interest

- Respiratory illness-associated hospitalizations with laboratory-confirmed influenza
  - Respiratory hospitalizations will be defined using ICD-9 and ICD-10 discharge diagnoses codes as listed in Appendix D.
  - Data on all respiratory hospitalizations will be collected for the entirety of the surveillance period (influenza season).
  - The respiratory hospitalizations will be linked with data on influenza testing to determine if the hospitalization was associated with laboratory-confirmed influenza.
    - Laboratory-confirmed influenza associated respiratory hospitalization will be defined by a positive influenza test within 14 days prior to hospitalization or no more than 3 days after hospital admission.

- Hospitalization will be defined as admission to an inpatient ward or an observation unit. Time spent only in the emergency department will not count as a hospitalization.
- Re-admissions that occur within 30 days of the index hospitalization will be counted as part of the index hospitalization. Readmissions that occur >30 days after the index hospitalization will be considered new hospitalization events.

- ICU admission among persons hospitalized with laboratory-confirmed influenza-associated respiratory hospitalization
- Invasive mechanical ventilation among persons hospitalized with laboratory-confirmed influenza-associated respiratory hospitalization
- In-hospital death among persons hospitalized with laboratory-confirmed influenza-associated respiratory hospitalization
- Acute respiratory illness-associated outpatient visits with laboratory-confirmed influenza
  - Acute respiratory illness-associated outpatient visit will be defined using the ICD-9 and ICD-10 discharge codes listed in Appendix D.
  - Data on all acute respiratory illness-associated outpatient visits will be collected for the entirety of the surveillance period (influenza season).
  - The acute respiratory illness outpatient visit will be linked with data on influenza testing to determine if the visit was associated with a positive influenza laboratory test.

Appendix D provides a more detailed list of the variables used to define outcomes of interest.

5.6 Summary of Data Elements for Primary Objectives

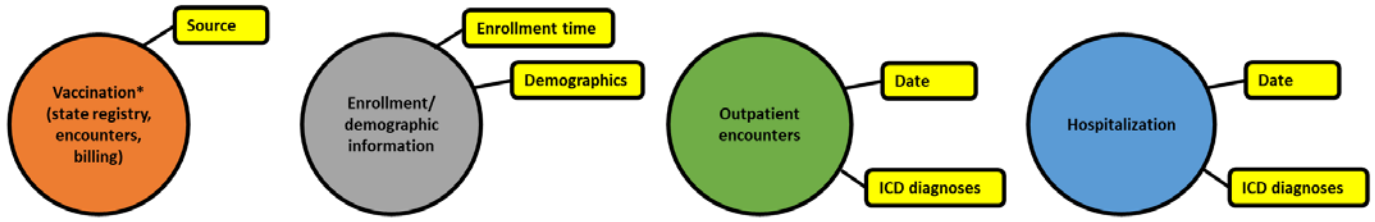
Please see Appendix B for more detailed list of data elements

- For the entire cohort:

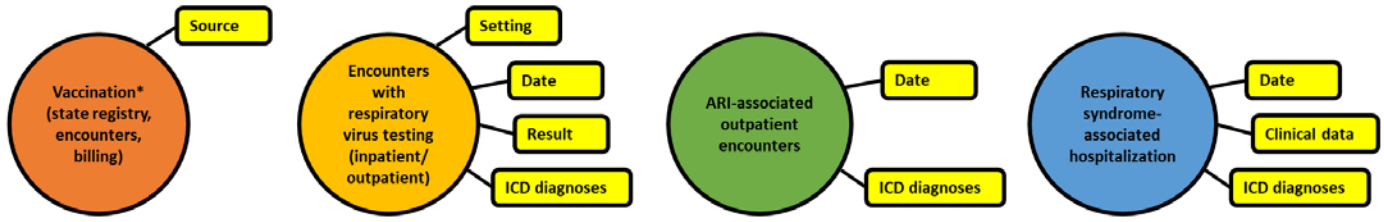
- Demographic information (age, sex, race, ethnicity)
- Date of enrollment in health plan and/or date of first encounter in the health system in the 12 months before the start of influenza season (as applicable)
- Healthcare utilization (primary/secondary insurance type, number of medical encounters before and during influenza season). This is further defined to be the monthly number of healthcare encounters by setting (general practice, medical specialty, emergency department, urgent care, telehealth, or inpatient).
- Underlying high risk medical conditions (derived from ICD codes)
- Vaccination status (influenza and other vaccinations received dating back to 2010)

- All hospitalizations and outpatient encounters with respiratory virus testing during influenza season of interest:
  - Date of encounter (or date of admission)
  - Date of testing
  - Clinical setting
  - Influenza and other respiratory virus test type and result
  - Diagnosis codes from the encounter/admission
- Respiratory syndrome-associated hospitalizations during influenza season of interest:
  - Hospital admission and discharge dates
  - Diagnosis codes
  - Severe outcomes (ICU admission, mechanical ventilation, in-hospital mortality)
- ARI syndrome-associated outpatient encounters during influenza season of interest
  - Encounter date
  - Diagnosis codes

Data streams for entire cohort during to-be-determined lead-in period:

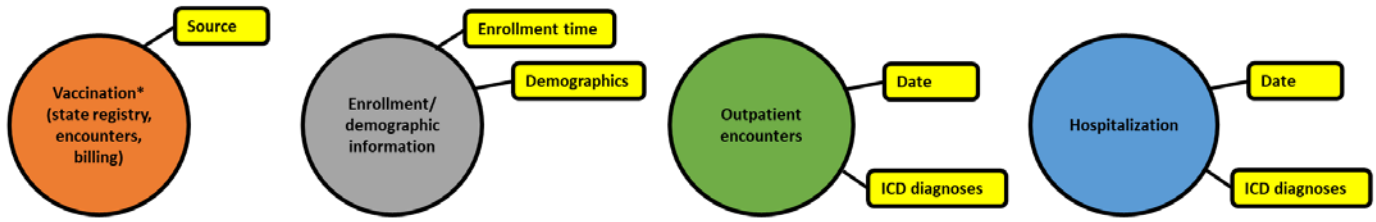


Data streams for influenza season of interest:

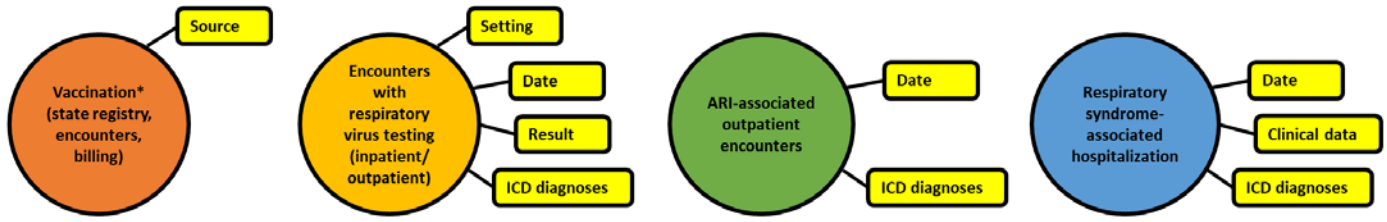


All sources should be linked by subject ID
*For influenza and other vaccinations received dating back to 2010, where possible.

Data streams for entire cohort during to-be-determined lead-in period:



Data streams for influenza season of interest:



All sources should be linked by subject ID
*For influenza and other vaccinations received dating back to 2010, where possible.

5.7 Summary of Methods for Secondary Objectives

After the primary objectives are met, a set of secondary objectives will be addressed with a deeper level of data collection or analysis. Funding of data collection or analysis for these secondary objectives will depend on resources and success of the primary objectives. Secondary objectives may involve some but not necessarily all participating sites.

The secondary objectives include capturing and assessing the validity of additional data elements (such as laboratory values, vital signs, and medications) to better characterize underlying medical conditions and severity of influenza virus infections. It is anticipated that the methods for assessing the validity of the additional data will be similar to the methods used to validate data for the primary objectives, including comparison of extracted data to data in the primary data source, searching for deviations from expected values, and comparing findings to external sources.

In addition to expanding the data elements being captured, sites participating in the secondary objectives may be asked to extract data from the 2019–2020 influenza season, to submit “prospective”, or near real-time, data from the 2020–2021 influenza season, or to expand outcome ascertainment beyond the pre-defined influenza season.

As more details of the methods for the secondary objectives are discussed and consensus reached with the participating sites, the methods and protocol will be amended.

6.0 Statistical Analysis

6.1 Analysis Plan

Objective 1: Assess the validity and biases associated with defining the source population based on care-seeking

Correctly capturing the health system's denominator is a critical component of the study objectives, thus all health systems will be asked to validate the eligibility definitions using their information from their membership or source population.

- Compare the demographics of participants defined using the five inclusion criteria, using appropriate bivariate statistics as appropriate.
- Compare, using appropriate bivariate statistics, the healthcare utilization between all known members and those participants defined using the five inclusion criteria.
- Compare the frequency of respiratory-associated hospitalization between the cohorts as defined using the five inclusion criteria.

Objective 2: Validation of influenza vaccination data

- Describe the frequency of influenza vaccination among cohort members and vaccine type received. Descriptions will include the full cohort and will be stratified by individual characteristics such as age group, high-risk condition, and prior healthcare utilization.
    - Frequency of vaccination will be compared across strata using appropriate bivariate statistics (e.g. chi-square tests or Fisher's exact tests).
- Among those determined to be vaccinated for influenza
    - Assess the proportion that were identified through various data sources (e.g., procedure codes from a medical visit, other notation in the medical chart, vaccine registry, billing data, etc.). Assess whether the source of vaccination data varies by individual characteristics, including age group, high-risk conditions, and prior healthcare utilization.

- Compare the completeness and consistency of data on date of vaccination and vaccine type between data sources and by patient characteristics such as age group, high-risk conditions, and prior healthcare utilization.
- Comparisons of data by source, for completeness, and for consistency and how these differ by patient characteristics will be conducted using appropriate bivariate tests of association and/or multivariate regression. As an example, regression analyses could include data source as the outcome of interest with patient characteristics as explanatory variables.

- Describe the timing of vaccine receipt among cohort members by age group, high risk condition, prior healthcare utilization, and vaccine type received.

  This description will be explored using a variety of methods, including time to vaccination, median week of vaccination, or frequency of vaccination at least two weeks prior to the start of influenza circulation. Comparison of timing by patient characteristics will be conducted using methods appropriate to the outcome type; for example, proportional hazards modeling for time to vaccination.

Objective 3: Biases associated with clinical testing

- Describe the frequency of clinical testing for influenza and other respiratory viruses in the cohort during an influenza season by setting (inpatient vs. outpatient), age group, high-risk status, influenza vaccination, prior healthcare utilization, and timing of encounter within the season.
- Describe the diagnoses associated with visits where clinical testing for influenza and/or other viruses was performed.

- Among hospitalizations with respiratory illness during the influenza season, describe the frequency and types of clinical testing used.
    - Characteristics and predictors of receipt of diagnostic test for influenza will be assessed using bivariate tests of association and/or multivariate regression with receipt of test as outcome of interest and patient and clinical characteristics (including age, vaccination status, high-risk conditions, timing of the clinical encounter within the season, prior healthcare utilization, diagnoses, etc.)
- Among outpatient visits for ARI during the influenza season, we will describe the frequency and types of clinical testing used.
    - Characteristics and predictors of receipt of diagnostic test for influenza will be assessed using bivariate tests of association and/or multivariate regression with receipt of test as outcome of interest and patient and clinical characteristics (including age, vaccination status, high-risk conditions, timing of the clinical encounter within the season, prior healthcare utilization, diagnoses, etc.)

Objective 4: Measure incidence of health outcomes related to influenza

- Incidence of laboratory-confirmed influenza-associated respiratory hospitalizations will be calculated by dividing the number of respiratory hospitalizations associated with a positive influenza laboratory test observed during each study season by the person-time of the cohort at risk during the corresponding season.
    - This will be calculated for the following risk groups: age group, high-risk conditions, vaccinated for influenza, unvaccinated, race/ethnicity, socio-economic status, etc.
    - Incidence will be compared between risk groups using rate differences or relative rates

- Incidence of ICU admission, mechanical ventilation, and in-hospital death associated with influenza will be similarly calculated, with the respective numerators restricted to those laboratory-confirmed influenza-associated respiratory hospitalizations with the relevant outcomes identified.
    - This will be calculated for the following risk groups where sample size permits: age group, high-risk conditions, vaccinated for influenza, unvaccinated, race/ethnicity, socio-economic status, etc.
    - Incidence will be compared between risk groups using rate differences or relative rates
- Incidence of laboratory-confirmed influenza-associated acute respiratory illness (ARI)-associated outpatient visits will be calculated by dividing the number of ARI visits with a laboratory test positive for influenza observed during each study season by the person-time of the cohort at risk during the corresponding season.
    - This will be calculated for the following risk groups where sample size permits: age group, high-risk conditions, vaccinated for influenza, unvaccinated, race/ethnicity, socio-economic status, etc.
    - Incidence will be compared between risk groups using rate differences or relative rates

As multiple events are possible during a season, incidence estimates throughout this objective may be calculated in two ways: 1) counting only the first occurrence, and 2) counting the cumulative number across the season.

Objective 5: Assessment of vaccine effectiveness

- We will estimate the effect of influenza vaccination on risk of lab-confirmed influenza-associated respiratory hospitalization by age group, influenza type/subtype, and high-risk conditions
    - The risk of influenza-associated respiratory hospitalization among cohort members who were or were not vaccinated with the current season influenza will be compared using appropriate methods for longitudinal data with time varying exposure, including Poisson regression or proportional hazards modeling.
    - VE will be estimated as (1-adjusted relative risk) x 100.
    - We will assess and adjust for confounders as appropriate. These may include characteristics such as age, sex, site, race/ethnicity, high-risk health conditions, prior healthcare utilization, time of event during the influenza season, etc.
    - Data collected for this study are intended to be pooled across sites. VE will first be estimated for each site and heterogeneity in estimated VE across sites examined.
- We will estimate the effect of influenza vaccination on risk of lab-confirmed influenza-associated ARI outpatient visit among children (adults only if influenza testing allows for this) by age group, influenza type/subtype, and high-risk conditions
    - The risk of influenza-associated outpatient visits among cohort members who were or were not vaccinated with the current season influenza will be compared using appropriate methods for longitudinal data with time varying exposure, including Poisson regression or proportional hazards modeling.
    - VE will be estimated as (1-adjusted relative risk) x 100.

- We will assess and adjust for confounders as appropriate. This may include characteristics such as age group, sex, site, race/ethnicity, high-risk health conditions, prior healthcare utilization, time of event during the influenza season, etc.
- Data collected for this study are intended to be pooled across sites. VE will first be estimated for each site and heterogeneity in estimated VE across sites examined.

- VE analyses against influenza-associated respiratory hospitalizations will also be conducted using a test-negative case-control design
    - This analysis will be conducted among individuals who were hospitalized for acute respiratory illness during the influenza season and who were tested for influenza.
    - Cases will be defined as hospitalized individuals who tested positive for influenza.
    - Controls will be defined as hospitalized individuals who tested negative for influenza.
    - Influenza vaccination status will be determined for all cases and controls and the odds of vaccination will be compared using logistic regression.
    - VE will be estimated as (1 – adjusted odds ratio) x 100.
    - We will assess and adjust for confounders as appropriate. This may include characteristics such as age group, sex, site, race/ethnicity, high-risk health conditions, prior healthcare utilization, time of event during the influenza season, etc.
    - Data collected for this study are intended to be pooled across sites. VE will first be estimated for each site and heterogeneity in estimated VE across sites will be examined.

Beyond the primary objectives listed here, additional analyses may be pursued and will be considered by the joint steering committee.

6.2 Sample Size

Table 1 presents sample size requirements for the primary objective of VE against severe outcomes. Existing data from hospital-based surveillance was used to estimate the reported incidence of laboratory-confirmed hospitalizations, ICU admissions, and deaths.[25] Data from the Behavioral Risk Factor Surveillance System (BRFSS) and National Health Interview Survey (NHIS) was used to estimate vaccine coverage.[26]

For adults, we assumed vaccine coverage of 30% in adults aged 18-49 years, 42% in adults aged 50-64 years, and 65% in adults 65 years and older. We assumed a population made up of 33% of adults in each of the three age groups.

For children, we assumed vaccine coverage of 70% in children aged 6 months to 4 years and 50% in children aged 5 to 17 years. We assumed a population made up of 50% of children in each of the two age groups.

Table 1 Sample Size Estimations

		Person-years needed	
	Minimum Detectable VE	Adults	Pediatrics
VE against hospitalization	40%		398,319
	35%	197,593	569,374
	30%	292,719	842,278
	25%	456,014	1.3 million
	20%	766,799	
VE against ICU admission	40%		1.01 m
	35%	1.2 million	1.4 m
	30%	1.8 m	1.9 m
	25%	2.8 m	2.8 m
	20%	4.8 m	
VE against in-hospital death	40%		28.1 m
	35%	5.4 m	39.4 m
	30%	7.9 m	52.8 m
	25%	12.4 m	73.8 m
	20%	20.8 m	

6.3 Enhanced Data Collection Elements to Meet Secondary Objectives

For a more comprehensive list of data elements needed to meet the secondary objectives, see Appendix B.

- All inpatient/outpatient encounters for to-be-determined lead-in period (to refine high-risk conditions)
    - Medication prescribing/administration (e.g. asthma or immunosuppressive medications)
    - Laboratory testing/results (e.g. for diabetes, hemoglobin A1C tests)
- Respiratory syndrome-associated hospitalizations during influenza season of interest (all patients; discharge codes listed in Appendix D)

- Medication orders/administration (e.g. influenza antivirals, antibiotics, steroids, vasopressors)
- Expanded laboratory testing/results (e.g. CBC, CMP)
- Vital signs (e.g. heart rate, respiratory rate, blood pressure, temperature, O2 saturation, Glasgow Coma Scale)
- Non-invasive mechanical ventilation (e.g. CPAP, BiPAP, high flow nasal cannula)
- Radiography (e.g. chest x-ray)

- ARI syndrome-associated outpatient encounters during influenza season of interest (all patients; ICD codes TBD)
  - Medication orders/administration (e.g. influenza antivirals, antibiotics)
  - Expanded laboratory testing/results (e.g. CBC, CMP)
  - Vital signs (e.g. heart rate, respiratory rate, blood pressure, temperature, O2 saturation, Glasgow Coma)
  - Radiography (e.g. chest x-ray)

7.0 Data Sources and Management

7.1 Data Sources

Many of the required patient data variables are routinely captured in the EHR. Others may need to be added from additional sources such as participant health plan enrollment or administrative data, administrative claims, or vaccine registries linked to EHR data at the patient level. Reliance on open text fields, such as physician notes, will be kept to a minimum.

Each data element that is extracted will have an operational definition accounting for the coding structure, completeness, and limitations of the data source. This operational definition is particularly important to address situations that may arise when extracting data from health

records. For example, a concept (e.g. vaccination status) may be captured by more than one variable in a single provider database (e.g., recorded in vaccination records or in visit notes for self-reported) or in more than one database (e.g., EHR or vaccine registry). Thus the validity of the analyses will depend on consistent operational definitions.

Operational definitions for necessary data elements will be defined collaboratively by CDC, Westat, and network sites to ensure consistency and accuracy of definitions across sites. As the data coordinating center, Westat will receive data from the sites and derive variables for analysis. Alternatively, sites may choose to derive some or most data elements prior to submitting final datasets to Westat/CDC, based on the agreed-upon operational definitions. Appendix E displays an example of the types of data shared by the sites with Westat for processing.

At Westat, the study database will be housed in an integrated central research data warehouse (RDW) platform. The RDW will be fully integrated with the data management and tracking systems necessary for carrying out the processes associated with entry/upload, transmission, QA, version control, standardization, storage, and security.

7.2 Variables

A listing of the analytic variables necessary to meet the primary project objectives are shown in Appendix A. Depending on funding to address secondary objectives, additional variables will be added, including medications (antivirals, antibiotics, steroids, vasopressors), non-invasive mechanical ventilation, vital signs (such as heart rate, respiratory rate, blood pressure, temperature, O_2 saturation, Glasgow Coma Scale), radiography, and other laboratory tests [including diabetes, hemoglobin A1C, complete blood count (CBC), comprehensive metabolic panel (CMP), etc.]. A listing of the analytic variables necessary to meet the primary

and secondary project objectives is provided in Appendix B. Additionally, Appendix D contains the ICD codes and other variables used to define high-risk conditions, ARI hospitalizations, and outcomes.

7.3 Data Management

During the course of the study, research staff at each site will extract information from the EHR of participants, state or local vaccination registries, and billing records. Information for extraction includes data elements described in Section 7.2 and Appendices B and D. Sites will perform data validation on the extracted data as discussed in Section 7.4, below. Each site will create and maintain a database onsite that links demographic and clinical information extracted from the EHR, state or local vaccination registries, and billing records to a coded patient identifier. The key linking the coded identifier to the patient IDs will be kept at the individual sites. Additionally, the sites within a health network will also be given a coded identifier. Some details of the site will be included in the data, such as facility type (hospital, medical office, urgent care, ER, etc.), county, and state. Upon execution of an appropriate data use agreement (DUA) or data transfer agreement (DTA), a HIPAA-defined limited data set (LDS) will be forwarded (using a secured data transfer protocol) to the study coordinating center (Westat). Data transferred to Westat will not include identifying elements such as name, medical record number, postal address, or any other elements not allowed in a LDS. These datasets will contain individual-level records of pre-processed variables derived by the study site for the analysis necessary for the primary objectives.

Additional details about site data processing can be found in Appendix E, Proposed Data Structure to be shared by Sites with Westat. Westat will perform additional quality control and validation on the received data, as described in Section 7.4 below. Westat will derive the analytic

variables for sites sending data matching descriptions 1 and 2 above and concatenate the files to form one database. The database will be transferred to CDC using a secured transfer protocol for analysis (see Data Management Plan, Appendix F, for further detail).

7.4 Data Validation

Data will be validated at different points throughout the protocol and study period and will be an iterative process. If errors are found, Westat will coordinate with the site and the extraction will be re-programmed and data re-extracted and re-validated. Sites and Westat will both perform various aspects of this quality control and data validation. There are three main types of validation that will be conducted for this study:

1. Basic validation

The basic validation includes data quality checks such as confirmation that values are non-missing, values are of the correct type and length, and values are in the appropriate range. All variables will undergo basic validation. Expected variable type, length, and range will be included in the codebooks. Range checks will be particularly important for dates and healthcare utilization. Expected percent missing will be determined at the site-level. For example, some sites may do more influenza testing than others and thus the expected percent missing for those sites would be different.

2. Internal crosschecks

The internal crosscheck validation will include two types of checks. The first is comparing calculated proportions of various data elements in the extracted data to the proportions in the source data. For example, if a site generally performs influenza testing on 50% of its pediatric patients and the extracted data show only 5% that would indicate an error. Variables that will undergo this check are sex, race, ethnicity, insurance coverage, insurance

type, respiratory virus testing and results (percent tested and percent positive), vaccination status (by age and high-risk condition), invasive mechanical ventilation, ICU admission, in-hospital mortality, and high-risk conditions.

The second type of internal crosscheck is comparing related data elements, i.e., a value for one data element is checked against the value for another data element. For example, all patients with a pregnancy-related diagnosis code should have sex recorded as female. Checks of this type could include:

- Number of inpatient visits corresponds to number of admission dates
- Number of outpatient visits corresponds to number of dates of outpatient encounters
- If date of vaccination is non-missing then source of data (EHR, registry, administrative records, etc.) should be non-missing
- If the date of respiratory virus testing is non-missing than the type of test and the test result should be non-missing; likewise, the test result should be consistent with what is detectable by the test type
- A patient with a record for mechanical ventilation should also have an ICU admission date

Additionally, sites could crosscheck the high-risk conditions with other data not extracted for this study. For example, they could look at medication use among those coded with high-risk conditions commonly treated with medication (e.g. asthma, diabetes).

3. Comparisons with external data sources

Comparisons with external data sources includes comparing values to those recorded in the primary records as well as comparing rates, proportions, and distributions of variables across participating sites and to national, regional, or state data.

Comparison of extracted data to the primary records will be done on a limited basis, but can be informative for understanding flow of data into the data warehouse and appropriateness of structured data fields to the data of interest for this project. Appendix G includes some suggestions for data validation steps using primary medical or health records.

Variables for which rates, proportions, and distributions can be compared across participating sites and to national, regional, or state data include:

- Influenza vaccination coverage
- Respiratory virus testing and positivity
- Mechanical ventilation
- ICU admissions
- Proportion of patients with high-risk conditions

Westat will work with each site to review potential errors and decide on corrective action. In a few cases, sites may need to perform limited review of medical charts to clarify data elements flagged for review.

8.0 Ethical Considerations for Protection of Human Research Subjects

8.1 Institutional Review Board Review

Westat will serve as the single IRB of Record for this study for all participating sites and coordinating center for overseeing protections of human subjects research (45 C.F.R. § 46 114). The Westat IRB will enter into an IRB Authorization Agreement (IAA) that will include a communication plan with each institution prior to study implementation. IAAs and other documentation necessary in order to document compliance with the single IRB policy are maintained by Westat's IRB. Westat's IRB will use several mechanisms to communicate with sites, including email, phone calls and direct person-to-person communications as needed.

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

8.2 Patient Confidentiality

All patients in the dataset will be assigned a linkable patient identification code (i.e. study identification code). Sites will be responsible for assigning and maintaining the link between the patient's identifying information and study ID. Documents maintaining this link will never be transferred to the coordinating center or study investigators. Personal identifiers (patient's name, address, medical record number, and encounter number) will exist at the participating site, as part of the hospital administrative data but will be replaced by a random generated code (linkable patient identification code), which will allow linkage of data without CDC or the coordinating center (Westat) having any access to these personal identifiers. All study data and administrative documentation will be identified by the study identification code only, to maintain participant confidentiality. Limited datasets will be created for the study; the study will comply with each institution's human subjects, privacy, and information security laws, if any. All study data files will be stored separately from any study records that contain names or other personal identifiers. All local databases must be secured with password protected access systems.

Listings that link study (and personal) IDs to other identifying information must be stored in a separate, locked file (or encrypted) in an area with limited access (or maintained in a directory separate from any study specific data files/sets) at each participating facility. Links between the study identification codes and personal identifiers will be destroyed by the

participating site after publication of the findings (for additional information please see the Data Management Plan, Appendix F).

Westat's Data Management Plan (Appendix F) details how Westat will protect any identifiers from improper use or disclosure, how Westat will destroy the identifiers after study completion, and how the protected health information will not be reused for other research.

8.3 Request for Wavier of Informed Consent

The study relies on existing data already collected as part of patient's routine care or for billing purposes. No supplemental data collection will be done as part of this study. In addition, this study presents minimal risk to participants because there is no interaction or intervention with patients; therefore, a waiver of informed consent is requested. Minimal risk includes disclosure of clinical information on the patients' medical condition to persons outside of this protocol's defined study. Although patient information already available in the administrative databases will be collected, only information associated with a HIPAA limited dataset will be collected for the study. There is no risk to the participants' health from participation nor any impact on patients' current health care or therapeutic management plan because patients will not be contacted at any time. Consequently, patients will not be provided information about their participation.

Additionally, it will be impractical to conduct this study without waiving informed consent. By the time access to the datasets is available, most of the patients, if not all, will be out of the hospital (or some may have died during hospitalization), and the vast majority may have been hospitalized many years prior and may no longer live in the area or receive their care at the relevant study site. To contact each patient in this large, retrospective study for informed consent

or to notify them of study results would place an insurmountable burden on investigative staff and would prohibit successful completion of the study.

8.4 Benefits to Participants

There are no direct benefits for patients whose data contribute to this study. There may be future indirect benefits to the populations of the participating health systems, especially those with risk factors for severe illness from influenza. For example, information from this study may influence vaccination strategies for high-risk groups that may improve future outcomes for children, elderly adults, and those with high-risk conditions. In addition, understanding factors that make these groups at higher risk for influenza-associated hospitalization may help in developing and improving prevention and treatment guidelines.

8.5 Data Records Lifecycle and Destruction

Each participating study institution will store any paper study records in a physically secure location that is only accessible to authorized study staff. At close out, assuming no restrictions on data retention, the de-identified analytic files, documentation and all code used in processing will be archived in a way that would allow replication of the results. Each organization affiliated with the study, through subcontract or otherwise, must destroy data according to contractual specifications and must provide Westat with a certificate of destruction.

A certificate of destruction will be required for electronic and hard copy data and each must detail the type of data destroyed, how and when it was destroyed, and the signature of the authorized data security manager or corporate executive. In addition, any exceptions to the data destruction, e.g., data that must be maintained for internal records, must be identified in the certificate of destruction, along with a detailed rationale for why the data were not/could not be destroyed, at study conclusion.

8.6 Guidance for Decision Making

A project steering committee will provide high-level input into this project, with CDC and Westat having final approval and sign off on any decisions made. The project steering committee will consist of two individuals from each site (decided by the site), a Westat representative, and a CDC representative. Each site will have one vote. The day-to-day overall project management will occur through the Westat study lead who will interface directly with CDC; however, the steering committee will be consulted on over-arching project issues including final protocol decisions, adjudicating any protocol deviations that might occur, reviewing and confirming analysis plans, and making final decisions on analyses, manuscripts, and authorship as needed. Upon the completion of all study deliverables, at a minimum, aggregate tables from publications of this collaboration will be publicly shared as specified in U.S. Government Data Sharing guidelines. Additional data may be publicly shared to further satisfy the U.S. Government Data Sharing guidelines, as determined by consensus of steering committee members and per site data use agreements.

Appendix A: Outcomes, Exposures, and Modifiers for Study Objectives

Objective	Outcome Variables	Exposure Variables	Stratification Variables	Confounders/ Modifiers
Primary Objectives				
Objective 1: *Assess the validity and biases associated with defining the source population based on care-seeking.*	Respiratory hospitalizations	Cohort definitions Healthcare utilization Healthcare setting	High Risk Conditions Insurance	Age Sex Race Ethnicity
Objective 2: *Determine the internal and external validity of data on influenza vaccination*	Internal validity Accuracy of derived vaccine status variable in relation to manual review of records Contributions to conclusion about vaccination status by source Consistency and completeness of vaccination data available by source External validity Comparison of vaccine coverage and data completeness to values from other studies	Data source EHR Registry Billing/Admin. records	Vaccination date Vaccine type Vaccine route Vaccine lot number Setting of administration Num. of doses (<9 years)	
Objective 3: *Assess biases associated with clinical testing for influenza and*	Proportion of cohort enrollees tested for influenza and other respiratory viruses Types of influenza and other virus tests performed Proportion of respiratory hospitalizations tested Proportion of ARI outpatient visits tested		Age Healthcare setting High-risk conditions[1] Vaccination status	Sex Healthcare utilization Race Ethnicity

Objective	Outcome Variables	Exposure Variables	Stratification Variables	Confounders/ Modifiers
other respiratory viruses [2]			Testing date Timing of encounter Discharge diagnosis codes	 Insurance coverage Hospital length-of-stay
Objective 4: *Measure incidence of health outcomes related to influenza by pediatric and adult age groups, influenza type/subtype, and high-risk conditions*	Laboratory confirmed influenza-associated respiratory hospitalizations ICU admission Invasive mechanical ventilation In-hospital death Outpatient/Urgent care visits		Age Influenza type/subtype High-risk conditions [1]	Sex Healthcare Race Ethnicity Insurance coverage Hospital length-of-stay
Objective 5: *Estimate the effectiveness of current season influenza vaccine in preventing severe outcomes by age groups, influenza type/subtype, and high-risk conditions*	Laboratory confirmed influenza-associated respiratory hospitalizations ICU admissions Outpatient/Urgent care visits (pediatrics)	Influenza	Age Influenza type/subtype High-risk conditions [1]	Sex Healthcare Race Ethnicity Insurance coverage Hospital length-of-stay
Secondary Objectives				

Objective	Outcome Variables	Exposure Variables	Stratification Variables	Confounders/ Modifiers
Objective 1: *Assess feasibility of defining underlying conditions using combination of ICD, medication, and lab data*				
Objective 2: *Assess whether immunosuppression or use of immunosuppressive medications increases risk of severe outcomes or reduces VE*				
Objective 3: *Examine association between number and timing of priming doses with VE against outcomes in subsequent seasons (among children only)*				

Objective	Outcome Variables	Exposure Variables	Stratification Variables	Confounders/ Modifiers
Objective 4: *Examine association between prior season vaccination and current season VE (among adults only)*				
Objective 5: *Determine measures of disease severity at hospital admission and assess impact on measures of VE*				
Objective 6: *Measure incidence of secondary outcomes following influenza-related hospitalization*				

[1] High-Risk Conditions: chronic lung disease, asthma, COPD, chronic metabolic disease, diabetes mellitus, blood disorders/hemoglobinopathy, cardiovascular disease, coronary artery disease, heart failure, congenital heart disease, neuromuscular disorder, neurologic disorder, immunocompromised condition, solid organ malignancy, hematologic malignancy, solid organ transplant, hematopoietic stem cell transplant, chronic renal disease, gastrointestinal/liver disease, rheumatologic/autoimmune condition, pregnancy (in woman of childbearing age), prematurity (in children <2 years of age).

[2] Influenza (all types/subtypes), respiratory syncytial virus, adenovirus, parainfluenza (1-4), human metapneumovirus, rhinoviruses/enteroviruses, coronaviruses, other novel viruses.

Appendix B: Specification of Data Elements

See accompanying Excel file “VISIONDataElementsCodebook.”

Appendix C: Assessment of inclusion criteria

Retrospective cohorts for this protocol will be defined based on care-seeking behavior; however, deriving a cohort based on seeking care could introduce bias to estimates of incidence of influenza-associated outcomes and the effect influenza vaccination on reducing the incidence of such outcomes. To assess the validity and biases associated with the definition of the cohort, the first primary objective of the protocol will assess and compare the demographics, frequency of health-care utilization, and frequency of influenza-related outcomes between cohorts defined in different ways.

Following the protocol, five different inclusion criteria are being considered for defining retrospective cohorts for each influenza season. For the 2017/18 influenza season, or another season as agreed upon by the collaborating sites, each collaborating site will define a retrospective cohort using the definitions outlined in the Participant Eligibility section. **Of note:** only collaborating sites who have access to and can define a source population based on individual membership in a health system will describe characteristics of a cohort as defined using active participant membership.

The following table is an example of what will be filled out to describe the aggregate characteristics of the defined cohort. Of note, the influenza season is defined from September 1 through May 31 of the following year.

	In 12 months prior to start of influenza season, individuals who had:				
	≥1 care encounter [a] or ≥1 inpatient admission	≥1 ambulatory care encounter [b] or ≥1 inpatient admission	≥1 ambulatory care encounter	≥1 general practice encounter [c]	Active membership [d]
Number of unique patients in the cohort					
Demographics					
Age, in years (n, %)					
<2					
2–4					
5–17					
18–49					
50–64					
65–74					
75–84					
≥85					
Sex (n, %)					
Male					
Female					
Other					
Race (n, %)					
White					
Black					
Other					
Hispanic (n, %)					

Healthcare utilization					
In 12 months before start of influenza season					
General practice office visits, median (IQR) [e]					
Medical specialty office visits, median (IQR)					
Urgent care visits					
Emergency department visits, median (IQR)					
Inpatient admissions, median (IQR)					
During influenza season					
General practice office visits, median (IQR)					
Medical specialty office visits, median (IQR)					
Urgent care visits					
Emergency department visits, median (IQR)					
Inpatient admissions, median (IQR)					
Influenza-related outcomes during the influenza season					
Frequency of respiratory-associated hospitalizations (n, %) [f]					

[a] Care encounters include telephone-based care visits, an office-based ambulatory encounter, an urgent care encounter, or an emergency department encounter with the health system.

[b] Ambulatory care encounters include office-based visits to a general practice office (including but not limited to general pediatrics, general internal medicine, obstetrics/gynecology, or general family medicine), or office-based visits to a medical specialty office (including but not limited to cardiology clinic, diabetes clinic, rehabilitation clinic, gastrointestinal specialist, etc.).

[c] General practice encounters include office-based visits to a general practice office (including but not limited to general pediatrics, general internal medicine, obstetrics/gynecology, or general family medicine).

[d] Only applicable to "closed" health systems where individuals enroll as members and enrollment is tracked.

[e] Median number of visits per individual, with interquartile range (25^{th}–75^{th} percentiles).

[f] Respiratory-associated hospitalizations should include any qualifying admissions to an inpatient ward for at least 24 hours, or admissions where the discharge date is at least one calendar day after the admission date, if time in hours is not available. Qualifying respiratory admissions include those with a discharge code, in any positions, of 460-519 (for ICD-9 codes) or J00-J99 (for ICD-10 codes).

Appendix D: Diagnosis Codes and Other Variables Used to Define for High Risk Conditions, ARI Hospitalizations, and Study Outcome

This appendix includes example conditions and codes used to define high-risk conditions and outcomes. These codes may be modified to include additional conditions or diagnoses as objectives are refined. This list of codes can also be found in the data dictionary referenced in Appendix B.

High Risk Conditions

Description	ICD-9 Code	ICD-10 Code
Blood disorders	282.*, 283.*, 284*	D55.*, D56.0, D56.1, D56.2, D56.4, D56.5, D56.9, D57.0, D57.1, D57.2, D57.4, D57.8, D58.*, D59.*, D60.*, D61.*, D64.0, D64.1, D64.2, D64.3, D64.4, D64.8, D65.*, D66.*, D67.*, D68.*
Cerebrovascular disease	430, 431.*, 432.*, 433.*, 434.*, 435, 436, 437.*, 438.*, 348	I60.*, I61.*, I62.*, I63.*, I68.*, I69.*
Chronic lung disease	031.0*, 135.*, 277.0*, 273.4, 277.6*, 494.*, 495.*, 500.*, 501.*, 502.*, 503.*, 504.*, 505.*, 506.*, 508.*, 510, 513, 514.*, 515.*, 516.*, 517.*, 518.1*, 518.2*, 518.3*, 518.6*, 518.83, 519.9*, 519.0*, 748.4*, 748.5*, 748.6*, 759.3*, 770.2*, 770.7*, V42.6*, 714.81, 769, 770	D86.0, E84.*, E88.01, J47.*, J60.*, J61.*, J62.*, J63.*, J64.*, J65.*, J66.*, J67.*, J68.*, J69.*, J70.*, J81.*, J82.*, J84.*, J95.0, J96.*, J98.1, J99.*, P25.*, P26.*, P27.*, P28.*, Q33.*, T86.3, T86.8, Z94.2
Chronic lung disease (asthma)	493.*	J45.*
Chronic lung diseases (chronic obstructive pulmonary disease)	491.*, 492.*, 496.*	J40.*, J41.*, J42.*, J43.*, J44.*
Chronic lung disease (endemic mycoses)	115.*, 116, 116.1, 484.6, 117.3, 518.6, 117.5, 321, 117.7	B39.*, B40.*, B41.*, B44.*, B45.*, B46.0
Chronic lung disease (pulmonary tuberculosis)	011.*, 012.*	A15.*, A31.0
Heart disease	393.*, 394.*, 395.*, 396.*, 397.*, 398.*, 402.*, 404.*, 415, 416.*, 417.*, 423.*, 424.*, 425.*, 426.*, 427.1*, 427.2*, 427.3*, 427.4*, 427.5*, 427.6*, 427.8*, 429.*, 440.*, 446.*, V42.1*, V45.0*, V45.81, V45.82, 9971, 441.*, 442.*, 443.*, 444.*, 447.*, 4461	I01.*, I02.*, I05.*, I06.*, I07.*, I08.*, I09.*, I11.*, I13.*, I26.*, I27.*, I28.*, I31.*, I34.*, I35.*, I36.*, I37.*, I41.*, I42.*, I43.*, I44.*, I46.*, I48.*, I51.*, I52.*, I97.0, I97.1, M31.*, Z94.1, Z95.*, Z98.61, I71.*, I72.*, I73.*, I74.*, I75.*, I79.*
Heart disease (congenital heart disease)	745.*, 746.* ,747.*, 759.3	Q20.*, Q21.*, Q22.*, Q23.*, Q24.*, Q25.*, Q26.*, Q27.0, Q27.3, Q27.4, Q27.8, Q27.9, Q28.*, Q89.3
Heart disease (heart failure)	428.*	I50.*

Description	ICD-9 Code	ICD-10 Code
Heart disease (ischemic heart disease)	410.*, 411.*, 412.*, 414.*	I21.*, I22.*, I23.*, I24.*, I25.*
Immunosuppression	042.*, 43, 44, 136.3*, 279.*, 288.0*, 288.1*, 288.2*, 288.4*, 446.*, 710.0*, 710.1*, 710.2*, 710.3*, 710.4*, 714.*, V08.*, V42.2*, V42.7*, V42.8*, V42.9*, V42.1*, V42.6*, V42.0*, V424, V58.0*, V58.1*, 996.8, 710, 963.1	B20.*, B59.*, B97.3, D47.Z1, D70.*, D71.*, D72.*, D73.*, D76.*, D80.*, D81.*, D82.*, D83.*, D84.*, D89.*, M05.*, M06.*, M07.*, M08.*, M30.*, M31.*, M32.*, M33.*, M34.*, M35.0, M35.9, Q89.0, Z21*, Z48.2, Z51.0, Z51.1, Z94.*, Z79.5, Z79.82
Immunosuppression (malignancy)	140.*, 141.*, 142.*, 143.*, 144.*, 145.*, 146.*, 147.*, 148.*, 149.*, 150.*, 151.*, 152.*, 153.*, 154.*, 155.*, 156.*, 157.*, 158.*, 159.*, 160.*, 161.*, 162.*, 163.*, 164.*, 165.*, 166.*, 167.*, 168.*, 169.*, 170.*, 171.*, 172.*, 174.*, 175.*, 176.*, 177.*, 178.*, 179.*, 180.*, 181.*, 182.*, 183.*, 184.*, 185.*, 186.*, 187.*, 188.*, 189.*, 190.*, 191.*, 192.*, 193.*, 194.*, 195.*, 196.*, 197.*, 198.*, 199.*, 200.*, 201.*, 202.*, 203.*, 204.*, 205.*, 206.*, 207.*, 208.*	C00.*, C01.*, C02.*, C03.*, C04.*, C05.*, C06.*, C07.*, C08.*, C09.*, C10.*, C11.*, C12.*, C13.*, C14.*, C15.*, C16.*, C17.*, C18.*, C19.*, C20.*, C21.*, C22.*, C23.*, C24.*, C25.*, C26.*, C30.*, C31.*, C32.*, C33.*, C34.*, C37.*, C38.*, C39.*, C40.*, C41.*, C43.*, C44.*, C45.*, C46.*, C47.*, C48.*, C49.*, C4A.*, C50.*, C51.*, C52.*, C53.*, C54.*, C55.*, C56.*, C57.*, C58.*, C60.*, C61.*, C62.*, C63.*, C64.*, C65.*, C66.*, C67.*, C68.*, C69.*, C70.*, C71.*, C72.*, C73.*, C74.*, C75.*, C76.*, C77.*, C78.*, C79.*, C7A.*, C7B.*, C80.*, C81.*, C82.*, C83.*, C84.*, C85.*, C86.*, C88.*, C90.*, C91.*, C92.*, C93.*, C94.*, C95.*, C96.*, D03.*, D46.*
Liver disease	571.*, 572.1*, 572.2*, 572.3*, 572.4*, 572.5*, 572.6*, 572.7*, 572.8*	B18.*, I81.*, I85.*, K70.*, K71.*, K72.*, K73.*, K74.*, K75.*, K76.*, K77.*
Metabolic disease	255.*, 270.*, 271.*, 272.*, 277.*, 278.00, 278.01	E00.*, E01.*, E03.*, E05.*, E06.*, E15.*, E16.*, E20.*, E21.*, E22.*, E23.*, E24.*, E25.*, E26.*, E27.*, E28.*, E29.*, E31.*, E32.*, E34.*, E66.01, E66.2, Z68.4, E70.*, E71.*, E72.*, E74.*, E75.2, E76.*, E77.*, E78.*, E79.*, E80.*, E83.*, E85.*, E88.*
Metabolic disease (diabetes mellitus)	250*, 251.* 357.2*, 362.0*, 362.11, 366.41	E08.*, E10.*, E11.*, E13.*

Description	ICD-9 Code	ICD-10 Code
Neurological/Musculoskeletal disorders	290.*, 294.1*, 318.1*, 318.2*, 330.*, 331.*, 332.*, 333.0*, 333.4*, 333.5*, 333.6*, 333.7*, 333.8*, 333.9*, 334.*, 335.*, 336.*, 340.*, 341.*, 342.*, 343.*, 345, 344.0*, 358.0*, 358.1*, 359.*, 756.1*, 756.3*, 756.4*, 756.5*, 756.6*, 768.5*, 780.3, 780.72	H49.81, M12.0, M36.0, E75.02, E75.19, E75.4, F01.*, F02.*, F03.*, F71.*, F72.*, F73.*, F84.2, G10.*, G11.*, G12.*, G13.*, G14.*, G20.*, G21.*, G23.*, G24.*, G25.*, G26.*, G30.*, G31.*, G32.*, G35.*, G36.*, G37.*, G40.*, G45.*, G46.*, G60.*, G61.*, G62.*, G63.*, G64.*, G70.*, G71.*, G73.*, G80.*, G81.*, G82.*, G83.*, G90.3, G91.*, G93.*, G94.*, G95.*, G99.2, P91.*, Q00.*, Q01.*, Q02.*, Q03.*, Q04.*, Q05.*, Q06.*, Q07.*, Q76.*, Q77.*, Q78.*, Q79.*, Q85.*, Q87.4, Q90.*, Q91.*, Q92.*, Q93.*, Q96.*, R41.*, R53.2, R54.*
Renal disease	285.21, 403.*, 581.*, 582.*, 583.*, 585.*, 587.*, 588.0*, 588.1*, 590.0* 593.8, V42.0*, V56.*, V45.1*	I12.*, N01.*, N02.*, N03.*, N04.*, N05.*, N06.*, N07.*, N08.*, N11.*, N14.*, N15.*, N16.*, N18.*, N25.*, N26.*, N28.*, Q27.1, Q27.2, Q60.*, Z49.*, Z91.15, Z94.0, Z99.2

Respiratory Outpatient Visits and Hospitalizations

Respiratory outpatient visits and hospitalizations will be defined using the following ICD-9 and ICD-10 diagnosis codes. Codes can be in any position. For hospitalizations, only discharge codes should be considered. Encounters occurring in the outpatient clinic, emergency department, urgent care, or via telehealth should additionally include encounters with codes related to signs/symptoms (at the bottom of the table).

Description	**ICD-10* code**
Pulmonary anthrax	A22.1*
Whooping cough	A37*
Other specified sepsis	A41.89
Legionnaire's Disease	A48.1*
Cytomegaloviral pneumonitis	B25.0*
Viral infection of unspecified site	B34 *
Aspergillosis	B44 *
Adenovirus	B97.0*
Enterovirus	B97.1*
Coronavirus	B97.2*
Respiratory syncytial virus as the cause of diseases classified elsewhere	B97.4*
Other viral agents as the cause of diseases classified elsewhere	B97.8*
Acute suppurative otitis media	H66.0*
Suppurative otitis media, unspecified	H66.4*
Otitis media, unspecified	H66.9*
Otitis media in diseases classified elsewhere	H67 *
Diseases of the respiratory system	J00-J99 *
Other viral diseases complicating pregnancy, childbirth and the puerperium	O98.5*
Diseases of the respiratory system complicating pregnancy, childbirth and the puerperium	O99.5*
COVID-19	U00
COVID-19	U07.1
COVID-19	U49
Encounter for observation for suspected exposure to biological agents ruled out	Z03.81 *
Encounter for observation for other suspected diseases and conditions ruled out	Z03.89 *
Encounter for screening for respiratory tuberculosis	Z11.1 *
Encounter for screening for other bacterial diseases	Z11.2 *
Encounter for screening for other viral diseases	Z11.5 *
Encounter for screening for other viral diseases	Z11.59 *
Encounter for screening for other infectious and parasitic diseases	Z11.8 *

Encounter for screening for infectious and parasitic diseases, unspecified	Z11.9 *
Contact with and (suspected) exposure to other viral communicable diseases	Z20.82 *
Contact with and (suspected) exposure to other viral communicable diseases	Z20.828 *
Contact with and (suspected) exposure to other communicable diseases	Z20.89 *
Contact with and (suspected) exposure to unspecified communicable disease	Z20.9 *
Mucocutaneous lymph node syndrome [Kawasaki]	M30.3 *
Encounters occurring in the outpatient clinic, telehealth, emergency department, or urgent care should additionally capture encounters with these codes	
Hemorrhage from respiratory passages, cough, abnormalities of breathing, pain in throat and chest, other symptoms/signs involving the circulatory and respiratory system	R04-R09 *
Fever	R50 *
Headache	R51 *
Malaise and fatigue	R53 *
Shock, unspecified	R57.9 *
Symptoms and signs specifically associated with systemic inflammation and infection	R65 *
Chills without fever	R68.83 *

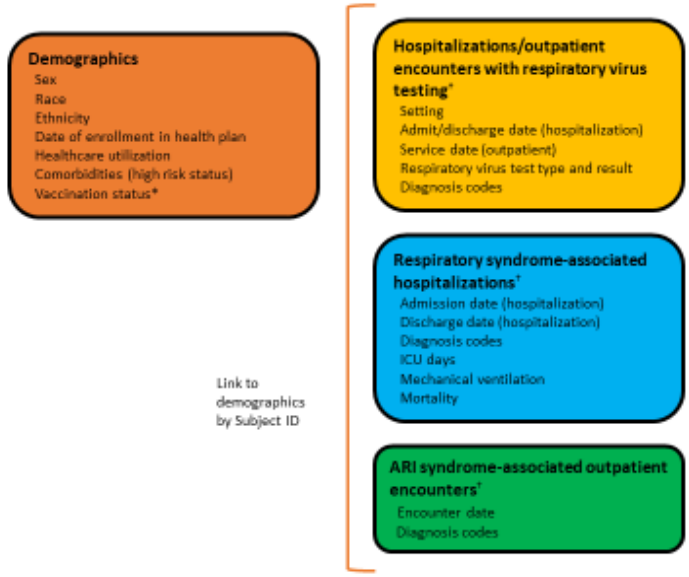
*For the complete list these of codes, please refer to the data dictionary referenced in Appendix B.

Appendix E: Proposed Data Structure to be Shared by Sites with Westat

Based on conversations with participating collaborating sites, study sites would prefer to pre-process individual-level records for each seasonal cohort and then share the cohort datasets with Westat & CDC. The proposed data structure would be one data package for each influenza season. For the primary objectives, data packages would be created for each season going back as early as the 2010–2011 season through the 2018–2019 influenza season. For secondary objectives, data packages would be created for the 2019–2020 influenza season and contemporary season, depending on whether the prospective data capture objective is exercised.

Each seasonal data package would include data as specified in Appendix B. Sites would be responsible for deriving data elements using the definitions from Appendix B and doing so prior to sending data to Westat.

Example 3: Pre-processed (by the study site) individual-level records for cohort are shared with Westat & CDC



All data linked and created variables developed prior to sending to Westat/CDC.

*For influenza and other vaccinations received dating back to 2010, where possible.
†For influenza season of interest.

Example 3: Pre-processed (by the study site) individual-level records for cohort are shared with Westat & CDC

All data linked and created variables developed prior to sending to Westat/CDC.

*For influenza and other vaccinations received dating back to 2010, where possible.
†For influenza season of interest.

Appendix F: Data Management Plan

See accompanying document “Data Management Plan.”

Appendix G: Suggestions for Site Data Validations using Primary Health Records

To ensure that extracted data reflect the underlying data from the primary health records, several validation steps are being requested, including review of a limited number of primary records. Below are suggestions for how many health records to review, how to stratify the sample that are reviewed, and how to report the results of the review.

- Perform primary record review on a minimum number of medical charts and compare the information in the primary record to the information captured through data extraction:
    - If data extraction methods or data storage platforms have changed during the study period, perform data validations for records from before and after the date when the change occurred.
    - If multiple health organizations contribute data to the site, perform data validations for each of the contributing organizations with differing data extraction methods or data storage platforms.
- A minimum number of charts should be reviewed for each of the following groups:
    - Unvaccinated for influenza (per registry, EMR or billing data)
    - Vaccinated for influenza (per registry, EMR or billing data)
    - Tested for influenza (per EMR or laboratory data stream)
    - Not tested for influenza (per EMR or laboratory data stream)

Sites who have participated in multi-site vaccination studies and have validation data from those studies can omit the unvaccinated and vaccinated groups from the primary record review.

- At a minimum for each of the 4 strata, above, 20 charts should be reviewed — for a total of 80 charts.
    - If sites are conducting chart reviews from multiple hospitals or health systems or organizations because of differences in data streams, data extraction methods, or data storage platforms, then the minimum number of chart reviews per group can be 10.
    - For example, if the site consists of 3 health systems/organizations, then chart reviews should be done for each of the health systems. If 10 charts are reviewed per group in a health system, then 40 total charts will be reviewed for each health system. Across 3 health systems, the total minimum number of charts would be 120.
- For each group, randomly sample among children and adults (e.g. vaccine records for 10 unvaccinated children, 10 records for unvaccinated adults, 10 records for vaccinated children, and 10 records for vaccinated adults).
- For those tested and not tested for influenza, randomly sample among children and adults with outpatient encounters and children and adults with inpatient admissions (e.g. 5 charts for children seen in the outpatient setting who were tested for influenza, 5 charts for children in the inpatient setting who were tested for influenza, 5 charts for children

seen in the outpatient setting who were not tested for influenza, 5 charts for children in the inpatient setting that were not tested for influenza, and the same pattern among adults).

- Validate data using known cohort members from relevant influenza seasons. We will not require that validations be performed on all study seasons, however sites should perform validation on seasons that are representative of the typical data extraction and data storage structure for the entire study.
- Validate against the following data elements at a minimum (more if needed)
    - Vaccination status
    - Influenza testing done and test results, if testing was done
    - Death
    - ICU admission
    - Mechanical ventilation
- Sites will not be required to review a minimum number of charts per data element or to achieve a certain percentage concordance between data obtained from data pull vs chart review.
- Use your best judgement to decide whether additional charts need to be reviewed or additional review of the EMR data pull programming needs to take place based on results
- Summarize results from validation in tables; examples of Tables 1 and 2 are below. Include additional tables for each season/period or site that undergoes validation.

TABLE 1. Characteristics of charts pulled for validation.

Study season:	
Characteristic	**Charts pulled (n)**
Pediatric outpatient encounters	
Adult outpatient encounters	
Pediatric inpatient admission	
Adult inpatient admissions	
Among charts pulled for inpatient admissions, number with:	
ICU admission	
Mechanical ventilation	
In-hospital death	

TABLE 2. Concordance between chart review and data pull.

Data Element	**Cases Reviewed (n)**	**Percent Agreement with chart (n, %)**	**Notes**
Influenza vaccination			
Influenza testing done			
Influenza test result			
ICU admission			
Mechanical ventilation			
In-hospital death			

Additional Notes:

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[4] https://www.cdc.gov/flu/about/burden/2018-2019.html

[5] https://gis.cdc.gov/grasp/fluview/FluHospChars.html

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Final Protocol
Virtual Network: Investigating the Risk of COVID-19-Associated Outcomes and COVID-19 Vaccine Effectiveness Using Integrated Medical and Public Health Records (VISION-COVID)

Centers for Disease Control and Prevention
& Westat

DRAFT vs 4.0: 6/9/2021

Study Summary

1. Title of Study

Investigating the Risk of COVID-19-Associated Outcomes and COVID-19 Vaccine Effectiveness Using Integrated Medical and Public Health Records

2. Investigators

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Participating sites

- HealthPartners Institute
- Kaiser Permanente Northwest
- Universities of California at Irvine, Los Angeles, San Diego, San Francisco and Davis
- University of Colorado, Denver
- Atrium Health
- Intermountain Healthcare
- Regenstrief Institute
- Columbia University
- Baylor, Scott and White Health

2.0 Protocol Objective

We aim to develop a multi-site collaboration to utilize electronic medical and public health records to address key questions about the clinical epidemiology of COVID-19 and COVID-19 vaccine effectiveness. Specifically, we will integrate additional sites (specifically, Atrium Healthcare, Intermountain Healthcare, Regenstrief Institute, Columbia University, and Baylor Scott and White Health) into an existing virtual network of healthcare systems that follows an IRB-approved protocol. Through this collaboration of healthcare systems and research organizations, the primary aim is to estimate the effectiveness of COVID-19 vaccination in preventing laboratory-confirmed COVID-19 associated health and medical utilization outcomes as well as the incidence of COVID-19 associated outcomes by socio-demographic and high-risk groups. Similar objectives will be accomplished for influenza virus disease and vaccination during periods of local influenza circulation. Deidentified individual-level data will be extracted from medical, laboratory, and vaccination records from each site and defined using a common codebook to accomplish these objectives.

3.0 Scientific Background

Burden of SARS-CoV-2

SARS-CoV-2 continues to be of broad global public health importance and concern due to the global burden of COVID-19 illness and other associated medical complications and severe outcomes identified to date, since the initial identification of the virus in Wuhan, China in December 2019. As of November 23, 2020 in the United States, SARS-CoV-2 infections have resulted in more than 12.1 million cases of COVID-19, with a current overall cumulative COVID-19 hospitalization rate of 228.7 per 100,000, and more than 255,000 deaths.[1] Early evidence points to significant burden of severe illness related to SARS-CoV-2 infection by race

and ethnicity, age, socio-economic status, and underlying health condition status.[2] Yet, there are numerous knowledge gaps regarding how COVID-19 and especially severe manifestations of disease impact on different socio-demographic and health risk groups.

Emerging data on race and ethnicity suggest an overrepresentation of non-Hispanic black patients among those hospitalized for COVID-19.[3] A study using integrated electronic health records identified adults with suspected and confirmed COVID-19 found that compared with non-Hispanic white patients, black patients had 2.7 times the odds of hospitalization, after adjusting for age, sex, comorbidities, and income.[4]

While all people are susceptible to infection with this novel virus, older adults have elevated rates of COVID-19-associated hospitalization and the majority of persons hospitalized with COVID-19 have underlying medical conditions.[5] In contrast to influenza disease which can be severe in both young children and older adults[6], this has not been true with COVID-19. Population data from China and Italy indicate that children are mildly affected in comparison to adults, representing approximately 5% of cases and less than 1% of admissions to hospital.[7] A report describing the burden of COVID-19 infection in North American pediatric intensive care units confirmed that severe COVID-19 can occur in children, though this occurs far less frequently than among adults.[8]

COVID-19 has also notably resulted in severe and life-threatening disease among working-age adults and those without prior underlying medical conditions. Further information is needed on the different manifestations or phenotypes of severe COVID-19 across age, health, and other risk groups.

Burden of other respiratory viruses and COVID-19

Respiratory viruses, including influenza and respiratory syncytial virus (RSV) among others commonly circulate in the United States during a typical influenza season. However, the incidence of other respiratory viruses during the 2020-21 influenza season and our ability to conduct surveillance may be impacted by COVID-19 in multiple ways. The circulation of seasonal influenza viruses may be reduced as a result of altered health behaviors (e.g., wearing masks, washing hands) and social distancing measures in response to COVID-19. For example, a quasi-experimental study assessing the trends in seasonal influenza cases from the 2014-2015 season to the 2019-2020 season in 11 countries and regions, found that in East Asia, the number of seasonal influenza cases in the 2019-20 season was lower after the onset of COVID-19 transmission compared to previous years.[9] Influenza testing practices may also change; indeed, influenza testing across the U.S. was higher than normal during April 2020 because of the COVID-19 pandemic.[10] Consequently, data collection on co-circulating respiratory viruses with SARS-CoV-2, especially with respect to testing, care-seeking behavior, and vaccination, will provide important context in interpreting COVID-19 results.

Clinical Features of Severe COVID-19

Although medically attended COVID-19 typically manifests as an acute respiratory disease, SARS-CoV-2 infection can also cause a variety of other clinical manifestations, including myocardial dysfunction, acute kidney injury and neurologic illness.[11] More information is needed on the different clinical phenotypes of COVID-19. Similar to research on severe influenza disease[12-16], distinctions can be made between virus disease resulting in acute lung injury and often bacterial superinfection, virus disease associated with extrapulmonary disease, and secondary complications to other organs systems, including neurological impairment. Information is also needed on how these different clinical phenotypes occur within the context of

otherwise healthy children and adults versus frail individuals with inadequate physiologic reserve.

Most VE studies view hospitalization as the hallmark of severe disease.[17] Yet, the decision to admit a patient is influenced by many factors (e.g., age, medical history, financial and family resources, clinical decision-making, resource availability) independent from the signs and symptoms of disease. Therefore, more information is needed to differentiate between the clinical severity COVID-19 versus other host and environment factors (such as the local attack rate and population susceptibility) that may be associated with the clinical threshold for hospital admission and discharge and how this may vary between hospitals, medical systems, and regions.

COVID-19 Vaccine Effectiveness

Although results on the immunogenicity of COVID-19 vaccines from Phase II trials[18-19] and early reports on the clinical effectiveness of the vaccines from Phase III trials are encouraging, there will soon be an urgent need for data on the field performance of these vaccines and their effectiveness in preventing laboratory-confirmed COVID-19-associated emergency department and urgent care (ED/UC) visits and hospitalizations.

Evaluating the real-world performance of COVID-19 vaccines is important for at least five reasons. First, since immune response to vaccines and their subsequent protection against infection and disease often vary by sex, age, underlying health status, and other host factors, the preventive benefit of new vaccines may differ in the general public compared to participants in randomized clinical trial.

Second, real-world assessments can examine preventive benefits months following vaccination in contrast to the relatively brief surveillance evaluations in Phase III trials. For example, if immune protection following vaccination wanes over time, the impact of waning on VE against medically attended COVID-19 can only be assessed over an extended period of evaluation. Similarly, real-world assessments will also be needed to determine if VE of new vaccines vary depending on the amount and duration of virus exposure and the extent of personal and community infection control measures. Such effects could result in differences in VE by sex, age, race and ethnicity, occupation, socio-economic status, rural versus urban settings, and other host and environmental factors.

Third, the field performance of vaccines depends in part on the conditions of their administration and adherence to cold-chain requirements. This will be especially challenging for some messenger RNA manufactured COVID-19 vaccines that must be stored at -70◦ Celsius.[20] Studies of the real-world management and administration of influenza vaccines often identified gaps in cold chain management that may have compromised vaccine immunogenicity.[21] Therefore, it is unclear whether challenges in the administration of new COVID-19 vaccines may result in compromised performance that would only be detected in downstream evaluations of their clinical VE.

Fourth, Phase III trials are focused on symptomatic SARS-CoV-2 infection as the primary outcome, and most of these will be relatively mild illnesses. Therefore, field studies are required to assess VE in preventing less frequent but severe outcomes, including COVID-19 associated hospitalizations and very severe outcomes, including intensive care unit (ICU) admissions, mechanical ventilation, and/or death. VE in preventing secondary complications and sequalae following COVID-19 must also be assessed in large prospective population evaluations. Certainly, information on VE against this continuum of medically attended COVID-

19 outcomes by socio-demographic, underlying health, and other risk groups will also require assessments with large populations.

Fifth, since Phase III trials evaluate each vaccine product separately, real-world evaluations are required to compare the field VE of different vaccine products in different population groups. It is likely that multiple vaccine produces will be rolled out to different populations, at different times, and in different geographic regions making such comparisons challenging.

3.1 Rationale and Justification

CDC communicates with medical and public health professionals and the public about the burden of SARS-CoV-2 and the importance of prevention and control measures, which will include COVID-19 vaccines when they are available. Timely information on COVID-19 burden and COVID-19 VE will inform public health models that determine public health policy, guidance, and resource allocations. This information will also be used to inform, educate, and guide the public on ways to protect themselves and their family from this new virus. Given widespread skepticism and hesitancy associated with the new COVID-19 vaccines,[22-23] timely information on the real-world value of COVID-19 vaccines in preventing severe disease and impairment is especially important.

To estimate the burden of COVID-19 and the effectiveness of newly available COVID-19 vaccines in preventing this burden, a prospective assessment of patients receiving care in ED/UC settings and hospitals is required. This effort expands the number of participating health systems and research organizations participating within the existing VISION-COVID network. The network is being expanded to cover more diverse populations in more geographic regions in the US since this increases the capacity to assess different COVID-19 vaccine types and increases the likelihood that the virus will be circulating within the study population. Increasing the total number of ED/UC visits and hospitalizations will also increase CDC's ability to conduct timely estimates of VE among early vaccine target groups and then ultimately among the general population. The combined observations across the network will also facilitate estimates of VE in relatively small risk groups and against low frequency but severe COVID-19 outcomes and sequalae.

4. Study Objectives

We aim to develop a multi-site collaboration to utilize medical, laboratory, vaccination, and other public health records to address key questions about the clinical epidemiology of COVID-19 and COVID-19 VE. Similar questions will be examined for influenza epidemiology and VE during periods of local influenza circulation. These objectives will be accomplished separately by different age strata adults and children. Specifically, we will integrate additional sites into an existing virtual network of healthcare systems, using a common research methodology, data platforms, and data dictionary. The following primary and secondary objectives are planned.

1. Primary Objectives

1. Estimate the COVID-19 vaccine effectiveness (VE) in preventing hospitalizations associated with laboratory-confirmed SARS-CoV-2 infection, and do so:

a. Using alternative case definitions for COVID-19 disease that will be linked with SARS-CoV-2 testing, including existing COVID-19 medical case definitions and broader syndromic manifestations of disease

b. Against severe inpatient outcomes, including ICU admission, invasive mechanical ventilation, prolonged length of stay (LOS), or death

c. By socio-demographic and high-risk groups, including age, race and ethnicity, socio-economic status, and underlying medical conditions

d. By COVID-19 vaccine product, vaccine type (e.g., mRNA-, plasmid DNA-, adenovirus-based), dose (e.g., one dose vs. two dose), and time since vaccination.

2. Among study sites with well-characterized source populations, estimate the rate of hospitalizations associated with laboratory-confirmed SARS-CoV-2 infection since February, 2020 by socio-demographic, underlying health, and other high-risk groups.

2. Secondary Objectives

1. Estimate COVID-19 VE in preventing ED/UC visits associated with laboratory-confirmed SARS-CoV-2 infection, and do so by the populations, outcomes, and vaccine types described in Primary Objective 1.

2. Estimate COVID-19 VE in preventing outpatient visits associated with laboratory-confirmed SARS-CoV-2 infection within the pediatric population, and do so by the populations, outcomes, and vaccine types described in Primary Objective 1.

3. Assess whether COVID-19 vaccination attenuates disease severity among those with breakthrough SARS-CoV-2 infections, as indicated by:

a. Estimating the odds of severe hospital outcomes (such as ICU admission, mechanical ventilation, prolonged LOS, or death) associated with COVID-19 among vaccinated versus unvaccinated hospitalized patients

b. Estimating such effects by age, underlying health status, vaccine type and doses, and other potential effect modifiers.

4. Rule-out whether COVID-19 vaccination is associated with increased likelihood of severe disease (i.e., enhanced disease) among those with breakthrough SARS-CoV-2 infections, as indicated by increased risks of severe outcomes (described in Primary Objective 4) among vaccinated patients.

5. Among study sites that can describe moderate- or long-term outcomes following index hospitalizations, estimate COVID-19 VE against secondary pulmonary and extrapulmonary complications and sequelae following discharge from a laboratory-confirmed COVID-19 hospitalization, and do so by the populations, outcomes and vaccine types described in Primary Objective 1.

6. Describe the clinical testing practices, primary and secondary clinical diagnoses, and other clinical factors and features associated with laboratory-confirmed SARS-CoV-2 infections diagnosed within pediatric outpatient clinics, ED/UC, and hospitals and how these different activities and manifestations vary by medical history and socio-demographic, underlying health, and other risk groups.

7. Estimate the influenza VE in preventing hospitalizations associated with laboratory-confirmed influenza virus infection during periods of local influenza

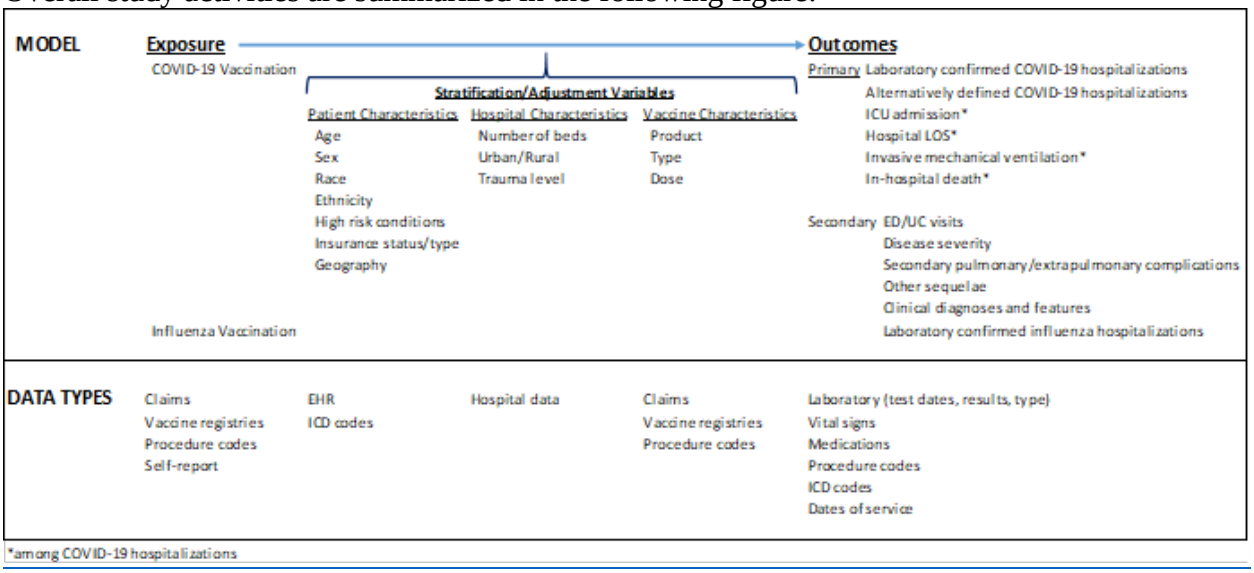
circulation at study sites, and do so by populations, outcomes, and vaccine types similar to those described in Primary Objective 1.

8. For study sites will well-characterized source populations, estimate the rate of hospitalizations associated with laboratory-confirmed influenza virus infection during periods of local influenza circulation at study sites, and do so by socio-demographic, underlying health, and high-risk groups.

5. Methods

1. Study design

Overall study activities are summarized in the following figure:



2. Participant eligibility

The initial analytic population is intentionally broad in order to examine a wide range of COVID-19 disease manifestations and the variety of patients that are tested for SARS-CoV-2 infections. Specifically, individuals of all ages who have an index ED/UC or inpatient encounter associated with any acute illness and/or have respiratory virus testing performed at an index ED/UC or inpatient encounter at a healthcare facility within the network during the study period will be included.

3. Observation time

SARS-COV-2 is a novel virus and it is unclear whether it will circulate with a defined seasonality. Consequently, the study period will begin on September 1, 2019 and could end on July 30, 2022. If SARS-CoV-2 is later determined to circulate with a known seasonality, analytic cohorts could be created to reflect seasonality a posteriori and objectives could be performed using these analytic cohorts.

4. Exposures and covariates of interest

Vaccination status

COVID-19 vaccination is the primary exposure of interest for COVID-19 VE objectives. Influenza vaccination is the exposure of interest for secondary influenza VE objectives. The target groups for VE evaluations and the criteria for full versus partial vaccination with either vaccine will follow the age- and risk-group specific and vaccine-specific guidance of the Advisory Committee on Immunization Practices (ACIP).

Documentation of vaccination status will rely on multiple sources of information. Electronic documentation by health records, state/local vaccine registries, all-payer claims or other billing databases is expected to be the primary method. However, self-report of vaccination status from ED/UC or hospital records may also be considered, especially for patient groups and settings where electronic records may be incomplete. All available vaccine information will be extracted from available sources, including date of vaccination, type of vaccine administered, vaccination route, location of vaccination, vaccine lot number and number of vaccine doses, and these variables will be added to the codebook. For vaccination data extracted from EHRs, sites will provide information on how vaccination data was pulled (for example, though use of CPT, CVX, or other internal immunization codes). Self-reports may also be extracted from EHRs, but it is not anticipated that separate chart abstraction or natural language processing will be required.

Network sites will provide information on the types and number of sources queried for vaccine data. Because each site is querying multiple sources, a hierarchy of sources will be established for each site or through joint consensus with collaborating partners.

For a subset of patients (number to be determined by joint consensus by the collaborating partners), accuracy of extracted vaccination data will be verified through manual review of source data (i.e. medical chart review). For study sites that rely in part on self-report vaccination status, a survey of patients will be conducted to verify their self-reported vaccination status similar to previously published methods of validating influenza vaccination documentation.[24]

Clinical Virus Testing Results

Data on all SARS-CoV-2, influenza virus, and other respiratory virus testing results will be extracted for index ED/UC visits and hospitalizations. For study sites applying a look-back period or building a patient cohort (referenced later in this section within "Population subgroups and covariates of interest"), clinical testing results will also be extracted for all included patients during the surveillance period. In particular, after identifying an index inpatient encounter (and later ED/UC encounter), any available prior clinical testing results will be examined to identify any positive test result for a virus (e.g., SARS-CoV-2) before said encounter. For each test result, sites will provide data on encounter type associated with the lab test, diagnoses (based on ICD code) associated with encounter during which testing occurred, date of specimen collection, type of test performed and test result. Network sites will provide information on how laboratory testing data was pulled (for example, through use of CPT or other procedure codes or from laboratory databases). For a subset of patients (number to be determined by joint consensus by the collaborating partners), accuracy of extracted laboratory data will be verified through manual review of source data (i.e. medical chart review or review of laboratory databases). Respiratory viruses for which data will be collected, in addition to influenza, include respiratory syncytial virus, adenovirus, parainfluenza virus, human metapneumovirus, rhinovirus, enterovirus, coronaviruses, and other viruses, including novel viruses.

High risk underlying medical conditions

For the common data set focused on patient ED/UC encounters or hospitalizations only, high risk underlying medical conditions will be defined using ICD-10 diagnosis codes (see Appendix A). However, site-specific methods may also be applied that draw on broader data sets (e.g., prescribed medications; claims), registries, and look-back periods to assess the presence of high risk conditions. Methods that allow for common versus site-specific approaches and how they apply to minimally versus fully adjusted VE models are described later in this section "Population subgroups and covariates of interest". High-risk underlying medical conditions include:

- Chronic lung disease;
  - Asthma;
  - COPD;
  - Pulmonary tuberculosis
  - Endemic mycoses
- Chronic metabolic disease;
  - Diabetes mellitus;
- Blood disorders;
- Cardiovascular disease;
  - Coronary artery disease;
  - Heart failure;
  - Congenital heart disease;
- Clinical obesity
- Neuromuscular disorder;
- Neurologic disorder;
- Immunocompromised condition;
  - Solid organ malignancy;
  - Hematologic malignancy;
  - Solid organ transplant;
  - Hematopoietic stem cell transplant;
- Chronic renal disease;
- Gastrointestinal/liver disease;
- Rheumatologic/Autoimmune condition;
- Prematurity (applicable only to pediatric population);
- Medical complexity (applicable only to pediatric population);
- Congenital heart disease (applicable only to pediatric population).

Additional underlying conditions, including, but not limited to, pregnancy, sickle cell disease, hypertension, and cystic fibrosis have also been associated with increased risk of severe influenza or COVID-19 disease and thus might be further defined and explored in the network.

Data on other host factors, healthcare context, and exposures of interest

Individual level data will be extracted and provided on:

- Patient age as of the start date of the observation period
- Sex
- Race and ethnicity
- Date of enrollment in the membership health plan or date of first qualifying healthcare encounter within the look-back period (the encounter that included the individual into the cohort) (only applicable to datasets for the fully adjusted VE

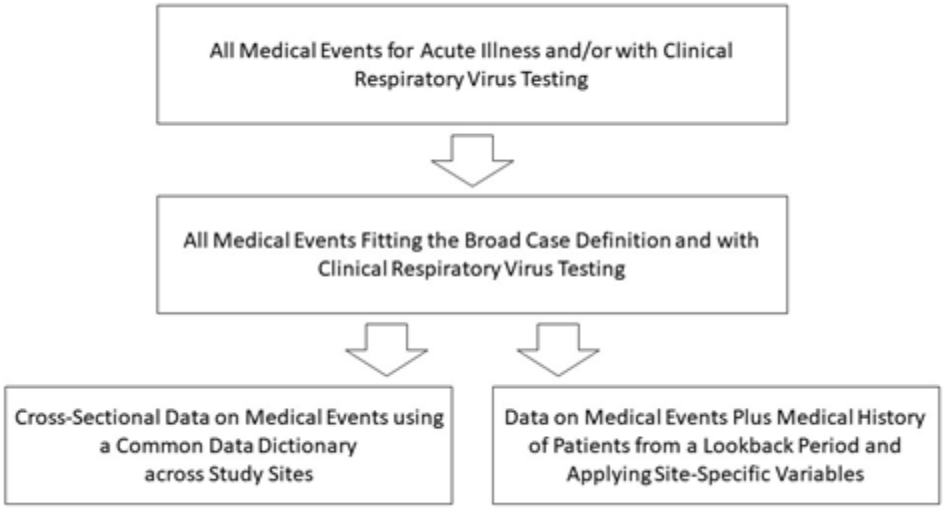
model, as referenced later in this section "Population subgroups and covariates of interest")

- Primary, secondary, tertiary and quaternary insurance type
- Census tract (Algorithms for determining census tract will be determined by group consensus and applied uniformly across the network sites) and similar methods to assess socio-economic status
- Characteristics of the hospitalization (e.g., admission source, discharge disposition, length of stay)
- Variables characterizing the facility (e.g., facility ownership, facility type, urban/rural classification, tertiary and teaching hospitals, geography)
- Variables related to clinical testing (e.g., cycle threshold value, type of PCR test, variable to standardize readings across machines)
- Proxy variables to identify healthcare workers, frontline workers, and essential workers

Additional factors of interest include respiratory support (such as supplemental oxygen non-invasive mechanical ventilation), clinical laboratory values, vital signs, clinical procedures that are indicative of illness severity, or medications used for treatment in the inpatient or outpatient setting. The available data elements and the best algorithms to ascertain these exposure variables will be examined and customized within each study site. As more details on host, environment, and exposure variables that are relevant to the clinical epidemiology of COVID-19 and COVID-19 VE are identified, the methods and protocol will be amended as needed.

Patient subgroups and covariates of interest for objectives centered on medical events

Most of the primary and secondary objectives of this effort center on two categories of medical events: ED/UC encounters and hospitalizations. Pediatric outpatient data will be integrated based on sites' feasibility. The following data structure applies to all types of events.



The first level of data centers on all medical events associated with acute illness (using a broad case definition) and/or included respiratory virus testing. This dataset will utilize the cross-sectional data available for that event, including but not limited to diagnostic and syndromic codes, demographic information, laboratory results, and vaccination data. This level of information will allow sites to describe clinical testing practices and reasons for medical care for the full denominator of events that could be considered.

The second level of data narrows this full set of events to those involving a broad case definition for diseases of interest and those for which clinical testing for infection occurred. From these events, a cross-sectional data set will be created using a common data dictionary across study sites. Within each site, a second set of data will be created which adds medical history to each patient event using a lookback period within their electronic records. This data will consist of common data elements across sites, but the patient inclusion criteria and specific variables may differ by site depending on data availability and structure. This same site-specific data set will also include prospective assessments (look-forward) of outcomes such as re-admissions, complications, and sequalae.

Patient subgroups and covariates of interest for objectives centered on rates and other population measures

Most study sites will also create data sets for cohorts based on health plan members and/or medical utilization history. For sites which can characterize source populations in this way, rates of laboratory-confirmed COVID-19 outcomes can be estimated using cohort denominators. Index pediatric outpatient, ED/UC and hospital events can also be examined within the prospective cohort framework in contrast to the cross-sectional approach described above.

5. Outcomes of interest

The primary outcome of interest centers on pediatric outpatient visits, ED/UC encounters or hospitalizations associated with an acute respiratory illness or other COVID-19-like illness (ARI/CLI) with laboratory-confirmed SARS-CoV-2 infection. Other outcomes of interest involve alternative case definitions (such as extra-pulmonary disease not included in ARI/CLI), specific types of medical utilization (e.g., intensive care unit admission, invasive mechanical ventilation, and in-hospital death), and secondary events that occur following the index events (such as secondary pulmonary and extrapulmonary complications and sequelae). Additional details in defining some of these outcomes are listed here:

- Hospitalizations, ED/UC encounters, and pediatric outpatient visits associated with an ARI/CLI or other acute illness associated with COVID-19 will be defined using ICD-10 diagnosis codes.
- Laboratory-confirmed infection diagnosis will be determined by examining clinical laboratory testing that was conducted up to 14 days prior to, during, and up to 3 days after the index medical event.
- Re-admissions that occur up to 14 days from hospital discharge may be considered part of the same medical event.
- Severe patient outcomes among persons hospitalized with laboratory-confirmed SARS-CoV-2 and influenza-associated respiratory hospitalization will include ICU admission, invasive mechanical ventilation, in-hospital death.

- Complications that occur during a respiratory hospitalization will initially be defined using ICD coded discharge diagnoses. Diagnoses will be initially aggregated into systems for acute respiratory, acute renal, acute neurological, acute cardiovascular, and acute inflammatory complications. Complications may be further refined using specific ICD codes, with the possibility of also using clinical laboratory data, vital signs, medications, and other interventions. These refinements will be discussed in a working group setting and will be implemented after network consensus.
- Healthcare encounters with ICD codes for outcomes of interest that occur within the 12 months following discharge date of a respiratory hospitalization or any COVID-19 tested hospitalization. The date, setting, and diagnostic codes from these encounters will enable analysis of complications, sequelae, frailty, and increased healthcare utilization after a SARS-CoV-2 infection. The time frame for capturing data on potential sequelae may be refined and ICD codes for outcomes of interest will be identified, which will be discussed in a working group setting and will be implemented after network consensus.
- The criteria described above can be applied to laboratory-confirmed influenza virus infections.

6. Summary of data elements for primary and secondary objectives

In addition to the data elements being captured in the codebook (Appendix A), additional data elements being pursued to meet the primary and secondary objectives are listed below. Elements with asterisk (*) will be further defined through working groups and network consensus:

1. All respiratory hospitalizations during the observation period:
   - LOS in general hospital ward and LOS in ICU (as determined by time and dates of admission, transfer, and discharge events)
   - Characteristics of the facility (e.g., facility type, facility ownership, trauma level, urban vs. rural location, number of beds, teaching vs. not)
   - Non-invasive respiratory support*;
   - Where patient is admitted from (home, long-term care facility, etc.)*;
   - Discharge disposition*;
   - Vital signs*;
   - Clinical laboratory values*;
   - Medications*.
   - Geographic clustering
2. All healthcare encounters that occur after respiratory hospital discharge*:
   - Encounter setting;
   - Encounter date; and
   - Diagnosis codes.

6. Statistical Analysis

1. Analysis Plan

The proposed analytic plan is subject to review and revision by key stakeholders, including CDC, Westat, and collaborating partners. Methods will be amended as necessary.

Rates

Rates will be estimated for:

- Hospitalizations associated with laboratory-confirmed SARS-CoV-2 infection between February 2020 and the end of the observation period
- Hospitalizations associated with laboratory-confirmed influenza virus infection during periods of local influenza circulation

The denominator will be the cumulative at-risk person-time contribution for individuals who meet the cohort definition. Sites with well-characterized source populations are anticipated to enumerate this person-time and estimate these hospitalizations rates, though sites, in consultation with CDC and Westat, may decide whether to contribute to the rate estimation. The operationalized definition of at-risk person-time will be discussed and agreed upon with the sites who elect to estimate rates, CDC, and Westat. Hospitalization rates will be estimated by socio-demographic and high-risk groups, including age, race and ethnicity, and underlying conditions. These methods for estimating hospitalization rates may be modified to estimate other rates of interest (e.g., rates of ED visits, rates of acute respiratory illness inpatient or outpatient encounters), as feasible.

Patterns of testing and care-seeking to inform national and local disease burden models

- Describe the frequency of clinical testing for SARS-CoV-2 (and for influenza separately) among encounters for ARI and other acute illness associated with COVID-19 by setting (e.g., inpatient, ED), age group, high-risk status, COVID-19 vaccination, current seasonal influenza vaccination, encounter outcomes, prior healthcare utilization, and timing of the encounter within the pandemic
    - This will be calculated by socio-demographic and high-risk groups
- Estimate the testing rate for SARS-CoV-2 and separately for influenza (and then also restricted to PCR testing)
    - This will be calculated by socio-demographic and high-risk groups
- Describe the frequency of clinical testing for SARS-CoV-2 and for influenza in the cohort during the observation period by setting, age group, presence of underlying conditions, prior healthcare utilization, and timing of encounter within the pandemic
- Assess patient and clinical characteristics and predictors of SARS-CoV-2 testing and influenza testing using bivariate tests of association and/or multivariate regression
    - Repeat this analysis but focusing on SARS-CoV-2 positivity (compared to SARS-CoV-2 negativity among persons tested) and similarly for influenza positivity
    - Assess separately for hospitalizations and ED encounters associated with an ARI/CLI and other acute illness associated with COVID-19
- Compare the distribution of settings for seeking care (e.g., telemedicine, ambulatory, urgent care, ED) among persons who meet the case definition for ARI/CLI and other acute illness associated with COVID-19 before and during the COVID-19 pandemic.

These analyses will be useful in evaluating potential biases associated with clinical testing for SARS-CoV-2 and influenza, as a component of estimating COVID-19 and influenza vaccine effectiveness.

COVID-19 vaccine effectiveness (VE) sample size considerations

For sample size or observation number considerations, analysis focused on the primary objective of VE against COVID-19-associated hospitalizations. Sites that will be contributing to this effort include all of the sites mentioned above, in addition to three non-Westat sites. The combined effort will involve up to eleven sites sending electronic medical data from hospital visits of patients with ARI/CLI or other acute illness associated with COVID-19, including COVID-19 vaccination status and laboratory testing results. The sites will be expected to send updated data every two weeks; thus, observation needs were estimated considering this bi-weekly schedule. The aim of this analysis is to determine the number of weeks required to accumulate sufficient data to achieve 80% power to detect a vaccine effectiveness of 60% using a minimally adjusted case control model. The model was simulated by generating data for the average weekly acute respiratory illness (ARI) visits for each site by age group and with assumptions for overall VE and VE by age groups.

The number of subjects is estimated by using the mean/median ARI/CLIs seen weekly over the course of a year as reported by each potential site or platform.

Table. Anticipated sites and number of ARI/CLIs by age group

Site or Platform	Median/ Mean Weekly Hospital Admissions for ARI/CLI Over 1 Year		
	Ages 18-49	Ages 50-64	Ages ≥65
Site 1	55	75	279
Site 2	93	129	378
Site 3	80	92	115
Site 4	7	9	23
Site 5	6	9	37
Site 6	22	28	62
Site 7	171	175	266
Site 8	152	195	346
Site 9	19	25	93
Site 10	81	90	213
Site 11	95	41	88

We assumed that sites will test between 25% and 50% of ARI/CLI patients for COVID-19 by RT-PCR (or by rapid antigen tests confirmed by PCR). We assumed between 4% and 10%

will test positive. We simulated scenarios where vaccination status can be confirmed for between one third and two thirds of patients. We assumed vaccine uptake and specifically completion of the 2-dose regimen will vary by age group and increase over-time. We assumed that the analytic period would begin when adults under age 65 years will have 5-8% 2-dose vaccination coverage and achieve 35-40% vaccination by the end of the year; adults over age 65 were assumed to start at 10-15% 2-dose vaccinated and achieve 65-70% vaccination by the end of the year.

Table. Simulation assumptions for each site

EMR Site	% Tested	% Positive	%Vaccine Status known	Age Group	Vaccine coverage rates by quarter
1	25%	4%	33%	<65	(5%, 10%, 20%, 35%)
				≥65	(10%, 20%, 35%, 65%)
2	50%	4%	66%	<65	(8%, 13%, 25%, 40%)
				≥65	(15%, 25%, 40%, 70%)
3	25%	5%	66%	<65	(8%, 13%, 25%, 40%)
				≥65	(15%, 25%, 40%, 70%)
4	50%	5%	66%	<65	(5%, 10%, 20%, 35%)
				≥65	(10%, 20%, 35%, 65%)
5	25%	6%	33%	<65	(5%, 10%, 20%, 35%)
				≥65	(10%, 20%, 35%, 65%)
6	50%	6%	33%	<65	(8%, 13%, 25%, 40%)
				≥65	(15%, 25%, 40%, 70%)
7	25%	8%	33%	<65	(8%, 13%, 25%, 40%)
				≥65	(15%, 25%, 40%, 70%)
8	50%	8%	33%	<65	(5%, 10%, 20%, 35%)
				≥65	(10%, 20%, 35%, 65%)
9	25%	9%	66%	<65	(5%, 10%, 20%, 35%)
				≥65	(10%, 20%, 35%, 65%)
10	50%	9%	33%	<65	(8%, 13%, 25%, 40%)
				≥65	(15%, 25%, 40%, 70%)
11	25%	10%	66%	<65	(8%, 13%, 25%, 40%)

				≥65	(15%, 25%, 40%, 70%)

Field VE for COVID-19 vaccines are assumed to be between 60% and 75%.

Simulated subjects were created for each site and age group according to the numbers in the above Table, assuming two weeks of accrual, and randomly assigned to a testing status, positivity status, and 2-dose vaccination status based on the assumptions in the above Table. Subjects assigned to be 2-dose vaccinated had their odds of test positivity adjusted by the assumed VE. Odds of being COVID-19 positive was analyzed using a marginal logistic model with vaccination as a main effect and clustering by site.

The simulation was repeated 1000 times and power calculated. This was repeated, accruing an additional two weeks of data each time, until 80% power was achieved. The following VE's were tested at both 60 and 75%.

1. Overall VE adjusted for group (18-49, 50-64, ≥65)
2. VE by age group, dichotomous (18-64, ≥65)
3. VE by age group, multinomial (18-49, 50-64, ≥65)

The results of the simulation were as follows:

1. To achieve 80% power to detect a VE of 60% or 75% for all adults adjusted by age group, we would need 4-6 weeks of data across sites.
2. To achieve 80% power to detect a VE of 60% to 75% for adults over age 65 years, we would need 6-8 weeks of data. For a VE strata of adults under age 65 years, we would need 14 weeks.
3. To achieve 80% power to detect a VE of 60% to 75% for adults aged 18-49 or 50-64 years, we would need 6 months of data.

COVID-19 VE estimation models

The primary statistical model for estimating COVID-19 VE will be the test-negative design (TND), whereby VE equals 1 − odds ratio [ratio of odds of vaccination among COVID-19-positive cases to the odds of vaccination among COVID-19-negative controls] × 100% using logistic regression. The TND has been used extensively to estimate VE against medically attended influenza virus illness and is believed to minimize biases associated with access to vaccines and healthcare seeking.[25-26]

COVID-19 VE will be estimated using multivariate logistic regression with laboratory-confirmed SARS-CoV-2 infection as the outcome and COVID-19 vaccination status as the exposure of interest. A set of covariates will be included in the model to adjust for potential confounding. A minimally adjusted model will include *a priori* determined covariates that are expected to be associated with both the likelihood of COVID-19 vaccination (and complete vs. partial vaccination [based on ACIP criteria]) and with the likelihood of COVID-19 positivity. A fully adjusted model will be estimated using a propensity score modeling approach. VE is calculated as a function of the adjusted odds ratio (aOR) where VE=1-aOR.

For the fully adjusted model, differences in vaccinated and unvaccinated subjects will be balanced for each site using inverse propensity score weighting. Propensity to vaccinate will be estimated with boosted regression trees and used to calculate average treatment effect (ATE) weights.[27] Variables to be used in predicting vaccination status include demographics (e.g. age, sex, race), high-risk medical conditions (e.g. lung disease, heart disease, immunosuppression),

healthcare utilization patterns, vaccination history, and other exposures of potential importance. Propensities and weights will be calculated using R package twang[28] or comparable software.

To estimate overall VE using fully adjusted models across sites, heterogeneity across site-specific VEs will be assessed using the Q and I^2 statistics. If heterogeneity is found to be substantial, only site-specific VEs will be reported. Otherwise, all site data will be pooled and an overall VE will be estimated using either a mixed-effects or generalized estimating equation model to account for correlation among observations within sites.

To address study objectives, VE models will be stratified by socio-demographic, health, and other risk groups, as data becomes available. VE models focused on ED or UC outcomes and models focused on children will apply the same methodology.

For the sites with well-characterized membership or source population data is available and thus the study population's person-time at risk can be estimated, COVID-19 VE will be calculated using survival analysis framework. The hazard ratio (HR) will be fit using calendar time to account for the exact calendar date of each COVID-19 case. Individuals may go from unvaccinated to vaccinated, and thus may contribute both unvaccinated and vaccinated person-time at risk. To allow for the vaccination status to be time-varying and to model possible re-infection, the Anderson and Gill (AG) extension of the Cox Proportional Hazard (PH) model will be used to estimate VE. Robust standard errors will be calculated using a sandwich covariance matrix to predict covariance among observations. COVID-19 VE will be calculated by estimating the hazard ratio of lab confirmed SARS-CoV-19 positivity among vaccinees and non-vaccinees; VE(%)=(1-HR)[Equation]100.

7. Data Sources and Management

1. Data Sources

Many of the required patient data variables are routinely captured in the EHR. Others may need to be added from additional sources such as participant health plan enrollment or administrative data, administrative claims, or vaccine registries linked to EHR data at the patient level. Reliance on open text fields, such as physician notes, will be kept to a minimum.

Each data element that is extracted will have an operational definition accounting for the coding structure, completeness, and limitations of the data source. This operational definition is particularly important to address situations that may arise when extracting data from health records. For example, a concept (e.g. vaccination status) may be captured by more than one variable in a single provider database (e.g., recorded in vaccination records or in visit notes for self-reported) or in more than one database (e.g., EHR or vaccine registry). Thus the validity of the analyses will depend on consistent operational definitions.

Operational definitions for necessary data elements will be defined collaboratively by CDC, Westat, and network sites to ensure consistency and accuracy of definitions across sites; this approach will also be applied to building patient cohorts using look-back periods or among sites with well-characterize source populations. Sites may choose to derive some or most data elements prior to submitting final datasets to Westat/CDC, based on the agreed-upon operational definitions. Alternatively, sites may submit their data to Westat, the data coordinating center, and Westat would derive variables for analysis.

As the data coordinating center, Westat will receive data from the sites. At Westat, the study database will be housed in an integrated central research data warehouse (RDW) platform.

The RDW will be fully integrated with the data management and tracking systems necessary for carrying out the processes associated with entry/upload, transmission, QA, version control, standardization, storage, and security.

2. Variables

The codebook is included as Appendix A. Depending on feasibility and prioritization, additional variables will be added, including medications (antivirals, antibiotics, steroids, vasopressors), non-invasive mechanical ventilation, vital signs (such as heart rate, respiratory rate, blood pressure, temperature, O_2 saturation, Glasgow Coma Scale), and other laboratory tests [including diabetes, hemoglobin A1C, complete blood count (CBC), comprehensive metabolic panel (CMP), etc.].

3. Data Management

During the course of the study, research staff at each site will extract information from the EHR of participants, state or local vaccination registries, and billing records, as available. Information for extraction includes data elements described in Section 7.2 and Appendices A and B. Sites will perform data validation on the extracted data as discussed in Section 7.4, below. Each site will create and maintain a database onsite that links demographic and clinical information extracted from the EHR, state or local vaccination registries, and billing records to a coded patient identifier. The key linking the coded identifier to the patient IDs will be kept at the individual sites. Additionally, the sites within a health network will also be given a coded identifier. Some details of the site will be included in the data, such as facility type and location, but no attempts will be made to identify facilities. Upon execution of an appropriate data use agreement (DUA) or data transfer agreement (DTA), a HIPAA-defined limited data set (LDS) will be forwarded (using a secured data transfer protocol) to the study coordinating center (Westat). Data transferred to Westat will not include identifying elements such as name, medical record number, postal address, or any other elements not allowed in a LDS. These datasets will contain individual-level records of pre-processed variables derived by the study site for the analysis necessary for the primary objectives.

Additional details about site data processing can be found in Appendix B, Proposed Data Structure to be shared by Sites with Westat. Westat will perform additional quality control and validation on the received data, as described in Section 7.4 below, and will concatenate the files to form one database. The database will be transferred to CDC using a secured transfer protocol for analysis (see Data Management Plan, Appendix C, for further detail).

4. Data Validation

Data will be validated at different points throughout the protocol and study period and will be an iterative process. If errors are found, Westat will coordinate with the site and the extraction will be re-programmed and data re-extracted and re-validated. Sites and Westat will both perform various aspects of this quality control and data validation. There are three main types of validation that will be conducted for this study:

1. Basic validation

The basic validation includes data quality checks such as confirmation that values are non-missing, values are of the correct type and length, and values are in the appropriate range. All variables will undergo basic validation. Expected variable type, length, and range will be included in the codebooks. Range checks will be particularly important for dates and healthcare utilization. Expected percent missing will be determined at the site-level. For

example, some sites may do more SARS-CoV-2 testing than others and thus the expected percent missing for those sites would be different.

2. Internal crosschecks

The internal crosscheck validation will include two types of checks and may be performed by Westat. The first is comparing calculated proportions of various data elements in the extracted data to the proportions in the source data. For example, if a site generally performs SARS-CoV-2 testing on 50% of its adult patients and the extracted data show only 5% that would indicate an error. Variables that will undergo this check are sex, race, ethnicity, insurance coverage, insurance type, respiratory virus testing and results (percent tested and percent positive), vaccination status (by age and high-risk condition), invasive mechanical ventilation, ICU admission, in-hospital mortality, and high-risk conditions.

The second type of internal crosscheck is comparing related data elements, i.e., a value for one data element is checked against the value for another data element. For example, all patients with a pregnancy-related diagnosis code should have sex recorded as female. Checks of this type could include:

- Number of inpatient visits corresponds to number of admission dates
- Number of outpatient visits corresponds to number of dates of outpatient encounters
- If date of vaccination is non-missing then source of data (EHR, registry, administrative records, etc.) should be non-missing
- If the date of respiratory virus testing is non-missing than the type of test and the test result should be non-missing; likewise, the test result should be consistent with what is detectable by the test type
- A patient with a record for mechanical ventilation should also have an ICU admission date

Additionally, sites could crosscheck the high-risk conditions with other data not extracted for this study. For example, they could look at medication use among those coded with high-risk conditions commonly treated with medication (e.g. asthma, diabetes).

3. Comparisons with external data sources

Comparisons with external data sources includes comparing values to those recorded in the primary records as well as comparing rates, proportions, and distributions of variables across participating sites and to national, regional, or state data.

Comparison of extracted data to the primary records will be done on a limited basis, but can be informative for understanding flow of data into the data warehouse and appropriateness of structured data fields to the data of interest for this project. CDC, Westat, and sites will reach consensus regarding appropriate methods and requirements for each site's data validation against primary records.

Variables for which rates, proportions, and distributions can be compared across participating sites and to national, regional, or state data include:

- SARS-CoV-2 and influenza vaccination coverage
- Respiratory virus testing and positivity
- Mechanical ventilation
- ICU admissions
- Proportion of patients with high-risk conditions

Westat will work with each site to review potential errors and decide on corrective action. In a few cases, sites may need to perform limited review of medical charts to clarify data elements flagged for review.

8. Ethical Considerations for Protection of Human Research Subjects

1. Institutional Review Board Review

Westat will serve as the single IRB of Record for this study for all participating sites and coordinating center for overseeing protections of human subjects research (45 C.F.R. § 46 114). The Westat IRB will enter into an IRB Authorization Agreement (IAA) that will include a communication plan with each institution prior to study implementation. IAAs and other documentation necessary in order to document compliance with the single IRB policy are maintained by Westat's IRB. Westat's IRB will use several mechanisms to communicate with sites, including email, phone calls and direct person-to-person communications as needed.

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

2. Patient Confidentiality

All patients in the dataset will be assigned a linkable patient identification code (i.e. study identification code). Sites will be responsible for assigning and maintaining the link between the patient's identifying information and study ID. Documents maintaining this link will never be transferred to the coordinating center or study investigators. Personal identifiers (patient's name, address, medical record number, and encounter number) will exist at the participating site, as part of the hospital administrative data but will be replaced by a random generated code (linkable patient identification code), which will allow linkage of data without CDC or the coordinating center (Westat) having any access to these personal identifiers. All study data and administrative documentation will be identified by the study identification code only, to maintain participant confidentiality. Limited datasets will be created for the study; the study will comply with each institution's human subjects, privacy, and information security laws, if any. All study data files will be stored separately from any study records that contain names or other personal identifiers. All local databases must be secured with password protected access systems.

Listings that link study (and personal) IDs to other identifying information must be stored in a separate, locked file (or encrypted) in an area with limited access (or maintained in a directory separate from any study specific data files/sets) at each participating facility. Links between the study identification codes and personal identifiers will be destroyed by the participating site after publication of the findings (for additional information please see the Data Management Plan, Appendix C).

Westat's Data Management Plan (Appendix C) details how Westat will protect any identifiers from improper use or disclosure, how Westat will destroy the identifiers after study completion, and how the protected health information will not be reused for other research.

3. Request for Wavier of Informed Consent

The study relies on existing data already collected as part of patient's routine care or for billing purposes. No supplemental data collection will be done as part of this study. In addition,

this study presents minimal risk to participants because there is no interaction or intervention with patients; therefore, a waiver of informed consent is requested. Minimal risk includes disclosure of clinical information on the patients' medical condition to persons outside of this protocol's defined study. Although patient information already available in the administrative databases will be collected, only information associated with a HIPAA limited dataset will be collected for the study. There is no risk to the participants' health from participation nor any impact on patients' current health care or therapeutic management plan because patients will not be contacted at any time. Consequently, patients will not be provided information about their participation.

Additionally, it will be impractical to conduct this study without waiving informed consent. By the time access to the datasets is available, most of the patients, if not all, will be out of the hospital (or some may have died during hospitalization), and the vast majority may have been hospitalized many years prior and may no longer live in the area or receive their care at the relevant study site. To contact each patient in this large, retrospective study for informed consent or to notify them of study results would place an insurmountable burden on investigative staff and would prohibit successful completion of the study.

4. Benefits to Participants

There are no direct benefits for patients whose data contribute to this study. There may be future indirect benefits to the populations of the participating health systems, especially those with risk factors for severe illness from SARS-CoV-2 and influenza. For example, information from this study may influence vaccination strategies for high-risk groups that may improve future outcomes for children, elderly adults, and those with high-risk conditions. In addition, understanding factors that make these groups at higher risk for SARS-CoV-2 and influenza-associated hospitalization may help in developing and improving prevention and treatment guidelines.

5. Data Records Lifecycle and Destruction

Each participating study institution will store any paper study records in a physically secure location that is only accessible to authorized study staff. At close out, assuming no restrictions on data retention, the de-identified analytic files, documentation and all code used in processing will be archived in a way that would allow replication of the results. Each organization affiliated with the study, through subcontract or otherwise, must destroy data according to contractual specifications and must provide Westat with a certificate of destruction.

A certificate of destruction will be required for electronic and hard copy data and each must detail the type of data destroyed, how and when it was destroyed, and the signature of the authorized data security manager or corporate executive. In addition, any exceptions to the data destruction, e.g., data that must be maintained for internal records, must be identified in the certificate of destruction, along with a detailed rationale for why the data were not/could not be destroyed, at study conclusion.

6. Guidance for Decision Making

A project steering committee will provide high-level input into this project, with CDC and Westat having final approval and sign off on any decisions made. The project steering committee will consist of two individuals from each site (decided by the site), a Westat representative, and a CDC representative. Each site will have one vote. The day-to-day

overall project management will occur through the Westat study lead who will interface directly with CDC; however, the steering committee will be consulted on over-arching project issues including final protocol decisions, adjudicating any protocol deviations that might occur, reviewing and confirming analysis plans, and making final decisions on analyses, manuscripts, and authorship as needed. Upon the completion of all study deliverables, at a minimum, aggregate tables from publications of this collaboration will be publicly shared as specified in U.S. Government Data Sharing guidelines. Additional data may be publicly shared to further satisfy the U.S. Government Data Sharing guidelines, as determined by consensus of steering committee members and per site data use agreements.

Summary of amendments

Date	Amendments
7/2/2020	Updated Section 1.0 Scientific Background, 2.0 Study Objectives, 3.1 Study Design, 4.0 Statistical Analysis
6/9/2021	Added Pediatric Study information to 1.5 Methods

Initial Statistical Analysis Plan

Statistical Analysis

Analysis Plan

Objective 1: Assess the validity and biases associated with defining the source population based on care-seeking

Correctly capturing the health system's denominator is a critical component of the study objectives, thus all health systems will be asked to validate the eligibility definitions using their information from their membership or source population.

- Compare the demographics of participants defined using the five inclusion criteria, using appropriate bivariate statistics as appropriate.
- Compare, using appropriate bivariate statistics, the healthcare utilization between all known members and those participants defined using the five inclusion criteria.
- Compare the frequency of respiratory-associated hospitalization between the cohorts as defined using the five inclusion criteria.

Objective 2: Validation of influenza vaccination data

- Describe the frequency of influenza vaccination among cohort members and vaccine type received. Descriptions will include the full cohort and will be stratified by individual characteristics such as age group, high-risk condition, and prior healthcare utilization.
    - Frequency of vaccination will be compared across strata using appropriate bivariate statistics (e.g. chi-square tests or Fisher's exact tests).

- Among those determined to be vaccinated for influenza
    - Assess the proportion that were identified through various data sources (e.g., procedure codes from a medical visit, other notation in the medical chart, vaccine registry, billing data, etc.). Assess whether the source of vaccination data varies by individual characteristics, including age group, high-risk conditions, and prior healthcare utilization.
    - Compare the completeness and consistency of data on date of vaccination and vaccine type between data sources and by patient characteristics such as age group, high-risk conditions, and prior healthcare utilization.
    - Comparisons of data by source, for completeness, and for consistency and how these differ by patient characteristics will be conducted using appropriate bivariate tests of association and/or multivariate regression. As an example, regression analyses could include data source as the outcome of interest with patient characteristics as explanatory variables.
- Describe the timing of vaccine receipt among cohort members by age group, high risk condition, prior healthcare utilization, and vaccine type received.

  This description will be explored using a variety of methods, including time to vaccination, median week of vaccination, or frequency of vaccination at least two weeks prior to the start of influenza circulation. Comparison of timing by patient characteristics will be conducted using methods appropriate to the outcome type; for example, proportional hazards modeling for time to vaccination.

Objective 3: Biases associated with clinical testing

- Describe the frequency of clinical testing for influenza and other respiratory viruses in the cohort during an influenza season by setting (inpatient vs. outpatient), age group, high-risk status, influenza vaccination, prior healthcare utilization, and timing of encounter within the season.
- Describe the diagnoses associated with visits where clinical testing for influenza and/or other viruses was performed.
- Among hospitalizations with respiratory illness during the influenza season, describe the frequency and types of clinical testing used.
    - Characteristics and predictors of receipt of diagnostic test for influenza will be assessed using bivariate tests of association and/or multivariate regression with receipt of test as outcome of interest and patient and clinical characteristics (including age, vaccination status, high-risk conditions, timing of the clinical encounter within the season, prior healthcare utilization, diagnoses, etc.)
- Among outpatient visits for ARI during the influenza season, we will describe the frequency and types of clinical testing used.
    - Characteristics and predictors of receipt of diagnostic test for influenza will be assessed using bivariate tests of association and/or multivariate regression with receipt of test as outcome of interest and patient and clinical characteristics (including age, vaccination status, high-risk conditions, timing of the clinical encounter within the season, prior healthcare utilization, diagnoses, etc.)

Objective 4: Measure incidence of health outcomes related to influenza

- Incidence of laboratory-confirmed influenza-associated respiratory hospitalizations will be calculated by dividing the number of respiratory hospitalizations associated with a positive influenza laboratory test observed during each study season by the person-time of the cohort at risk during the corresponding season.
    - This will be calculated for the following risk groups: age group, high-risk conditions, vaccinated for influenza, unvaccinated, race/ethnicity, socio-economic status, etc.
    - Incidence will be compared between risk groups using rate differences or relative rates
- Incidence of ICU admission, mechanical ventilation, and in-hospital death associated with influenza will be similarly calculated, with the respective numerators restricted to those laboratory-confirmed influenza-associated respiratory hospitalizations with the relevant outcomes identified.
    - This will be calculated for the following risk groups where sample size permits: age group, high-risk conditions, vaccinated for influenza, unvaccinated, race/ethnicity, socio-economic status, etc.
    - Incidence will be compared between risk groups using rate differences or relative rates
- Incidence of laboratory-confirmed influenza-associated acute respiratory illness (ARI)-associated outpatient visits will be calculated by dividing the number of ARI visits with a laboratory test positive for influenza observed during each study season by the person-time of the cohort at risk during the corresponding season.

- This will be calculated for the following risk groups where sample size permits: age group, high-risk conditions, vaccinated for influenza, unvaccinated, race/ethnicity, socio-economic status, etc.
- Incidence will be compared between risk groups using rate differences or relative rates

As multiple events are possible during a season, incidence estimates throughout this objective may be calculated in two ways: 1) counting only the first occurrence, and 2) counting the cumulative number across the season.

Objective 5: Assessment of vaccine effectiveness

- We will estimate the effect of influenza vaccination on risk of lab-confirmed influenza-associated respiratory hospitalization by age group, influenza type/subtype, and high-risk conditions
  - The risk of influenza-associated respiratory hospitalization among cohort members who were or were not vaccinated with the current season influenza will be compared using appropriate methods for longitudinal data with time varying exposure, including Poisson regression or proportional hazards modeling.
  - VE will be estimated as (1-adjusted relative risk) x 100.
  - We will assess and adjust for confounders as appropriate. These may include characteristics such as age, sex, site, race/ethnicity, high-risk health conditions, prior healthcare utilization, time of event during the influenza season, etc.
  - Data collected for this study are intended to be pooled across sites. VE will first be estimated for each site and heterogeneity in estimated VE across sites examined.

- We will estimate the effect of influenza vaccination on risk of lab-confirmed influenza-associated ARI outpatient visit among children (adults only if influenza testing allows for this) by age group, influenza type/subtype, and high-risk conditions
    - The risk of influenza-associated outpatient visits among cohort members who were or were not vaccinated with the current season influenza will be compared using appropriate methods for longitudinal data with time varying exposure, including Poisson regression or proportional hazards modeling.
    - VE will be estimated as (1-adjusted relative risk) x 100.
    - We will assess and adjust for confounders as appropriate. This may include characteristics such as age group, sex, site, race/ethnicity, high-risk health conditions, prior healthcare utilization, time of event during the influenza season, etc.
    - Data collected for this study are intended to be pooled across sites. VE will first be estimated for each site and heterogeneity in estimated VE across sites examined.
- VE analyses against influenza-associated respiratory hospitalizations will also be conducted using a test-negative case-control design
    - This analysis will be conducted among individuals who were hospitalized for acute respiratory illness during the influenza season and who were tested for influenza.
    - Cases will be defined as hospitalized individuals who tested positive for influenza.
    - Controls will be defined as hospitalized individuals who tested negative for influenza.

- Influenza vaccination status will be determined for all cases and controls and the odds of vaccination will be compared using logistic regression.
- VE will be estimated as (1 – adjusted odds ratio) x 100.

- We will assess and adjust for confounders as appropriate. This may include characteristics such as age group, sex, site, race/ethnicity, high-risk health conditions, prior healthcare utilization, time of event during the influenza season, etc.
- Data collected for this study are intended to be pooled across sites. VE will first be estimated for each site and heterogeneity in estimated VE across sites will be examined.

Beyond the primary objectives listed here, additional analyses may be pursued and will be considered by the joint steering committee.

1.1 Sample Size

Table 1 presents sample size requirements for the primary objective of VE against severe outcomes. Existing data from hospital-based surveillance was used to estimate the reported incidence of laboratory-confirmed hospitalizations, ICU admissions, and deaths.[26] Data from the Behavioral Risk Factor Surveillance System (BRFSS) and National Health Interview Survey (NHIS) was used to estimate vaccine coverage.[26]

For adults, we assumed vaccine coverage of 30% in adults aged 18-49 years, 42% in adults aged 50-64 years, and 65% in adults 65 years and older. We assumed a population made up of 33% of adults in each of the three age groups.

For children, we assumed vaccine coverage of 70% in children aged 6 months to 4 years and 50% in children aged 5 to 17 years. We assumed a population made up of 50% of children in each of the two age groups.

Table 1 Sample Size Estimations

		Person-years needed	
	Minimum Detectable VE	Adults	Pediatrics
VE against hospitalization	40%		398,319
	35%	197,593	569,374
	30%	292,719	842,278
	25%	456,014	1.3 million
	20%	766,799	
VE against ICU admission	40%		1.01 m
	35%	1.2 million	1.4 m
	30%	1.8 m	1.9 m
	25%	2.8 m	2.8 m
	20%	4.8 m	
VE against in-hospital death	40%		28.1 m
	35%	5.4 m	39.4 m
	30%	7.9 m	52.8 m
	25%	12.4 m	73.8 m
	20%	20.8 m	

1.2 Enhanced Data Collection Elements to Meet Secondary Objectives

For a more comprehensive list of data elements needed to meet the secondary objectives, see Appendix B.

- All inpatient/outpatient encounters for to-be-determined lead-in period (to refine high-risk conditions)

- Medication prescribing/administration (e.g. asthma or immunosuppressive medications)
- Laboratory testing/results (e.g. for diabetes, hemoglobin A1C tests)

- Respiratory syndrome-associated hospitalizations during influenza season of interest (all patients; discharge codes listed in Appendix D)
  - Medication orders/administration (e.g. influenza antivirals, antibiotics, steroids, vasopressors)
  - Expanded laboratory testing/results (e.g. CBC, CMP)
  - Vital signs (e.g. heart rate, respiratory rate, blood pressure, temperature, O2 saturation, Glasgow Coma Scale)
  - Non-invasive mechanical ventilation (e.g. CPAP, BiPAP, high flow nasal cannula)
  - Radiography (e.g. chest x-ray)
- ARI syndrome-associated outpatient encounters during influenza season of interest (all patients; ICD codes TBD)
  - Medication orders/administration (e.g. influenza antivirals, antibiotics)
  - Expanded laboratory testing/results (e.g. CBC, CMP)
  - Vital signs (e.g. heart rate, respiratory rate, blood pressure, temperature, O2 saturation, Glasgow Coma)
  - Radiography (e.g. chest x-ray)

Final Statistical Analysis Plan

Statistical Analysis

Analysis Plan

Objective 1: Assess the validity and biases associated with defining the source population based on care-seeking

Correctly capturing the health system's denominator is a critical component of the study objectives, thus all health systems will be asked to validate the eligibility definitions using their information from their membership or source population.

- Compare the demographics of participants defined using the five inclusion criteria, using appropriate bivariate statistics as appropriate.
- Compare, using appropriate bivariate statistics, the healthcare utilization between all known members and those participants defined using the five inclusion criteria.
- Compare the frequency of respiratory-associated hospitalization between the cohorts as defined using the five inclusion criteria.

Objective 2: Validation of influenza vaccination data

- Describe the frequency of influenza vaccination among cohort members and vaccine type received. Descriptions will include the full cohort and will be stratified by individual characteristics such as age group, high-risk condition, and prior healthcare utilization.
    - Frequency of vaccination will be compared across strata using appropriate bivariate statistics (e.g. chi-square tests or Fisher's exact tests).

- Among those determined to be vaccinated for influenza
    - Assess the proportion that were identified through various data sources (e.g., procedure codes from a medical visit, other notation in the medical chart, vaccine registry, billing data, etc.). Assess whether the source of vaccination data varies by individual characteristics, including age group, high-risk conditions, and prior healthcare utilization.
    - Compare the completeness and consistency of data on date of vaccination and vaccine type between data sources and by patient characteristics such as age group, high-risk conditions, and prior healthcare utilization.
    - Comparisons of data by source, for completeness, and for consistency and how these differ by patient characteristics will be conducted using appropriate bivariate tests of association and/or multivariate regression. As an example, regression analyses could include data source as the outcome of interest with patient characteristics as explanatory variables.
- Describe the timing of vaccine receipt among cohort members by age group, high risk condition, prior healthcare utilization, and vaccine type received.

  This description will be explored using a variety of methods, including time to vaccination, median week of vaccination, or frequency of vaccination at least two weeks prior to the start of influenza circulation. Comparison of timing by patient characteristics will be conducted using methods appropriate to the outcome type; for example, proportional hazards modeling for time to vaccination.

Objective 3: Biases associated with clinical testing

- Describe the frequency of clinical testing for influenza and other respiratory viruses in the cohort during an influenza season by setting (inpatient vs. outpatient), age group, high-risk status, influenza vaccination, prior healthcare utilization, and timing of encounter within the season.
- Describe the diagnoses associated with visits where clinical testing for influenza and/or other viruses was performed.
- Among hospitalizations with respiratory illness during the influenza season, describe the frequency and types of clinical testing used.
    - Characteristics and predictors of receipt of diagnostic test for influenza will be assessed using bivariate tests of association and/or multivariate regression with receipt of test as outcome of interest and patient and clinical characteristics (including age, vaccination status, high-risk conditions, timing of the clinical encounter within the season, prior healthcare utilization, diagnoses, etc.)
- Among outpatient visits for ARI during the influenza season, we will describe the frequency and types of clinical testing used.
    - Characteristics and predictors of receipt of diagnostic test for influenza will be assessed using bivariate tests of association and/or multivariate regression with receipt of test as outcome of interest and patient and clinical characteristics (including age, vaccination status, high-risk conditions, timing of the clinical encounter within the season, prior healthcare utilization, diagnoses, etc.)

Objective 4: Measure incidence of health outcomes related to influenza

- Incidence of laboratory-confirmed influenza-associated respiratory hospitalizations will be calculated by dividing the number of respiratory hospitalizations associated with a positive influenza laboratory test observed during each study season by the person-time of the cohort at risk during the corresponding season.
    - This will be calculated for the following risk groups: age group, high-risk conditions, vaccinated for influenza, unvaccinated, race/ethnicity, socio-economic status, etc.
    - Incidence will be compared between risk groups using rate differences or relative rates
- Incidence of ICU admission, mechanical ventilation, and in-hospital death associated with influenza will be similarly calculated, with the respective numerators restricted to those laboratory-confirmed influenza-associated respiratory hospitalizations with the relevant outcomes identified.
    - This will be calculated for the following risk groups where sample size permits: age group, high-risk conditions, vaccinated for influenza, unvaccinated, race/ethnicity, socio-economic status, etc.
    - Incidence will be compared between risk groups using rate differences or relative rates
- Incidence of laboratory-confirmed influenza-associated acute respiratory illness (ARI)-associated outpatient visits will be calculated by dividing the number of ARI visits with a laboratory test positive for influenza observed during each study season by the person-time of the cohort at risk during the corresponding season.

- This will be calculated for the following risk groups where sample size permits: age group, high-risk conditions, vaccinated for influenza, unvaccinated, race/ethnicity, socio-economic status, etc.
- Incidence will be compared between risk groups using rate differences or relative rates

As multiple events are possible during a season, incidence estimates throughout this objective may be calculated in two ways: 1) counting only the first occurrence, and 2) counting the cumulative number across the season.

Objective 5: Assessment of vaccine effectiveness

- We will estimate the effect of influenza vaccination on risk of lab-confirmed influenza-associated respiratory hospitalization by age group, influenza type/subtype, and high-risk conditions
  - The risk of influenza-associated respiratory hospitalization among cohort members who were or were not vaccinated with the current season influenza will be compared using appropriate methods for longitudinal data with time varying exposure, including Poisson regression or proportional hazards modeling.
  - VE will be estimated as (1-adjusted relative risk) x 100.
  - We will assess and adjust for confounders as appropriate. These may include characteristics such as age, sex, site, race/ethnicity, high-risk health conditions, prior healthcare utilization, time of event during the influenza season, etc.
  - Data collected for this study are intended to be pooled across sites. VE will first be estimated for each site and heterogeneity in estimated VE across sites examined.

- We will estimate the effect of influenza vaccination on risk of lab-confirmed influenza-associated ARI outpatient visit among children (adults only if influenza testing allows for this) by age group, influenza type/subtype, and high-risk conditions
    - The risk of influenza-associated outpatient visits among cohort members who were or were not vaccinated with the current season influenza will be compared using appropriate methods for longitudinal data with time varying exposure, including Poisson regression or proportional hazards modeling.
    - VE will be estimated as (1-adjusted relative risk) x 100.
    - We will assess and adjust for confounders as appropriate. This may include characteristics such as age group, sex, site, race/ethnicity, high-risk health conditions, prior healthcare utilization, time of event during the influenza season, etc.
    - Data collected for this study are intended to be pooled across sites. VE will first be estimated for each site and heterogeneity in estimated VE across sites examined.
- VE analyses against influenza-associated respiratory hospitalizations will also be conducted using a test-negative case-control design
    - This analysis will be conducted among individuals who were hospitalized for acute respiratory illness during the influenza season and who were tested for influenza.
    - Cases will be defined as hospitalized individuals who tested positive for influenza.
    - Controls will be defined as hospitalized individuals who tested negative for influenza.

- Influenza vaccination status will be determined for all cases and controls and the odds of vaccination will be compared using logistic regression.
- VE will be estimated as (1 – adjusted odds ratio) x 100.

- We will assess and adjust for confounders as appropriate. This may include characteristics such as age group, sex, site, race/ethnicity, high-risk health conditions, prior healthcare utilization, time of event during the influenza season, etc.
- Data collected for this study are intended to be pooled across sites. VE will first be estimated for each site and heterogeneity in estimated VE across sites will be examined.

Beyond the primary objectives listed here, additional analyses may be pursued and will be considered by the joint steering committee.

1.3 Sample Size

Table 1 presents sample size requirements for the primary objective of VE against severe outcomes. Existing data from hospital-based surveillance was used to estimate the reported incidence of laboratory-confirmed hospitalizations, ICU admissions, and deaths.[26] Data from the Behavioral Risk Factor Surveillance System (BRFSS) and National Health Interview Survey (NHIS) was used to estimate vaccine coverage.[26]

For adults, we assumed vaccine coverage of 30% in adults aged 18-49 years, 42% in adults aged 50-64 years, and 65% in adults 65 years and older. We assumed a population made up of 33% of adults in each of the three age groups.

For children, we assumed vaccine coverage of 70% in children aged 6 months to 4 years and 50% in children aged 5 to 17 years. We assumed a population made up of 50% of children in each of the two age groups.

Table 1 Sample Size Estimations

		Person-years needed	
	Minimum Detectable VE	Adults	Pediatrics
VE against hospitalization	40%		398,319
	35%	197,593	569,374
	30%	292,719	842,278
	25%	456,014	1.3 million
	20%	766,799	
VE against ICU admission	40%		1.01 m
	35%	1.2 million	1.4 m
	30%	1.8 m	1.9 m
	25%	2.8 m	2.8 m
	20%	4.8 m	
VE against in-hospital death	40%		28.1 m
	35%	5.4 m	39.4 m
	30%	7.9 m	52.8 m
	25%	12.4 m	73.8 m
	20%	20.8 m	

1.4 Enhanced Data Collection Elements to Meet Secondary Objectives

For a more comprehensive list of data elements needed to meet the secondary objectives, see Appendix B.

- All inpatient/outpatient encounters for to-be-determined lead-in period (to refine high-risk conditions)

- Medication prescribing/administration (e.g. asthma or immunosuppressive medications)
- Laboratory testing/results (e.g. for diabetes, hemoglobin A1C tests)

- Respiratory syndrome-associated hospitalizations during influenza season of interest (all patients; discharge codes listed in Appendix D)
  - Medication orders/administration (e.g. influenza antivirals, antibiotics, steroids, vasopressors)
  - Expanded laboratory testing/results (e.g. CBC, CMP)
  - Vital signs (e.g. heart rate, respiratory rate, blood pressure, temperature, O2 saturation, Glasgow Coma Scale)
  - Non-invasive mechanical ventilation (e.g. CPAP, BiPAP, high flow nasal cannula)
  - Radiography (e.g. chest x-ray)
- ARI syndrome-associated outpatient encounters during influenza season of interest (all patients; ICD codes TBD)
  - Medication orders/administration (e.g. influenza antivirals, antibiotics)
  - Expanded laboratory testing/results (e.g. CBC, CMP)
  - Vital signs (e.g. heart rate, respiratory rate, blood pressure, temperature, O2 saturation, Glasgow Coma)
  - Radiography (e.g. chest x-ray)

Summary of Amendments

Date	Amendments
N/A	No Amendments