COMIRB Protocol

COLORADO MULTIPLE INSTITUTIONAL REVIEW BOARD
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Protocol #: 16-1785
Project Title: Evaluation of Moderate to Severe Influenza Disease in Children 6 months to 8 years in Colorado
Principal Investigator: Edwin Asturias, MD
Version Date: 7/27/16

I. Hypotheses and Specific Aims:
Children 6 months to 8 years of age with moderate to severe influenza have a higher risk of hospitalization, intensive care unit (ICU) admission, antibiotic use and complications compared with children with mild influenza illness.
Specific Aims:

Aim #1: To determine the validity of the moderate to severe endpoint for influenza as a predictor for hospitalization among children aged 6 months to 8 years evaluated at Children's Hospital Colorado (CHCO) emergency department (ED) and urgent cares (UC) during the 2016-2017 influenza season.

Aim #2: To prospectively evaluate the usefulness of the moderate to severe influenza endpoint against additional severity measures such as ICU admission, antibiotic and antiviral use, parental and child absenteeism and recurrent healthcare visits among children aged 6 months to 8 years evaluated at ED and UC centers in Colorado.

Aim # 3: To compare the healthcare costs associated with management of moderate to severe versus mild influenza disease.

Exploratory Objectives:
1) To compare the moderate to severe influenza definition, and other severity measures such as ICU admission, hospitalization, antibiotic, antiviral use, child and caregiver absenteeism among patients vaccinated with injectable influenza vaccine (IIV) versus unvaccinated individuals.
2) To evaluate severity measures such as hospitalization, ICU admission, antibiotic, antiviral use, caregiver and child absenteeism among children with influenza like illness who test negative for influenza.
3) To determine whether clinical measurements taken at ED/UC presentation such as systemic inflammatory response syndrome (SIRS) criteria, adjusted heart rate, oxygen saturation and temperature predict hospitalization, ICU admission and having polymerase chain reaction (PCR)-confirmed influenza. We will also consider the prediction value of peak temperature and temperature duration.

II. Background and Significance:
Influenza is an important cause of morbidity in children, annually causing 1-7 hospitalizations per 10,000 in US children under the age of 18 years (1-6). Children are

among those at high risk of serious outcomes and hospitalization for influenza and influenza-related complications (7, 8). The social and economic impacts of influenza range from significant healthcare costs and decreased productivity due to parental absenteeism (9). Annual influenza vaccination is the most effective strategy to prevent influenza illness, and is recommended for all children aged greater than 6 months of age. The Center for Disease Control and Prevention (CDC) estimates that for the 2013-2014 influenza season, influenza vaccination prevented approximately 7.2 million illnesses associated with influenza (10).

While the ultimate goal of vaccination is to prevent influenza infection, prevention of severe disease would provide the greatest public health impact in terms of benefits to the individual and society. Influenza vaccine effectiveness has been traditionally studied against lab-confirmed influenza, or medically-attended illness, but influenza vaccination has been shown to be effective in reducing hospitalization in children (11-14).

More recently, a multicenter, phase 3, randomized controlled quadrivalent influenza vaccination study conducted in Asia, Central America and Europe showed that influenza vaccination was highly effective in reducing moderate to severe influenza, defined as fever greater than 39^0C, or presence of otitis media defined by the American Academy of Pediatrics (AAP) guideline criteria, lower respiratory tract infection (shortness of breath, pulmonary congestion, pneumonia, bronchiolitis, bronchitis, wheezing, croup), or serious extrapulmonary manifestations (e.g., myocarditis, encephalitis, seizure) (15). The same moderate to severe influenza endpoint has been shown in a Finnish study to be clinically meaningful, in terms of illness duration, child and parental absenteeism, and antibiotic use (16). However, the relationship between this definition of moderate to severe influenza and important clinical and public health outcomes such as ED visits, hospitalization, ICU admission, use of antimicrobials and recurrent health care utilization has not been evaluated prospectively in US children.

The purpose of the proposed study is to validate that the definition of moderate to severe influenza in children predicts greater risk of healthcare endpoints such as hospitalization, increased length of stay, use of antimicrobials (including antivirals), absenteeism, increased duration of illness, and increased healthcare costs.

Understanding and validating the relationship between moderate to severe influenza and these clinically relevant endpoints is critical to establishing relevant surrogate markers of clinical and public health outcomes. If shown to be clinically relevant, this definition of moderate to severe influenza can be an important endpoint for assessing influenza vaccine effectiveness.

III. **Preliminary Studies/Progress Report:**

CHCO provides an ideal site for the study of influenza in children. CHCO is a large tertiary institution with a large catchment area of Denver Metro, Aurora and surrounding states. It serves 67% of children in the state of Colorado. From December 1, 2010 to April 30, 2014, there were 409 patients admitted to CHCO with PCR-confirmed influenza; 62% of these were defined as high-risk (16), and 38% were vaccinated against influenza during the same season. Accurate immunization data was available for 83% of patients via the Colorado Immunization Information System (CIIS). Clinical presentation and

hospital-based outcomes such as length of hospitalization among children admitted with influenza are shown in Table 1.

Table 1. Children Admitted To CHCO with Influenza, 2010-2014

Children admitted to CHCO with influenza N = 395	< 3 years N = 156	>3 years N = 239
Otitis media	10 (6)	6 (3)
Pneumonia	7 (5)	22 (9)
Hypoxia	19 (12)	141 (59)
Fever	133 (85)	207 (87)
Median duration of fever, days (range)	2 (1-17)	4 (1-64)
Tachypnea	64 (41)	91 (38)
Antibiotics	88 (56)	157 (66)
Median duration of antibiotics, days (range)	7 (0-23)	8 (0-77)
Pediatric Intensive Care Unit (PICU)	55 (35)	81 (34)
PICU length of stay, days	2 (1-100)	3(1-83)
Death	1 (1)	2 (1)
Median duration of hospitalization, days (range)	3 (1-100)	3 (1-128)
Vaccinated during current season against influenza	39 (25)	87 (36)

Preliminary data from the 2013-2014 and 2014-2015 influenza seasons demonstrated that among 11,997 patients who presented to CHCO ED, UC or outpatient clinics for an acute respiratory illness, 1398 (12%) underwent viral testing (either respiratory pathogen panel multiplex PCR or influenza PCR). 1375 patients were admitted for a respiratory illness, and of these, 994 (72%) underwent viral testing Additional data regarding ED visits during these time periods are shown in Table 2.

Table 2. Children Presenting to CHCO ED or UC with Acute Respiratory Illness, 2013-2014 and 2014-2015

CHCO data:	2013-2014	2014-2015	Total
ED/UC/Clinic visits due to an acute respiratory illness	5900	6097	11997
ED visits due to an acute respiratory illness, limited to patients < 8 yrs	4510	4595	9105
ED visits limited to CHCO, Uptown Urgent Care, South Urgent Care with an acute respiratory illness, limited to patients < 8 yrs	2703	2809	5512
ED visits with above restrictions further limited to Jan to March	1290	1745	3035
Limit visits to < 8 yrs Jan to March, no repeat visits	**1244**	**1688**	**2932**
Admission for acute respiratory illness,	454	486	940

Jan -Mar

IV. Research Methods

The study comprises a prospective analysis of children presenting to CHCO ED, and North Campus UC with an influenza-like illness (ILI) during the 2016-2017 influenza season. Once enrolled in the study, we will collect respiratory samples (nasopharyngeal (NP) specimens), socio demographic, and clinical data including variables of interest outlined above, and follow the clinical outcome of these children for 14 days after their initial presentation. A complete list of the variables being collected can be found in Appendix A.

A. Outcome Measure(s):

Primary outcome measure /Endpoints:

1) Hospitalization in patients presenting to the CHCO Main ED or North Campus UC with influenza

Secondary outcome measures/Endpoints:

1) ICU admission in patients presenting to the CHCO Main ED or North Campus UC with influenza
2) Antiviral use in patients presenting to the CHCO Main ED or North Campus UC with influenza
3) Antibiotic use in patients presenting to the CHCO Main ED or North Campus UC with influenza
4) Number of visits to the ED or healthcare provider in patients presenting to the CHCO Main ED or North Campus UC with influenza
5) Number of days of absenteeism from school or daycare in patients presenting to the CHCO Main ED or North Campus UC with influenza
6) Number of days of absenteeism from work in caregivers of children presenting to the CHCO Main ED or North Campus UC with influenza
7) Healthcare costs associated with ED visits or hospitalization in patients presenting to the CHCO Main ED or North Campus UC with influenza

Exploratory Outcome measures/Endpoints:

1) Vaccination status in subjects testing positive for influenza:

   a. Injectable influenza vaccine (IIV) receipt in patients presenting to the CHCO Main ED or North Campus UC with moderate to severe influenza
   b. IIV receipt in patients presenting to the CHCO Main ED or North Campus UC who are hospitalized
   c. IIV receipt in patients presenting to the CHCO Main ED or North Campus UC who are admitted to the ICU
   d. Number of days of fever in patients who received IIV presenting to the CHCO Main ED or North Campus UC
   e. Number of days of caregiver and child absenteeism in patients who received IIV presenting to the CHCO Main ED or North Campus UC

f. IIV receipt in patients presenting to the CHCO Main ED or North Campus UC who received antibiotics
g. IIV receipt in patients presenting to the CHCO Main ED or North Campus UC who received antivirals

2) Influenza-like-illness among subjects testing negative for influenza:
a. Hospitalization in patients with ILI who test negative for influenza
b. ICU admission in patients with ILI who test negative for influenza
c. Duration of fever in patients with ILI who test negative for influenza
d. Number of days of absenteeism from work in caregivers of patients with ILI who test negative for influenza
e. Number of days of absenteeism from school in patients with ILI who test negative for influenza
f. Antibiotic use in patients with ILI who test negative for influenza
g. Antiviral use in patients with ILI who test negative for influenza

3) Fever, vital sign data and extrapulmonary complications:
a. Number of days of fever in patients presenting to the CHCO Main ED or North Campus UC with influenza
b. Peak temperature at any time during illness in patients presenting to the CHCO Main ED or North Campus UC with influenza
c. Modified SIRS criteria met in patients presenting to the CHCO Main ED or North Campus UC with influenza
d. Initial and peak adjusted heart rate in patients presenting to the CHCO Main ED or North Campus UC with influenza
e. Oxygen saturation in patients presenting to the CHCO Main ED or North Campus UC with influenza
f. Extrapulmonary complications in patients presenting to the CHCO Main ED or North Campus UC with ILI

Definitions:
Influenza like illness (ILI): child with temperature of ≥ 37.8^0C and at least one of the following: cough, sore throat, runny nose or nasal congestion

Influenza: child with respiratory test that is positive for influenza by PCR

Moderate to severe influenza: child with influenza and one or more of the following criteria:
1. fever > 39^0C,
2. presence of otitis media defined by AAP guideline criteria,
3. lower respiratory tract infection (shortness of breath, pulmonary congestion, pneumonia, bronchiolitis, bronchitis, wheezing, croup), or
4. serious extrapulmonary manifestations (e.g., myocarditis, encephalitis, seizure)(15).

Mild influenza: child with ILI symptoms, but do not have any of the criteria for moderate to severe influenza

SIRS: Defined as the presence of two or more of the following, one of which must be abnormal temperature or leukocyte count:

1. core temperature <36 or >38.5°C
2. tachycardia (or bradycardia in infants),
3. tachypnea

Modified SIRS criteria (18): same definition as SIRS criteria excluding neutrophil criteria, i.e. the presence of two or more of the following, one of which must be abnormal temperature :

1. core temperature <36 or >38.5°C
2. tachycardia (or bradycardia in infants),
3. tachypnea

Tachycardia and tachypnea definitions by age:

Age group	Tachycardia	Bradycardia	Respiratory rate
1 month-1 year	>180	<90	>34
2-5 years	>140	NA	>22
6-12 years	>130	NA	>18

B. Description of Population to be Enrolled:

Population:

Children 6 months to 8 years of age seeking evaluation and management of ILI at the Main CHCO ED or North Campus UC will be eligible for participation in the study. The study will commence during the influenza season as determined by the department of microbiology and epidemiology at CHCO (the influenza season commences when there are 3 positive influenza PCR tests within a week). The study will continue for 5 months following the start of the influenza season.

Inclusion criteria:

1) Age 6 months $\leq$ 8 years
2) Presentation to the CHCO Main ED or North Campus UC with signs and symptoms of ILI (temperature of $\geq 37.8^0$C and at least one of the following: cough, sore throat, runny nose or nasal congestion)
3) Patients seen during the 2016-2017 influenza season

Exclusion criteria:

1) Respiratory symptom duration > 14 days
2) Prior enrollment in study
3) Nurse only visit

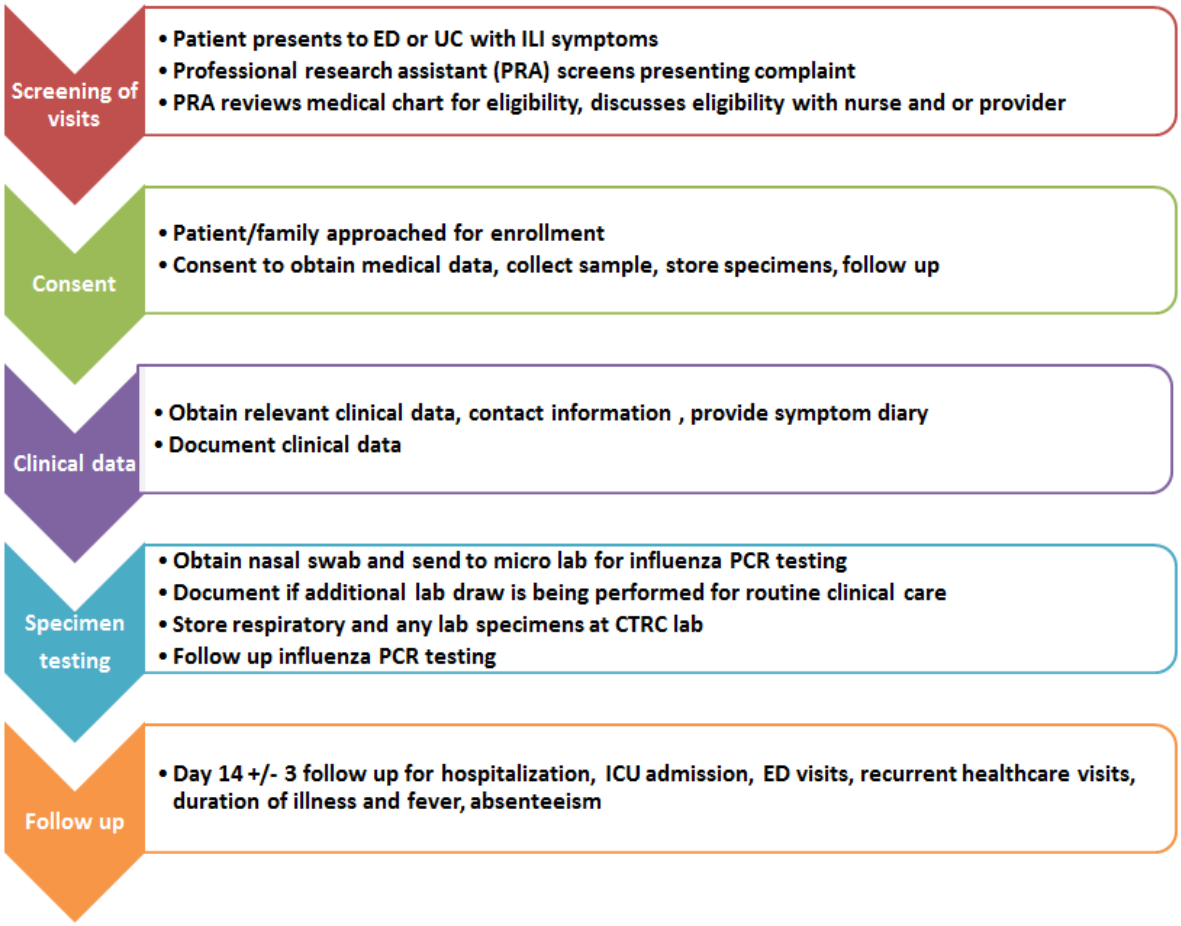
C. Study Design and Research Methods

This will be a prospective observational cohort study conducted at the CHCO Main ED and North Campus UC.

Surveillance Methods:
The study group will review the CHCO Main ED or North Campus UC visits for patients meeting study criteria presenting with ILI. Screening will be conducted by designated professional research assistants (PRAs) at each site. The study team has a treatment relationship with potential subjects, since one of the co-investigators is an ED physician, thus enabling screening of potential patients. The parents/legal guardians of eligible patients will be approached for consent to obtain respiratory specimens for PCR testing, interviewed to obtain medical information pertaining to the current and future ILI visits, asked permission to obtain additional information (vaccination status, influenza vaccination type [LAIV] or IIV) and medical comorbidities) from the primary care provider, and to bank residual blood and respiratory samples. A memory aid card will be provided to the family member upon discharge from the ED/UC setting as an aide memoire, and the medical chart will be reviewed for additional clinical and demographic information. On day 14(+/-3) following the initial visit, caregivers of all participants who test positive for influenza will be contacted by phone to provide additional follow-up information regarding child and parental absenteeism, additional healthcare visits, duration of illness. Additionally, a random sample of participants whose influenza test is negative in a 1 to 4 ratio will be contacted for follow-up. A second chart review will occur at this time for details regarding additional visits or admissions. Data will be managed with REDCap (Research Electronic Data Capture) tools hosted at the University of Colorado (19) and exported to SAS 9.3 (Cary, NC) for statistical analyses.

A flow diagram summarizing the study methods is shown in Figure 1.

Figure 1. Flow diagram summarizing methods for proposed surveillance study



Specimen Testing:

Nasal (NP) swabs will be obtained for testing by trained nurses/medical staff. If a respiratory sample has already been collected as part of routine clinical care, this will replace the study NP swab, and no additional testing will be required. Influenza testing will be conducted at the microbiology lab at CHCO. Testing is conducted using the Cepheid Xpert® influenza real time RT- PCR. This test detects influenza A and influenza B and provides the influenza A 2009 H1N1 subtype. It is run daily during the influenza season, with most results available in 3 hours on average once specimens have been received by the lab. Our lab undergoes annual individualized quality control, with stable performance, the details of which can be provided upon request. This test has sensitivity of 100% and specificity of 95-100%, (depending on the influenza strain). Specific data regarding the excellent sensitivity and specificity of the test is available at: http://www.cepheid.com/administrator/components/com_productcatalog/library-files/1412ce637a3184a887a44f8e287b67ec-Xpert-Flu-Datasheet-US-0418-02.pdf.

Once testing has occurred, family members will be given a number to call (PRA phone number) if they would like to have results of the influenza PCR test. If the flu test is being performed for clinical purposes we will use that result.

Biobanking of Samples:
We will obtain consent from parents/legal guardians regarding banking residual respiratory and blood samples obtained during routine clinical care. All left-over blood (whole blood, serum, and plasma) samples collected for clinical purposes will be stored in the CHCO CTRC lab (depending on the assay and sample) in case repeat or additional testing is requested. These samples can be used for future research after they have been discharged from care.

D. Description, Risks and Justification of Procedures and Data Collection Tools:

Description, risks and justification of procedures:
Respiratory specimens will be collected using a nasopharyngeal (NP) FLOQSwab and placed in Universal Transport Media (Copan Diagnostics Inc., Murrieta, CA). NP swabs will be collected for study purposes. If a respiratory specimen has already been collected for clinical purposes during the ED or UC visit, these will be used for testing, and no additional testing will be required. NP swabs, nasal washes or nasopharyngeal samples will be permitted for the study. This source is cleared by the FDA for the FA respiratory pathogen panel (RPP) and the collection method is standard clinical and research practice at our institution. We have successfully used this system to collect leftover clinical specimens for a number of previous and ongoing studies. Risks of the procedure are minimal, and include mild local discomfort at the time of specimen collection.

Data collection tools:
Study data will be collected and managed using REDCap (Research Electronic Data Capture). REDCap is a secure web application designed to support data capture for research studies, providing user-friendly web-based case report forms, real-time data entry validation (e.g. for data types and range checks), audit trails and a de-identified data export mechanism to common statistical packages (SPSS, SAS, Stata, R/S-Plus).

The system was developed by a multi-institutional consortium which includes University of Colorado–Denver and was initiated at Vanderbilt University. The database is hosted at the University of Colorado–Denver Development and Informatics Service Center (DISC), which will be used as a central location for data processing and management. REDCap data collection projects rely on a thorough study-specific data dictionary defined in an iterative self-documenting process by all members of the research team with planning assistance from the DISC. This iterative development and testing process results in a well-planned data collection strategy for individual studies. REDCap also includes a powerful tool for building and managing online surveys. The research team can create and design surveys in a web browser and engage potential respondents using a variety of notification methods. REDCap is flexible enough to be used for a variety of types of research and provides an intuitive user interface for database and survey design and data entry.

Patients will be assigned a sequential study number for the database that will have no relationship to any patient identifying information. The legend will be maintained until data editing is complete, and then the link will be destroyed. During the study period, the legend will be stored in a secure manner in a locked room with limited access, and computerized data will be similarly maintained in a secure fashion by the study team at CHCO. Data will only be publicly presented in aggregate form. This minimizes the risks related to invasion of privacy and breach of confidentiality.

E. Potential Scientific Problems:

A potential limitation of the study is potential selection bias due to the inability to test all patients who present with ILI to the ED. This is due to a high volume of patients presenting to the ED, as shown in Table 1. We will select patients based on age, restrict the season to once the influenza season has commenced, and will attempt to include all patients during this time period, which aims to avoid the skewing of data to more patients with co-morbidities or higher severity of illness who will undergo testing during routine clinical care.

There is also a possibility for recall bias regarding vaccination status and other medical history obtained from the parents/legal guardians. We will verify this information with the electronic medical record, which is linked to the CIIS. The CIIS is a lifelong immunization record tracking system managed by the Colorado Department of Public Health and Environment (CDPHE). Approximately 85% of Colorado primary care practices utilize the registry. In addition, if vaccination status cannot be determined from the electronic medical record, a member of the study team will contact the primary care Physician (PCP) for vaccination information. The combination of verification from the PCP as well as the CIIS registry will increase the accuracy of influenza vaccination status.

The study may have limited external validity and cannot provide population-based estimates of moderate to severe influenza, given its design.

F. Data Analysis Plan:

For all study objectives, we will present data descriptively using frequencies for categorical variables and measures of central tendency for continuous variables. We will explore bivariable associations between moderate to severe versus mild influenza for covariates including demographic factors and clinical factors outlined above. Proportions will be compared using Chi-square test. Mean values will be compared using student's t test for normally-distributed data, otherwise Wilcoxon-Rank-Sum test will be used.

Aim #1/Primary Endpoint Analysis: We will use logistic regression to estimate odds ratios (and 95%CI) for hospitalization, adjusted for significant covariates at the level of $P < 0.2$ on bivariable analysis; and other covariates selected *a priori* that could affect outcomes such as hospitalization (age group, high risk medical condition, vaccination status, influenza type). We will verify to ensure statistical assumptions are met for each model. The intraclass correlation coefficient will be estimated and a multi-level model will be used if we need to account for multiple visits per child. If we use a multi-level model, the optimal covariance structure will be determined through the examination of information criteria statistics and graphical techniques.

Aim #2/Secondary Endpoint #1-6 Analysis: We will use logistic regression to estimate each of our dichotomous secondary outcomes of interest, ICU admission, antibiotic,

antiviral use, adjusted for significant covariates at the level of $P < 0.2$ on bivariable analysis; and other covariates selected *a priori* that could affect outcomes such as hospitalization (age group, high risk medical condition, vaccination status, influenza type). We will verify to ensure statistical assumptions are met for each model. The intraclass correlation coefficient will be estimated and a multi-level model will be used if we need to account for multiple visits per child. If we use a multi-level model, the optimal covariance structure will be determined through the examination of information criteria and graphical techniques. We will also explore our secondary outcomes of interest expressed as continuous variables (number of recurrent visits to the ED, duration of absenteeism in days). We will use a log linear model to compare these variables between the mild versus moderate to severe influenza groups and will exponentiate the coefficients to yield geometric mean ratios.

Aim #3/Secondary Endpoint #7 Analysis: An economic analysis will be conducted to compare the healthcare costs in the mild and moderate to severe influenza groups. We will work with the finance department at CHCO to obtain charge data for each influenza-related ED visit and hospitalization. Direct costs associated with healthcare utilization will be obtained by collecting hospital charge data and applying a cost to charge ratio to estimate costs. Mean costs and standard deviations for each group will be determined and compared using t tests for normally distributed data, and presented as median (IQR) costs with analysis conducted using non parametric tests for non-normally distributed data. Relative healthcare costs will be modeled on log-transformed data using linear regression or a generalized linear model, depending on the data distribution.

Exploratory Objective #1-2/Exploratory Endpoints #1-2: In addition to the primary and secondary outcomes outlined above, we will also assess the odds ratios and 95% CI of several exploratory dichotomous outcomes –moderate to severe influenza, hospitalization, ICU admission, antibiotics and antiviral use among patients with IIV versus unvaccinated children using log linear regression in a manner similar to the above specific aims. For continuous variables (duration of fever, number of days of absenteeism), we will use a log linear model as described for our prior secondary outcomes.
We will conduct a similar analysis as outlined above for patients with influenza like illness who test negative for influenza using the clinical severity outcome measures outlined.

Exploratory Objective #3/Exploratory Endpoint#3: We will determine the predictive value for hospitalization, ICU admission and having PCR-confirmed influenza of duration of fever, SIRS criteria, adjusted heart rate, respiratory rate and oxygen saturation using logistic regression models with two-way interactions between factors in the model when needed. We will use the Brier score to assess overall model performance and the c statistic to assess discriminative ability. In addition to logistic regression, we will explore machine learning methods for the predictive modeling of these three outcomes. The predictive value of peak temperature will also be assessed using a logistic regression model.

To compare temperature trajectories between hospitalized and non-hospitalized, we will use a linear mixed model. This will allow us to use all of the longitudinal temperature measurements to measure the mean temperature trajectory of patients in one group (e.g. hospitalized patients) compared to the other (e.g. non-hospitalized patients). We will accomplish this by including an interaction term between time and hospitalization status, which will give us hospitalization status-specific trajectories. We will do this for each

dichotomous outcome: hospitalization, ICU status, influenza diagnosis. This method is preferred over subgroup analysis because it will optimize statistical power.

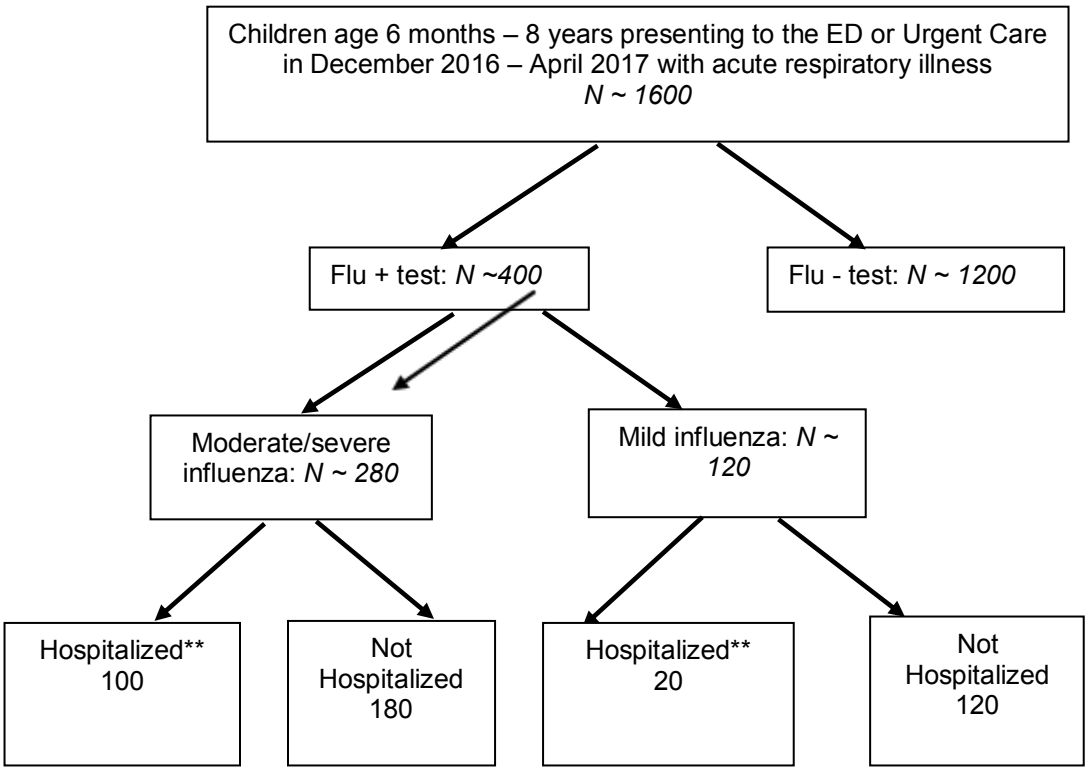
Two sensitivity analyses will be conducted. Firstly, analyses will be restricted to patients presenting to the main CHCO ED. Secondly, to further evaluate whether temperature > 39^0C is a predictor of healthcare utilization or poorer outcomes, an analysis of each of the secondary outcome measures will be conducted. Firstly, we will compare all moderate to severe versus mild influenza cases. If these reach statistical significance with an odds ratio >1, we will then repeat the analysis with a definition of moderate to severe influenza as solely temperature > 39^0C.

Power and sample size calculations:

Using historical data from our institution, a sample size of 408 patients (of which we assume 30% have mild flu and 70% have moderate/severe flu) will achieve 80% power at a 0.05 significance level to detect an odds ratio of approximately 2 for hospitalization among the moderate/severe compared to the mild cases, accounting for the inclusion of correlated covariables in our multivariable model. Assuming that 25% of patients tested will be influenza positive (19) during the influenza season; we will need to test approximately 1632 subjects (Figure 1). A sample size of 151 patients with the same assumptions, power and significance level will detect an odds ratio of 3 for hospitalization among the moderate/severe compared with mild cases, so 604 subjects will need to be tested.

Using these sample size estimates (using sample size of 408), assuming 50% vaccination status, and a ratio of IIV to LAIV receipt among vaccinated individuals of 9:1, we will have 80% power at a 0.05 significance level to detect an odds ratio of 3 for hospitalization among the mild versus moderate to severe cases, among patients vaccinated with IIV. We won't be adequately powered to detect a statistically significant difference for LAIV recipients.

Figure 1. Flowchart to produce the analysis sample*



*N's are conservative estimates based on data from Children's Hospital Colorado collected during the 2014-2015 flu season
**Primary outcome of interest

G. Summarize Knowledge to be Gained:

Influenza is an important public health and clinical challenge, and contributes to a significant burden of disease among children. Understanding and validating the relationship between moderate to severe influenza and clinically relevant endpoints such as ED visits, hospitalizations and ICU admissions is critical to establishing relevant surrogate markers of clinical and public health outcomes. If shown to be clinically relevant, this definition of moderate to severe influenza can be an important endpoint for assessing influenza vaccine effectiveness.

H. References:

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Appendix A data variables to be collected

PHI:
Study ID: MRN: HAR:
Visit Date:
Child's last name, first name:
Primary, secondary, additional Caregiver name, relationship to child, phone number, number of days per week working
ZIP County: State:
PCP name(s) and number
Date of birth: Age: _____years _____months _____days

Demographic and clinical information
Visit type
Sex
Race: Ethnicity:
Attends daycare/school :
Height (cm): Weight (kg): BMI:
Second hand smoke exposure
Reason for visit

Symptoms
Symptom onset and type
Fever onset and number of days of fever
medical conditions
influenza vaccination status
high risk medical comorbidities:

Vital Signs
Initial Temperature (°C): Initial Heart rate: Initial Respiratory rate: Initial oxygen saturation (on room air): Initial systolic blood pressure: Initial diastolic blood pressure:
Highest temperature in ED (°C):: Heart rate during this time:
Initial PEWS: Highest PEWS recorded in ED:
Meets SIRS criteria? □Yes □no
Signs:
Diagnosis

Test results
Influenza test results
Bacterial pathogens: source: date of test: result:
Viral pathogens: source: date of test: result:
Radiology: CXR CT chest other: result:
Other lab results: date: type: CBC with differential, CRP, ESR, PCT result:
Treatment
oseltamivir or other antiviral
antibiotics
steroids
other treatments

Outcomes
□ Sent home from ED □ Observation □ Hospitalized □death □other _____
Hospital length of stay, days _____
Admitted to ICU? □yes □no

ICU length of stay,days _____
Reason for ICU admission:
Oxygen use, duration
Heated high flow use, duration
BiPAP use, duration (days)
CPAP use, duration (days)
Intubation, duration (days)
ECMO use, duration (days)
Death

Follow up:
Child absenteeism and number of days
Parent/caregiver absenteeism and number of days
Duration of illness
Duration of fever
Antipyretic use