Supplemental Online Content

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eMethods

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

Study Population and Data Source

We performed a retrospective cohort study of children 5-17 years with an outpatient ICD-10 diagnosis of influenza during the 2016-2017 to 2019-2020 influenza seasons using the Tennessee Medicaid database. Outpatient clinic, urgent care, and emergency department influenza diagnoses were included in the study. The Tennessee Medicaid database contains administrative, pharmacy, and clinical data on over 13 million children, encompassing more than half of children and adolescents in the state of Tennessee. The database is supplemented with robust linkages to Vital Records statistics and state hospitalization registries and provides a validated longitudinal source for calculation of population-based incidence rates. The Tennessee Medicaid program has a large overrepresentation of vulnerable populations, including children from households with socioeconomic disadvantage and those with comorbidities.

Influenza Infection and Season Definition

Seasonal influenza activity in the state of Tennessee obtained from the CDC Flu Activity & Surveillance program was used to define the influenza season for each year of the study. Outpatient influenza infections were identified using ICD-10 diagnoses codes for influenza: J09, J09X, J09X1, J09X2, J09X3, J09X9, J10, J100, J1001, J1008, J101, J102, J108, J1081, J1082, J1083, J1089, J11, J110, J1100, J1108, J111, J112, J118, J1181, J1182, J1183, J1189. Recent studies demonstrate that ICD-10 codes have greater validity than ICD-9 codes for influenza infection and influenza ICD-10 codes have been successfully used in other influenza surveillance systems. The specificity of influenza diagnosis is directly related to circulating prevalence of the virus. To increase the specificity of influenza cases and mitigate the potential for misclassification of influenza diagnoses included in the study, the influenza

season definition in the study comprised the 13 consecutive weeks that contained the maximum number of influenza cases for each geographic census division, similar to previous published studies. The maximum number of influenza cases in Tennessee was defined as the calendar week with the greatest frequency of laboratory-confirmed cases for the referenced season.

Outcome

The primary outcome of influenza-associated serious neuropsychiatric events was defined as the presence of an influenza-associated neuropsychiatric event resulting in hospitalization. For each influenza episode, follow-up started on diagnosis date and continued through the earliest occurrence of the outcome event, 10^{th} day of follow-up, loss of enrolment, end of season, or death. We used an algorithm that has been validated for use in identifying pediatric neuropsychiatric events (PMID: 35393609). The algorithm has a positive predictive value of ~90% for identifying neuropsychiatric events that are present on admission and directly related to hospitalization as compared to physician record review. Categorization of clinical significance of neuropsychiatric events (critical, important, or unclear) and subtype (neurologic or psychiatric) were originally developed on the basis of consensus expert opinion among a study team of pediatric psychiatrists, general pediatricians, pediatric hospitalists, pharmacoepidemiologists, and complex care pediatricians. The critical category included homicidal, suicidal, or self-harm ideation or attempts; the important category included mood disorders (including anxiety and stress), psychosis, hallucination, altered mental status, ataxia or movement disorders, encephalitis or encephalopathy, and seizures; and the unclear significance category consisted of dizziness, headache, sleeping disorders, and vision changes (PMID: 35393609).

Incidence rate of serious neuropsychiatric events was calculated by dividing the number of events by the total influenza person-time and expressed per 100,000 person-weeks of influenza. The person-week of time was used as influenza duration is typically around 7 days and this timeframe was thought to be more easily interpretable. Individuals could contribute person-time to more than one influenza season. Within each season, however, an individual's follow-up was censored at the earliest of loss of enrollment, death, end of the study, or defined outcome event. Therefore, an individual with a neuropsychiatric hospitalization would have his/her follow-up censored at the neuropsychiatric hospitalization date. We reported 95% Poisson Confidence Intervals using exact method. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline. Analyses were performed in R, version 4.1.2.

Neurologic and Psychiatric Conditions

Neurologic co-morbid conditions were defined as a neurologic complex chronic condition using the Pediatric complex chronic conditions classification system version 2. Psychiatric co-morbid conditions were defined using the Pediatric Mental Health Disorders classification system. A look-back period of one year prior to influenza diagnosis was used to identify neurologic and psychiatric co-morbid conditions.

Antiviral Exposure

Antiviral exposure was defined as any antiviral-dispensing Medicaid claim (oseltamivir, zanamivir, or baloxavir). Antiviral exposure ascertainment time began 2 days prior to the influenza diagnosis and continued through the earliest occurrence of the outcome event, 10th day of follow-up, loss of enrolment, end of season, or death. A re-review of 100 random

encounters within the study population was performed to confirm prevalence of antiviral exposure.

Children at High-risk for Influenza Complications

Children at high risk for influenza complications were identified using the American Academy of Pediatrics, Infectious Disease Society of America, and Centers for Disease Control and Prevention definitions for high-risk children and included: age < 5 years, chronic neurological conditions (neurological conditions defined using the pediatric complex chronic conditions (CCC) classification system version 2), asthma diagnosis, pregnancy or post-partum status, obesity diagnosis, complex chronic conditions (categorized as immunosuppressive CCC, and non-neurologic CCCs)(PMID: 35867691, PMID: 34216629). A look-back period of one year prior to influenza diagnosis was used to identify high-risk co-morbid conditions. Individuals residing in a nursing home or other chronic care facility and those of Indigenous American and Alaska Native race and ethnicity were not considered as they are not separately identifiable in the database. Children with long-term aspirin use were excluded due to the low frequency of aspirin use in children.

Institutional Review Board Approval

This study of deidentified data claims data did not involve human participants; therefore, the VUMC IRB determined it was not subject to review and waived the requirement for informed consent. This study was approved by the Tennessee Department of Health institutional review board.