Summer 8-11-2020

Analysis of Seasonal Influenza Virologic and Hospitalization Trends among Children in the United States from 2010-2019

Samantha Mandel

ABSTRACT

ANALYSIS OF SEASONAL INFLUENZA VIROLOGIC AND HOSPITALIZATION TRENDS AMONG CHILDREN IN THE UNITED STATES FROM 2010-2019

By

Samantha Rose Mandel

July 31, 2020

Background:
Each year, millions of children get sick with seasonal flu, thousands of children are hospitalized, and some children die from flu. While the U.S. has a comprehensive influenza surveillance system reporting on current flu activity, and the Centers for Disease Control and Prevention (CDC) publishes weekly updates on their website (FluView), there is a lack of literature analyzing trends among the virus types causing flu and flu-related hospitalizations among children over multiple flu seasons. This study aimed to identify tends over time (2010-2019) in the proportion of children with lab-confirmed flu and hospitalized for flu, along with the proportion of virus types children are infected with.

Methods:
A secondary data analysis was conducted using the existing U.S. national influenza surveillance data assembled and provided by the CDC. The study included children in the United States with lab-confirmed flu or with flu-associated hospitalization during the 2010-2011 flu season through the 2018-2019 flu season. Data from hospitalization surveillance and virologic surveillance were analyzed across all 9 flu seasons.

Results:
Trends in the proportion of seasonal flu and flu-related hospitalizations among children showed a significant decrease over time (2010-2019). Additionally, trends in the proportion of flu A(H3N2) virus among children showed a significant decrease over time. While this study revealed a strong, positive relationship between the proportion of flu and flu-related hospitalizations among young children (0-4 yr) and older children (5-24 yr), a strong, negative relationship was observed between the proportion of flu and flu-related hospitalizations among children (0-4 yr) and older adults (65+).

Conclusion:
A significant decrease in proportion of flu and flu hospitalizations among children was observed over time, revealing a trend of decreased burden of flu among children compared to other age groups. A significant relationship was observed between children and older adults, revealing that as trends of flu among children decreased, trends increased among older adults. Trends in seasonal flu and flu-related complications have important implications for flu prevention and control efforts.

ANALYSIS OF SEASONAL INFLUENZA VIROLOGIC AND HOSPITALIZATION TRENDS AMONG CHILDREN IN THE UNITED STATES FROM 2010-2019

by

SAMANTHA R. MANDEL

B.S., UNIVERSITY OF GEORGIA

A Thesis Submitted to the Graduate Faculty
of Georgia State University in Partial Fulfillment
of the
Requirements for the Degree

MASTER OF PUBLIC HEALTH

ATLANTA, GEORGIA
30303

APPROVAL PAGE

ANALYSIS OF SEASONAL INFLUENZA VIROLOGIC AND HOSPITALIZATION TRENDS AMONG CHILDREN IN THE UNITED STATES FROM 2010-2019

By

Samantha R. Mandel

Approved:

Richard Rothenberg, MD, MPH
Committee Chair

Heather Bradley, PhD, MHS
Committee Member

July 31, 2020

Author's Statement Page

In presenting this thesis as a partial fulfillment of the requirements for an advanced degree from Georgia State University, I agree that the Library of the University shall make it available for inspection and circulation in accordance with its regulations governing materials of this type. I agree that permission to quote from, to copy from, or to publish this thesis may be granted by the author or, in his/her absence, by the professor under whose direction it was written, or in his/her absence, by the Associate Dean, School of Public Health. Such quoting, copying, or publishing must be solely for scholarly purposes and will not involve potential financial gain. It is understood that any copying from or publication of this dissertation which involves potential financial gain will not be allowed without written permission of the author.

Samantha Rose Mandel

TABLE OF CONTENTS

LIST OF TABLES.....6

LIST OF FIGURES.....7

INTRODUCTION.....8

LITERATURE REVIEW.....9
- Overview of Influenza 9
- Clinical Presentation.....9
- Risk Factors.....10
- Influenza Virus Types.....11
- Disease Burden.....12
- Influenza Surveillance.....14
- Prevention and Treatment.....15

MANUSCRIPT..... 17
- Introduction.....17
- Methods.....19
- Results.....20
- Discussion.....21

REFERENCES.....23

TABLES.....26

FIGURES.....30

List of Tables

Table 1. Virologic Flu Surveillance: Total Flu Serotypes | Proportion of Children Variable
Table 2. Virologic Flu Surveillance: Flu Serotypes by Virus Type | Proportion of Children Variable
Table 3. Flu Hospitalization Surveillance: Flu Hospitalization Rate | Proportion of Children Variable
Table 4. Pearson Correlation Coefficients Among Variables

List of Figures

Figure 1. Percentage of State Population Represented by Participating FluSurv-NET Counties
Figure 2. Proportion of flu among children (0-4 yr) per flu season
Figure 3. Proportion of flu hospitalizations among children (0-4 yr) per flu season
Figure 4. Proportion of flu A(H3N2) among children (0-4 yr) per flu season
Figure 5. Proportion of flu virus among children (0-4) over time by virus type (total)
Figure 6. Proportion of flu virus types among children (0-4 yr) over time by virus type
Figure 7. Total flu virus serotypes by age group over time (2010-2019)

Introduction

Influenza (flu) is a contagious respiratory illness caused by influenza viruses. Flu can be a serious disease that can lead to severe illness with complications, hospitalization and sometimes even death [1]. While flu can make anyone sick, certain groups of people are a high risk of developing serious flu complications requiring hospitalization, including young children.

Each year, millions of children get sick with seasonal flu, thousands of children are hospitalized, and some children die from the flu. CDC estimates that since 2010, flu-related hospitalizations among children younger than 5 years ranges from 7,000 to 26,000 in the United States [2]. Since the 2004-2005 flu season, flu-related deaths in children reported to CDC during regular flu seasons ranged from 37 deaths (during the 2011-2012 season) to 188 deaths (during the 2017-2018 season) [2].

Flu vaccination can prevent illness, hospitalization and death in children. A study published in 2017 was one of the first to show that flu vaccination can significantly reduce a child's risk of dying from the flu, highlighting the importance of children receiving a seasonal flu vaccine each year [3]. Unfortunately, flu continues to cause a heavy burden among this vulnerable population [4]. This is partially due to the variability in how well the flu vaccine works to protect against flu illness from year to year.

Flu vaccines are made to protect against either three or four different influenza viruses research shows are most likely to spread and cause illness among people during the upcoming flu season. Since flu viruses are constantly changing, flu vaccines may be updated from one season to the next based on which flu viruses are making people sick, how the viruses are spreading, and how well the previous season's flu vaccines protected against the circulating flu viruses.

The purpose of this study was to identify the trends of seasonal flu viruses that most commonly circulate among children in the United States hospitalized for influenza since the 2010-2011 influenza season. Understanding these trends is useful for guiding prevention and control efforts surrounding flu-burdened children. National and regional data was assessed from the U.S. influenza surveillance systems. Lab-confirmed hospitalization data was analyzed to identify trends in hospitalization rates among children over a nine consecutive flu seasons. Circulating virus subtypes and lineages from U.S. virologic surveillance were compared with hospitalization rates among children to analyze patterns in seasonal flu viruses and flu-related hospitalizations among children.

Literature Review

Overview of Influenza:

Influenza (or "flu") is a contagious respiratory illness caused by influenza viruses that can cause mild to severe illness, and at times can lead to hospitalization or even death. When a person infected with flu coughs, sneezes or talks, droplets containing flu viruses can spread up to six feet. These droplets can land in mouths and noses or possibly breathed into the lungs of others. Influenza can also spread from touching a surface or object that has a flu virus on it [5]. Someone who is contagious with flu illness may be able to infect others asymptomatically and up to 5-7 days after becoming sick. Children and some people with compromised immune systems may be able to spread the flu virus for longer than seven days [5].

Influenza can be unpredictable. The timing and duration of flu seasons can vary each year, but typically activity beings to increase in October, peaks between December and February and can last as late as May [6]. Influenza A and B viruses are the two main types of flu viruses that routinely spread in humans and are responsible for seasonal flu epidemics each year [7]. Throughout a flu season, different types and subtypes of influenza viruses circulate and cause illness. The variety of flu viruses spreading can affect people differently based on differences in their immune systems [8].

Clinical Presentation:

While it can be difficult to tell the difference between flu and the common cold, flu illness is generally worse with more intense symptoms [9]. Symptoms of flu can include fever, cough, sore throat, runny or stuffy nose, body aches, headaches, chills and fatigue. Some people may experience vomiting and diarrhea [10]. It's possible that some people infected with flu will show no symptoms (asymptomatic) or have only respiratory symptoms without a fever. Because signs and symptoms may vary between mild and severe, clinical presentation alone may not provide a precise measure of flu severity [11].

Most people who develop flu illness will recover in several days to less than two weeks[10]. Some people will develop complications (such as pneumonia) that can result in hospitalization or death, but most often this occurs in high risk populations (young children, older adults, pregnant women, and people with underlying medical conditions) [11]. Other possible serious complications of flu can include myocarditis, encephalitis, myositis, and multi-organ failure. Flu can also make chronic medical problems worse[11].

While some studies analyzing flu severity have found contradictory results among symptoms, complications and underlying conditions, others suggest differences in severity among the different flu viruses that cause flu illness[11]. For example, some evidence suggests that influenza A(H1N1)pdm09 virus results in more severe complications among people (such as ICU admission and pneumonia) compared to other flu virus subtypes [11].

Risk Factors:

While flu can make anyone ill, certain people are at greater risk of developing serious flu-related complications. High risk groups include adults 65 years and older, people with certain chronic medical conditions, pregnant women, children younger than 5 years of age, and especially those younger than 2 years of age. Both health and age play a factor in increasing a person's risk of serious complications from flu. For example, older adults and young children, have increased exposure to influenza in communal settings, like nursing homes and schools [12].

Certain chronic medical conditions such as asthma, chronic lung disease, heart disease, diabetes, and weakened immune systems can increase a person's risk for hospitalization and other severe outcomes [12–14]. About half of children hospitalized for flu have at least one pre-existing high risk medical condition [15,16]. Despite seasonal variation, certain groups of children are consistently at higher risk for flu-associated hospitalization [15].

There are important age-related differences in the epidemiology, clinical presentation, and outcomes of people hospitalized with flu, by virus type and subtype [11,12,16]. Chaves et al. found that children hospitalized with A(H1N1)pdm09 or influenza B more frequently had a longer hospital stay (more than 5 days) compared to those hospitalized with influenza A(H3N2). Additionally, ICU admissions and pneumonia diagnoses occurred more frequently among children hospitalized with A(H1N1)pdm09. Risk factors for hospitalization may differ during a season when a novel virus emerges and needs to be evaluated rapidly to inform interventions [14].

Most studies fail to control for potential confounding factors, such as age and underlying medical conditions [11]. Evaluating age- and health-related differences in flu-associated hospitalization rates can better inform surveillance, prevention and treatment efforts among specific age groups [12].

Influenza Virus Types:

There are four types of influenza viruses: A, B, C and D [17]. Influenza A and B are the virus types that circulate each flu season in the United States. Two influenza A subtypes and two influenza B lineages cocirculate at different proportions during annual flu epidemics [8]. Influenza A viruses are the only flu viruses known to cause flu pandemics, which can occur when a new or different influenza A virus emerges that can both infect people and can easily spread between people [17]. Influenza A viruses are divided into subtypes based on two proteins on the surface of the virus, known as hemagglutinin (H) and neuraminidase (N). Subtypes of influenza A viruses that routinely circulate in people include A(H1N1)pdm09 and A(H3N2) [17]. While influenza A viruses are classified into subtypes, influenza B viruses are classified into two lineages: B/Yamagata and B/Victoria [17].

Flu has been described as "an unvarying disease caused by a varying virus" [11]. Through 'antigenic drift', flu virus genes can mutate, leading to changes to their surface proteins. Antigen drift happens continually over time as the virus replicates [18]. Through 'antigenic shift', major changes in the flu virus can occur, resulting in a new virus subtype in humans. When shifts occur, most people have little or no immunity against the new virus. Shifts in influenza viruses occur less frequently than drifts [18]. Influenza A viruses have evolved and emerged or re-emerged during the past century [8]. In 1977, H1 viruses re-emerged and began to cocirculate with H3 viruses [8]. As flu viruses continue to evolve, it will be necessary to revisit previous analyses to determine whether morbidity and mortality patterns remain or change [8].

The notion that flu illness caused by different virus types and subtypes is clinically indistinguishable, suggesting that different flu types and subtypes have no difference on the severity of flu illness, has been challenged [11]. Studies have estimated that clinical presentation, severity, and risk of severe flu-related complications may differ across virus types and subtypes [11]. It's important to understand the association of virus type and subtype on flu severity due to its implications for the clinical management of flu patients and preparedness for seasonal epidemics [11]. Most studies conclude influenza A virus to be the predominant virus type to circulate during most seasons compared to influenza B virus [8,12,15]. Caini et al. claims that it's important to study influenza virus subtypes separately to find differences in the outcomes and severity.

Influenza A viruses were further studied by subtype and found A(H3N2) predominated during most seasons compared to A(H1N1) [12]. Numerous studies have found flu-associated hospitalizations and deaths are highest in H3N2-predominant seasons, suggesting symptoms and

severity of flu may be worse for this subtype [11,16]. Chaves et al. found that studies conducted prior to the 2009 H1N1 pandemic comparing disease severity in children by virus type and subtype have often suggested that influenza B viruses cause milder flu illness compared to influenza A viruses. Despite common assumptions that A(H3N2) infections result in more severe flu illness and that influenza B infections are milder, a literature review studying the characteristics of different flu virus types and subtypes didn't reveal such differences [11]. Some studies found influenza A(H1N1)pdm09 to be associated with more severe flu illness compared to other influenza strains [8,11]. Another analysis found that influenza B was associated with influenza complications similar to those associated with influenza A(H3N2) viruses, while some studies suggest influenza A(H1N1)pdm09 was not as clinically severe compared to seasonal influenza A and B viruses in previous seasons [16]. Chaves et al. found that of the children with severe influenza, most were associated with influenza B virus (48.9%), followed by A(H1N1)pdm09 (26.9%) and A(H3N2) virus (24.1%).

Budd (2019) studied differences in risk of flu-associated disease by influenza virus subtypes among birth cohorts, comparing pre-pandemic and pandemic and later periods. They found that since the 2009 H1N1 influenza pandemic, there has been a paradigm shift finding more severe flu disease and burden during H1NI predominant seasons rather than H3 predominant seasons [8]. This more recent literature conflicts with previous findings. Studies analyzing influenza A(H1N1)pdm09 suggest that knowing the causal virus may be an important element for healthcare providers, especially with the virus subtype being associated with a higher risk of unfavorable outcomes [11]. Comparing the A(H1N1)pdm09-associated clinical severity with that caused by H3N2 and B viruses is helpful to understand the predictors of severity among hospitalized persons [16]. Additional well-designed studies are needed to strengthen the evidence showing differences in death and hospitalization rates among different virus subtypes [11]. Studying the implications of flu virus types and subtypes can produce more accurate cost-benefit estimates of flu vaccination campaigns and other prevention and control strategies [11].

Disease Burden:

While the numbers can vary, in the United States, millions of people get sick, hundreds of thousands are hospitalized, and thousands of people die from flu every year [19]. The burden of influenza can differ substantially from season to season depending on the characteristics of circulating viruses, the timing of the season, population immunity to circulating viruses, flu

vaccine effectiveness, and how many people received a seasonal flu vaccine [20]. While the impact of flu varies widely, it places a substantial burden on the health of people in the U.S. each year[14,20].

Flu viruses change constantly and as a result can cause significant morbidity and mortality during seasonal epidemics and periodic pandemics [8]. Since 1976, the highest rates of severe flu-related illness and death usually occur in seasons where H3 viruses are most commonly circulating [8]. Influenza A hospitalization rate and death rate was higher during pre-pandemic H3 predominant seasons compared to H1 predominant season for all ages [8,12]. While older adults continue to have a higher mean hospitalization rate during seasons when H3N2 viruses are predominant over H1 predominant viruses, younger adults had higher mean hospitalization rates during H1 predominant seasons [8].

Immunologic imprinting suggests that the flu virus that an individual is first infected with has a lasting impact on their immunology and on subsequent immune responses. Antigen imprinting or antigenic seniority suggests relative immune responses to each subsequent strain one is infected with and the antibody response is highest against viruses a person is exposed to in childhood [8]. Analyzing influenza by birth cohort rather than traditional age groups suggests that initial influenza A virus subtype exposure may affect the clinical impact of influenza in subsequent years [8]. This type of analysis can help with the understanding of the complex factors at play affecting the clinical impact of flu virus infection.

Patients admitted to an ICU and patients who died during hospitalization are typically classified as having had severe influenza illness [16]. Dawood et al. found the median length of hospitalization to be 3-4 days. A study found that the highest rates of hospitalizations occurred among children less than 6 months of age. This could be because a flu vaccine is not approved for children less than 6 months of age [15]. Forty percent of hospitalized children had at least 1 underlying medical condition, putting them at higher risk for severe influenza. Of the 75% of children who received a chest radiograph, 32-38% showed evidence of pneumonia. Additionally, 11-14% of hospitalized children required intensive care unit admission and 3-7% required mechanical ventilation [15]. Rates of influenza-associated hospitalization in children varied as much as 3-fold from season to season. This calls for multi-season surveillance [15].

Caini et al. found overall hospitalizations and flu-associated deaths were highest in A(H3N2)-predominant seasons, followed by influenza B- or influenza A(H1N1)-predominant seasons. These study findings were not based on individual-level clinical data but instead

modeled data [11]. It's important to note that the number of flu illnesses, hospitalizations and deaths is thought to be higher than what is reported by states because not all cases are detected and reported. CDC estimates the influenza burden using a combination of multiple sources of estimates to account for likely under-reporting [20]. Annual flu burden estimates show the substantial health impact of flu and stresses the need to ensure vaccination of everyone 6 months and older. Understanding clinical characteristics and severity of different flu types and subtypes may help in detecting changes early to possibly indicate the emergence of a novel virus strain. Detecting novel influenza viruses early is imperative to prevent the spread of a new virus that could turn into a pandemic. Early detection of novel viruses is important for communication purposes to better prepare for the impact of seasonal epidemics [11]. Additionally, having better characterization of patients hospitalized for flu can improve flu burden estimates based on hospitalization surveillance [14].

Influenza Surveillance

The U.S. influenza surveillance system is a collaborative effort between CDC, state, local and territorial health departments, public health and clinical laboratories, vital statistics offices, clinicians, clinics and emergency departments [21]. Information from data sources is collected to report and predict current influenza activity, determine what flu viruses are circulating, detect changes in flu viruses, and measure the impact of flu illness, hospitalizations and deaths. Maintaining an influenza surveillance system is important because flu viruses are constantly changing, therefore ongoing data collection and virus characterization is needed. Since the 2009 H1N1 influenza pandemic, the overall mean number of specimens tested per flu season increased, increasing flu laboratory testing [8]. With flu viruses shifting and drifting, surveillance can detect these changes and inform public health response. Flu surveillance and research is also used to monitor the impact flu has on different fragments of the population [21].

The following U.S. surveillance systems capture clinically significant influenza-associated illness: The World Health Organization (WHO) Collaborating Laboratories System, the U.S. Influenza Hospitalization Surveillance Network (FluSurv-NET), and the National Center for Health Statistics (NCHS) Mortality Surveillance System [8]. Hundreds of public health and clinical labs located throughout the U.S. participate in flu surveillance through the WHO Collaborating Lab System. Laboratory data provides useful information on timing and intensity of flu activity as well as characterization data for what virus types are circulating and the age

groups being affected [21]. FluSurv-NET conducts population-based surveillance for laboratory-confirmed flu-associated hospitalizations among children and adults through a network of acute care hospitals. Data are used to estimate the annual influenza disease burden and burden averted by influenza vaccination, as well as estimating the seasonal influenza severity. Additionally, this data informs the use and effects of influenza vaccines and antivirals [21]. NCHS collects death certificate data from state vital statistics offices for all deaths in the U.S. This data is used to calculate the percentage of deaths that occur in a given week that had pneumonia and/or flu listed as the cause of death [21].

Flu hospitalization surveillance is collected through FluSurv-NET. This system identifies cases from laboratory reports and actively reviews hospital records to compare demographic and clinical characteristics of cases by type and subtype of flu viruses [16]. Detailed demographic and medical history were collected, including age, sex, medical comorbidities, flu vaccination status, and antiviral medications. This detailed patient data allows us to evaluate important demographic and clinical features, epidemiologic exposures and specific clinical outcomes. It's important to note that lab testing is ordered at the discretion of a clinician providing care. This could lead to bias towards more severe cases and under-estimation of burden due to un-tested potential cases [15,16]. Monitoring the incidence and clinical characteristics of flu-related hospitalizations over multiple seasons and surveillance sites is important to understand the flu disease burden in all ages, measuring the impact of current prevention programs, and guiding future prevention and treatment strategies [12,15].

Prevention and Treatment:

The best way to prevent seasonal influenza illness and its potentially serious complications is to get an annual flu vaccine. While there are many different flu viruses, flu vaccines prevent against the three or four viruses research suggests will be most commonly circulated that season [22]. Three-component (trivalent) flu vaccines contain an H3N2, H1N1 and B virus. Four-component (quadrivalent) flu vaccines have an additional B virus component. Flu vaccination can reduce flu illness, doctors' visits and missed work and school because of flu, as well as prevent flu-related hospitalizations. Because of their increased risk, children and older adults are considered some of the priority groups for flu vaccination, among others [12].

It is recommended that everyone 6 months and older get a flu vaccine each year because flu viruses are constantly changing. Flu vaccines may need to be updated from one season to the

next to protect against the viruses that research suggests may be most common during the upcoming flu season. Recent studies show flu vaccine can reduce the risk of overall flu illness by approximately 40-60%, depending on how well the vaccine matches what flu viruses are circulating throughout the season [23]. Since influenza vaccines were developed, H1 viruses exhibited fewer substantial antigenic changes, needing fewer vaccine strain updates than H3 viruses[8]. Additionally, annual flu vaccination is recommended because a person's immune protection from the vaccine declines over time. Some children aged 6 months through 8 years will require two doses of flu vaccine spaced at least 4 weeks apart for best protection from flu [15]. Typically this includes children in this age group getting vaccinated for the first time and those who have only previously gotten one dose of vaccine [24]. For children and adults who need only one dose, getting vaccinated early (i.e. July or August) may be associated with reduced protection against flu infection later in the flu season, especially among older adults.

While CDC recommends everyone 6 months and older get a flu vaccine by the end of October each season, as long as flu viruses are circulating, people can receive a flu vaccine later in the season, even in January or later. It's best to get vaccinated before flu viruses begin spreading in a community so a person's body develops the antibodies needed to provide the best protection against flu illness.

Most people with flu experience mild illnesses and do not need medical care or antiviral drugs [25]. For people who get sick with flu and are in high risk groups (i.e. young children and older adults) or are very sick, should receive prompt medical care. There are antiviral drugs that can be used to treat flu illness. Antiviral drugs are prescription medications that can make illness milder and shorten the time you are sick. They can also prevent serious flu complications, like pneumonia. Antiviral drugs work best when taken soon after illness onset to treat people who are very sick or hospitalized for flu and people who have a greater chance of developing serious flu complications because of their age or having an underlying medical condition [25]. While there are studies that show early antiviral medication works best for treating influenza, one study found that fewer than half of children with positive influenza received antiviral treatment during their hospital stay [15]. This stresses the importance for antiviral treatment guidance targeting high risk populations in outpatient settings [14].

Manuscript

Introduction

Influenza (flu) is a contagious respiratory illness caused by influenza viruses that can cause mild to severe illness. Serious outcomes of flu infection can result in hospitalization or death [1]. Young children, especially children younger than two years, are at high risk of developing serious flu-related complications requiring hospitalization. Complications of flu among children can include pneumonia, dehydration, worsening of long-term medical problems (i.e. heart disease or asthma), brain dysfunction, and sinus problems and ear infections [2].

Each year, millions of children get sick with seasonal flu, thousands of children are hospitalized, and some children die from flu. CDC estimates that since 2010, flu-related hospitalizations among children younger than 5 years ranges from 7,000 to 26,000 in the United States [2]. Since the 2004-2005 influenza season when flu-related pediatric deaths became a nationally notifiable condition, flu-related deaths in children reported to CDC during regular flu seasons ranged from 37 deaths (during the 2011-2012 season) to 188 deaths (during the 2017-2018 season) [2].

Flu vaccination can prevent illness, hospitalization and death in children. A study published in 2017 was one of the first to show that flu vaccination can significantly reduce a child's risk of dying from the flu, highlighting the importance of children receiving a seasonal flu vaccine each year [3]. While the percentage of children receiving their annual flu vaccination in the U.S. has been increasing over the years (~63% among children 6 months- 17 years during the 2018-2019 flu season), flu continues to cause a heavy burden among this vulnerable population [4]. This is partially due to the variability in how well the flu vaccine works to protect against flu illness from year to year.

Flu vaccines are made to protect against either three or four different influenza viruses research shows are most likely to spread and cause illness among people during the upcoming flu season. Since flu viruses are constantly changing, flu vaccines may be updated from one season to the next based on which flu viruses are making people sick, how the viruses are spreading, and how well the previous season's flu vaccines protected against the circulating flu viruses.

The purpose of this study was to identify the trends of seasonal flu viruses that most commonly circulate among children in the United States hospitalized for influenza since the 2010-2011 influenza season. Understanding these trends is useful for guiding prevention and

control efforts surrounding flu-burdened children. This study is aiming to determine whether certain flu viruses increase the burden of flu among children ages 0-4 years and to determine the relationship between the proportion of flu among children and the proportion flu hospitalizations among children across seasons. Based on previous literature, it's predicted that influenza A viruses have an increased burden among children compared to other flu virus types.

National and regional data was assessed from the U.S. influenza surveillance systems. Lab-confirmed hospitalization data was analyzed to identify trends in hospitalization rates among children over nine consecutive flu seasons. Circulating virus subtypes and lineages from U.S. virologic surveillance were analyzed and compared with hospitalization rates among children to analyze patterns in seasonal flu viruses among children hospitalized for flu. Understanding these trends will help to better conceptualize the burden of flu among children.

Methods

Study

This study was a cross-sectional, secondary analysis of existing U.S. national influenza surveillance data provided by the CDC (2010-2019). The study population for this analysis included children with laboratory-confirmed influenza monitored through public health laboratory virologic surveillance and children with influenza-associated hospitalization residing in the United States, monitored through the Influenza Hospitalization Surveillance Network (FluSurv-NET).

Variables

For each flu season, positive flu specimens and weekly hospitalization rates were analyzed. CDC's influenza seasons are tracked from Week 40 through Week 39 of the following year. Young children were further analyzed against all other ages by creating proportion variables (children 0-4 yrs/all other ages) in each data set.

Hospitalization cases for influenza are confirmed by a laboratory test. It's important to note that testing is clinician-directed, meaning that someone with influenza will only be confirmed and captured by surveillance if a clinician orders an influenza test and the test is positive.

For each season, public health laboratory data on the circulating virus subtype (Influenza A) and lineage (Influenza B) are presented by age group (0-4 years, 5-24 years, 25-64 years and

65+ years) [26]. Influenza virus subtypes A(H1N1)pdm09 and A(H3N2) were tracked along with virus lineages B/Victoria and B/Yamagata. This data was obtained from the virologic surveillance system. Two virus subtypes from the virologic data, flu H3N2v (variant flu) and H1N1 (pre 2009 virus), were excluded from this analysis.

Data Source

The Influenza Division at CDC collects and analyzes the information provided by the collaborative surveillance system conducted by the CDC and its partners in state, local, and territorial health departments, public health and clinical laboratories, vital statistics offices, healthcare providers, clinic and emergency departments. A weekly influenza surveillance report, FluView, is prepared by CDC's Influenza Division with data they compile from the U.S. influenza surveillance system. Additionally, FluView Interactive is an online application managed by the Influenza Division that allows for more in-depth exploration of flu surveillance data. The comprehensive system contains five categories of flu surveillance[21]. Data from hospitalization surveillance and virologic surveillance were used for this analysis.

The U.S. Influenza Hospitalization Surveillance Network (FluSurv-NET) is a population-based surveillance network covering more than 27 million people, representing 9 percent of the U.S. population. The network consists of more than 70 counties in 13 states that participate in the 10 Emerging Infections Program (EIP) states (CA, CO, CT, GA, MD, MN, NM, NY, OR, and TN) and the Influenza Hospitalization Surveillance Program (IHSP) (Figure 1)[27(p)]. The IHSP started during the 2009-2010 season in effort to enhance influenza surveillance following the 2009 H1N1 flu pandemic. IHSP sites have fluctuated over the years, but since the 2013-2014 influenza season include MI, OH and UT [21]. Detailed demographic and medical history are collected and displayed in this surveillance system, including age, sex, medical comorbidities, flu vaccination status, and antiviral medications. This detailed patient data allows us to evaluate important demographic and clinical features, epidemiologic exposures and specific clinical outcomes.

U.S. virologic surveillance data is sourced from approximately 100 public health laboratories and more than 300 clinical laboratories throughout all 50 states, Puerto Rico, Guam and the District of Columbia (DC). The labs perform subtyping tests on respiratory samples from patients exhibiting influenza like illness (ILI) and report data regarding flu virus type and subtypes through either the U.S. WHO Collaborating Laboratories System or the National

Respiratory and Enteric Virus Surveillance System (NREVSS). Flu testing practices differ in public health and clinical laboratories. While clinical labs primarily test for diagnostic purposes, providing useful information on timing and intensity of flu activity, public health labs help us understand what flu virus types, subtypes, and lineages are circulating and the age groups being affected. Since the distribution and proportion of positive flu specimens by age and virus subtype and lineage are reported from public health laboratories, public health laboratory virologic surveillance data from this system were utilized for this analysis [21].

Statistical Methods

Secondary data was downloaded from CDC's FluView Interactive application. Microsoft Excel was used to organize and clean the data. SAS 9.4 was used for re-coding variables and performing statistical analyses. An alpha level of 0.05 was used for all statistical tests.

Linear regression models were analyzed (proc reg in SAS) to observe possible trends among variables: the proportion of flu among children over time, the proportion flu-related hospitalizations among children over time, and the proportion of flu virus types among children over time.

The following correlations were tested (proc corr in SAS) across flu seasons: proportion of flu among children (0-4 yr) and proportions of flu among other age groups (5-24 yr, 25-64 yr, 65+ yr), proportion of flu-related hospitalizations among children (0-4 yr) and proportion of flu-related hospitalizations among other age groups (5-17 yr, 18-49 yr, 50-64 yr, 65+ yr), and proportion of flu among children (0-4 yr) and proportion of flu-related hospitalizations among children (0-4 yr).

Results

Trends reveal that the proportion of flu among children (0-4 yr) has been decreasing over time (2010-2019) (-0.008; CI: [-0.014, -0.001]; p=0.0383; Table 1; Figure 2). Similarly, trends show the proportion of flu-related hospitalizations among children (0-4 yr) has been decreasing over time (2010-2019) (-0.020; CI: [-0.034, -0.006]; p=0.0129; Figure 3; Table 3). While this downward trend was also revealed in the proportion of flu A(H3N2) virus among children (0-4 yr) over time (2010-2019) (-0.010; CI: [-0.018, -0.003]; p=0.0129; Figure 4), no other virus type revealed a significant trend (Figure 5, Figure 6, Table 2).

The proportion of flu among children (0-4 yr) and the proportion of flu among older children (5-24 yr) have a fairly strong, positive relationship (r = 0.8307, p=0.0055). However,

the analysis shows a fairly strong, negative relationship between the proportion of flu among children (0-4 yr) and the proportion of flu among older adults (65+ yr) (r = -0.762, p=0.0170).

Similar to the virologic data, the proportion of flu-related hospitalizations among children (0-4 yr) and the proportion of flu hospitalizations among older children (5-17 yr) have a fairly strong, positive relationship (r = 0.886, p=0.0015). Likewise, the proportion of flu hospitalizations among young children (0-4) has a moderately, positive relationship with the proportion of flu hospitalizations among adults (18-49 yr) (r=0.68350, p=0.0424). However, the analysis shows a fairly strong, negative relationship between the proportion of flu hospitalizations among children (0-4 yr) and proportion of flu hospitalizations among older adults (65+ yr) (r = -0.853, p=0.0035) (Figure 7).

Lastly, there appears to be a very strong, positive relationship between the proportion of flu among children (0-4 yr) and the proportion of flu hospitalizations among children (0-4 yr) (correlation= 0.9183, p=0.005).

Discussion

Since the 2010-2011 flu season, data has revealed a downward trend in the proportion of flu among young children (0-4 yr). This decrease was similarly revealed in the proportion of flu hospitalizations among children. The Pearson correlation coefficient revealed that the proportion of flu among children had a strong, positive relationship with the proportion of flu-related hospitalizations among children (Table 4). This reinforces our findings that over time, as the proportion of flu among children decreased, the proportion of flu-hospitalizations among children similarly decreased. The analysis also indicated a strong, negative relationship between the proportion of flu among children and the proportion of flu among older adults over time. This finding reveals that as the proportion of flu and flu hospitalizations among children decreased, the proportion of flu and flu hospitalizations among older adults increased over time. This finding is significant as it uncovers that children have experienced less of a burden from flu compared to older age groups in the past decade.

This study also found that the proportion of flu A(H3N2) virus among children (0-4 yr) decreased over time; however, there is insufficient evidence to conclude trends among other virus types in this age group over time. Though numerous studies have found overall flu burden to be highest among H3N2-predominant seasons, this analysis reinforces current literature proposing there are contradictory results suggesting no differences among flu virus types and

subtypes on overall flu burden. Additional well-designed studies are needed to strengthen the evidence showing differences in flu burden among different virus subtypes.

Limitations

Surveillance systems that rely on case reports only reveal information about positive tests; therefore, we have limited knowledge regarding the people who test negative or never got a flu test. The use of influenza data as an indicator for rates of flu activity may not reveal the true burden of flu over time. Available data could be an underestimation of total flu cases, as the data only includes people who sought healthcare for their symptoms.

Not all positive flu samples were subtyped in the virologic data. Influenza B virus lineage was not specified until the 2015-2016 influenza season. Additionally, the flu hospitalization data isn't presented by virus subtype among age groups; therefore, studying the trends in virus subtypes and lineages by age among flu hospitalizations if limited. Future research assessing flu hospitalization data by virus subtypes and lineages and age may help identify common factors leading to flu burden among specific age groups. Additionally, future research analyzing the risk factors for hospitalizations among different age groups during a flu season when a novel virus emerges would be beneficial.

Conclusion

While the U.S. has a comprehensive influenza surveillance system reporting on current flu activity, and the Centers for Disease Control and Prevention (CDC) publishes weekly updates on their website (FluView), there is a lack of literature analyzing trends among the virus types causing flu and flu-related hospitalizations among children over multiple flu seasons. In this study, a decrease in proportion of flu and proportion of flu-related hospitalizations among children was observed over time (2010-2019). From the analysis on virus types, a decrease in the proportion of influenza A(H3N2) among children was observed over time. While the proportion of flu among young children had a positive relationship with the proportion of flu among older children, the proportion of flu among children had a negative relationship with the proportion of flu among older adults. Similar relationships were seen among the hospitalization data (Figure 6). Trends in seasonal flu and flu-related complications have important implications for flu prevention and control efforts. Understanding these trends over time can result in targeting more vulnerable audiences with strong flu vaccine recommendations and control strategies.

References

1. About Flu | CDC. Published January 6, 2020. Accessed February 23, 2020. https://www.cdc.gov/flu/about/index.html

2. CDC. Children & Influenza (Flu). Centers for Disease Control and Prevention. Published December 30, 2019. Accessed March 31, 2020. https://www.cdc.gov/flu/highrisk/children.htm

3. Flannery B, Reynolds SB, Blanton L, et al. Influenza Vaccine Effectiveness Against Pediatric Deaths: 2010–2014. *Pediatrics*. 2017;139(5). doi:10.1542/peds.2016-4244

4. Flu Vaccination Coverage, United States, 2018–19 Influenza Season | FluVaxView | Seasonal Influenza (Flu) | CDC. Published September 25, 2019. Accessed March 31, 2020. https://www.cdc.gov/flu/fluvaxview/coverage-1819estimates.htm

5. CDC. How Flu Spreads. Centers for Disease Control and Prevention. Published August 27, 2018. Accessed March 5, 2020. https://www.cdc.gov/flu/about/disease/spread.htm

6. The Flu Season | CDC. Published November 7, 2019. Accessed March 1, 2020. https://www.cdc.gov/flu/about/season/flu-season.htm

7. CDC. Understanding Flu Viruses. Centers for Disease Control and Prevention. Published July 10, 2019. Accessed March 5, 2020. https://www.cdc.gov/flu/about/viruses/index.htm

8. Budd AP, Beacham L, Smith CB, et al. Birth Cohort Effects in Influenza Surveillance Data: Evidence That First Influenza Infection Affects Later Influenza-Associated Illness. *J Infect Dis*. 2019;220(5):820-829. doi:10.1093/infdis/jiz201

9. CDC. Cold Versus Flu. Centers for Disease Control and Prevention. Published December 30, 2019. Accessed March 1, 2020. https://www.cdc.gov/flu/symptoms/coldflu.htm

10. Flu Symptoms & Complications | CDC. Accessed March 5, 2020. https://www.cdc.gov/flu/symptoms/symptoms.htm

11. Caini S, Kroneman M, Wiegers T, El Guerche-Séblain C, Paget J. Clinical characteristics and severity of influenza infections by virus type, subtype, and lineage: A systematic literature review. *Influenza Other Respir Viruses*. 2018;12(6):780-792. doi:10.1111/irv.12575

12. Czaja CA, Miller L, Alden N, et al. Age-Related Differences in Hospitalization Rates, Clinical Presentation, and Outcomes Among Older Adults Hospitalized With Influenza—U.S. Influenza Hospitalization Surveillance Network (FluSurv-NET). *Open Forum Infect Dis*. 2019;6(7). doi:10.1093/ofid/ofz225

13. CDC. People at High Risk of Flu. Centers for Disease Control and Prevention. Published August 27, 2018. Accessed March 5, 2020. https://www.cdc.gov/flu/highrisk/index.htm

14. Appiah GD, Chung JR, Flannery B, et al. Hospitalization following outpatient medical care for influenza: US influenza vaccine effectiveness network, 2011-12-2015-16. *Influenza Other Respir Viruses*. 2019;13(2):133-137. doi:10.1111/irv.12616

15. Dawood FS, Fiore A, Kamimoto L, et al. Burden of seasonal influenza hospitalization in children, United States, 2003 to 2008. *J Pediatr*. 2010;157(5):808-814. doi:10.1016/j.jpeds.2010.05.012

16. Chaves SS, Aragon D, Bennett N, et al. Patients hospitalized with laboratory-confirmed influenza during the 2010-2011 influenza season: exploring disease severity by virus type and subtype. *J Infect Dis*. 2013;208(8):1305-1314. doi:10.1093/infdis/jit316

17. CDC. Types of Influenza Viruses. Centers for Disease Control and Prevention. Published November 18, 2019. Accessed March 5, 2020. https://www.cdc.gov/flu/about/viruses/types.htm

18. CDC. How Flu Viruses Can Change. Centers for Disease Control and Prevention. Published October 15, 2019. Accessed March 5, 2020. https://www.cdc.gov/flu/about/viruses/change.htm

19. Why CDC Estimates the Burden of Season Influenza in the U.S. | CDC. Published October 25, 2018. Accessed March 10, 2019. https://www.cdc.gov/flu/about/burden/why-cdc-estimates.htm

20. How CDC Estimates the Burden of Seasonal Influenza in the U.S. | CDC. Published November 22, 2019. Accessed March 5, 2020. https://www.cdc.gov/flu/about/burden/how-cdc-estimates.htm

21. U.S. Influenza Surveillance System: Purpose and Methods | CDC. Published February 24, 2020. Accessed March 5, 2020. https://www.cdc.gov/flu/weekly/overview.htm

22. Preventive Steps | CDC. Accessed March 5, 2020. https://www.cdc.gov/flu/prevent/prevention.htm

23. Vaccine Effectiveness: How Well Do the Flu Vaccines Work? | CDC. Published February 10, 2020. Accessed July 30, 2020. https://www.cdc.gov/flu/vaccines-work/vaccineeffect.htm

24. Children & Influenza (Flu) | CDC. Accessed March 5, 2020. https://www.cdc.gov/flu/highrisk/children.htm#anchor_1577721999236

25. Treatment: What You Need to Know | CDC. Accessed March 5, 2020. https://www.cdc.gov/flu/treatment/treatment.htm

26. Public Health Laboratory Virologic Age Surveillance. Accessed April 1, 2020. https://gis.cdc.gov/grasp/fluview/flu_by_age_virus.html

27. Influenza Hospitalization Surveillance Network (FluSurv-NET) | CDC. Published July 8, 2020. Accessed July 21, 2020. https://www.cdc.gov/flu/weekly/influenza-hospitalization-surveillance.htm

Table 1. Virologic Flu Surveillance: Total Flu Serotypes | Proportion Among Children

Virologic Flu Surviellance Data
Total Flu Serotypes By Age Group

	0-4 yr		5-24 yr		25-64 yr		65+ yr		All Ages		Proportion of Children (0-4 yr)
	Case Count	(%)	Case Count	(%)	Case Count	(%)	Case Count	(%)	Case Count	(%)	(0-4 yr)/All Ages
Flu Season											
2010-11	4990.00	14.33	11796.00	12.70	10268.00	9.65	4583.00	5.94	31637.00	10.17	0.16
2011-12	2672.00	7.67	5878.00	6.33	5372.00	5.05	2815.00	3.65	16737.00	5.38	0.16
2012-13	5026.00	14.43	12150.00	13.08	12092.00	11.37	9848.00	12.77	39116.00	12.57	0.13
2013-14	3253.00	9.34	7367.00	7.93	14638.00	13.76	4313.00	5.59	29571.00	9.50	0.11
2014-15	3707.00	10.64	11072.00	11.92	11355.00	10.68	14182.00	18.39	40316.00	12.95	0.09
2015-16	2845.00	8.17	7660.00	8.25	10641.00	10.00	4073.00	5.28	25219.00	8.10	0.11
2016-17	3083.00	8.85	11550.00	12.44	11635.00	10.94	12315.00	15.97	38583.00	12.40	0.08
2017-18	3943.00	11.32	11785.00	12.69	16020.00	15.06	16544.00	21.45	48292.00	15.52	0.08
2018-19	5308.00	15.24	13622.00	14.67	14348.00	13.49	8452.00	10.96	41730.00	13.41	0.13

Table 2. Virologic Flu Surveillance: Flu Serotypes by Virus Type| Proportion Among Children

Virologic Flu Surviellance
Flu Serotypes by Virus Type with Proportion of Children

Flu Season	Virus Type	0-4 yrs	5-24 yrs	25-64 yrs	65+ yrs	Total	Proportion of Children (0-4 yrs)
2010-11	A (H3)	2509	3770	4592	3685	14556	17.24%
2010-11	A (H1N1)pdm09	1272	4064	4089	382	9807	12.97%
2010-11	A (Subtyping not Performed)	77	104	145	89	415	18.55%
2010-11	B (Lineage Unspecified)	1132	3858	1442	427	6859	16.50%
2011-12	A (H3)	1779	3471	3323	2451	11024	16.14%
2011-12	A (H1N1)pdm09	506	1191	1324	129	3150	16.06%
2011-12	A (Subtyping not Performed)	59	88	115	50	312	18.91%
2011-12	B (Lineage Unspecified)	328	1128	610	185	2251	14.57%
2012-13	A (H3)	3364	7498	8747	8510	28119	11.96%
2012-13	A (H1N1)pdm09	261	498	876	95	1730	15.09%
2012-13	A (Subtyping not Performed)	21	47	106	228	402	5.22%
2012-13	B (Lineage Unspecified)	1380	4107	2363	1015	8865	15.57%
2013-14	A (H3)	322	959	1196	1115	3592	8.96%
2013-14	A (H1N1)pdm09	2592	5268	11852	2468	22180	11.69%
2013-14	A (Subtyping not Performed)	23	78	164	58	323	7.12%
2013-14	B (Lineage Unspecified)	316	1062	1426	672	3476	9.09%
2014-15	A (H3)	3113	9108	9154	12852	34227	9.10%
2014-15	A (H1N1)pdm09	25	37	89	12	163	15.34%
2014-15	A (Subtyping not Performed)	33	81	108	119	341	9.68%
2014-15	B (Lineage Unspecified)	536	1846	2004	1199	5585	9.60%
2015-16	A (H3)	309	1513	1080	852	3754	8.23%
2015-16	A (H1N1)pdm09	1876	3419	6918	1906	14119	13.29%
2015-16	A (Subtyping not Performed)	34	72	176	80	362	9.39%
2015-16	B (Victoria Lineage)	207	765	398	153	1523	13.59%
2015-16	B (Yamagata Lineage)	214	943	1341	797	3295	6.49%
2015-16	B (Lineage Unspecified)	205	948	728	285	2166	9.46%
2016-17	A (H3)	2100	7919	8130	9728	27877	7.53%
2016-17	A (H1N1)pdm09	140	196	378	160	874	16.02%
2016-17	A (Subtyping not Performed)	17	57	75	83	232	7.33%
2016-17	B (Victoria Lineage)	336	1169	542	191	2238	15.01%
2016-17	B (Yamagata Lineage)	347	1546	1958	1872	5723	6.06%
2016-17	B (Lineage Unspecified)	143	663	552	281	1639	8.72%
2017-18	A (H3)	2175	5985	8983	11487	28630	7.60%
2017-18	A (H1N1)pdm09	781	1443	2292	821	5337	14.63%
2017-18	A (Subtyping not Performed)	34	63	129	140	366	9.29%
2017-18	B (Victoria Lineage)	192	655	293	97	1237	15.52%
2017-18	B (Yamagata Lineage)	578	2692	3444	3460	10174	5.68%
2017-18	B (Lineage Unspecified)	183	947	879	539	2548	7.18%
2018-19	A (H3)	1820	6525	4464	4494	17303	10.52%
2018-19	A (H1N1)pdm09	2859	5423	8744	3573	20599	13.88%
2018-19	A (Subtyping not Performed)	224	360	519	191	1294	17.31%
2018-19	B (Victoria Lineage)	193	691	296	59	1239	15.58%
2018-19	B (Yamagata Lineage)	37	137	154	106	434	8.53%
2018-19	B (Lineage Unspecified)	175	486	171	29	861	20.33%

Table 3. Flu Hospitalization Surveillance: Flu Hospitalization Rate| Proportion Among Children

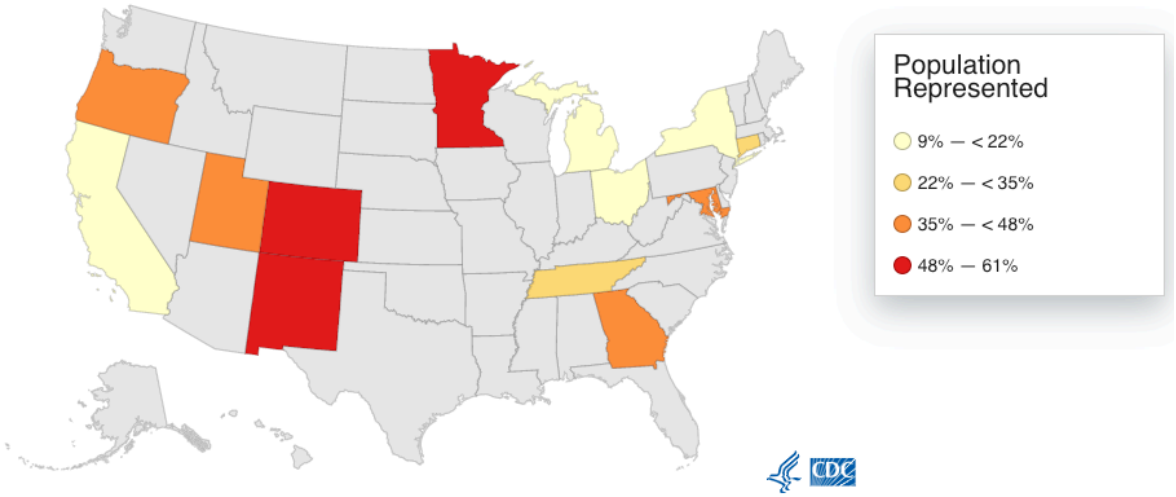
Influenza Hospitalization Surveillance Network (FluSurv-NET)
Rate of Flu Hospitalizations Per 100,000

	0-4 yr		5-17 yr		18-49 yr		50-64 yr		65+ yr		All Ages		Proportion of Children (0-4 yr)
	Hosp Rate	(%)	Hosp Rate	(%)	Hosp Rate	(%)	Hosp Rate	(%)	Hosp Rate	(%)	Hosp Rate	(%)	(0-4 yr)/All Ages
Flu Season													
2010-11	46.40	10.11	9.10	7.69	11.40	7.12	21.90	4.58	64.00	3.81	152.80	5.28	0.30
2011-12	16.00	3.49	4.00	3.38	4.20	2.62	8.10	1.70	30.20	1.80	62.50	2.16	0.26
2012-13	66.90	14.58	14.60	12.33	16.10	10.06	40.90	8.56	183.90	10.95	322.40	11.14	0.21
2013-14	47.30	10.31	9.40	7.94	21.50	13.43	53.70	11.24	84.70	5.04	216.60	7.48	0.22
2014-15	57.30	12.48	16.60	14.02	18.10	11.31	53.40	11.18	308.50	18.36	453.90	15.68	0.13
2015-16	42.40	9.24	9.70	8.19	16.40	10.24	45.10	9.44	84.70	5.04	198.30	6.85	0.21
2016-17	40.80	8.89	15.50	13.09	17.90	11.18	62.70	13.12	274.80	16.36	411.70	14.22	0.10
2017-18	71.00	15.47	19.50	16.47	30.00	18.74	112.80	23.61	437.20	26.02	670.50	23.16	0.11
2018-19	70.90	15.45	20.00	16.89	24.50	15.30	79.20	16.58	212.00	12.62	406.60	14.04	0.17

Table 4. Pearson Correlation Coefficients Among Variables

Variable	Proportion of Flu Among Children (0-4 yr)	Proportion of Flu-Related Hospitalizations Among Children (0-4 yr)
Proportion of Flu Among Children (0-4 yr)	Correlation: 0.918 p-Value:0.001 N=9	1.000
Proportion of Flu Among Older Children (5-24 yr)	Correlation: 0.831 p-Value: 0.006 N=9	Correlation: 0.685 p-Value:0.042 N=9
Proportion of Flu Among Adults (25-64 yr)	Correlation: 0.002 p-Value: 0.997 N=9	Correlation: 0.284 p-Value:0.459 N=9
Proportion of Flu Among Older Adults (65+ yr)	Correlation: -0.762 p-Value:0.017 N=9	Correlation: -0.883 p-Value:0.002 N=9
Proportion of Flu-Related Hospitalizations Among Children (0-4 yr)	1.000	Correlation: 0.918 p-Value:0.001 N=9
Proportion of Flu-Related Hospitalizations Among Older Children (5-17 yr)	Correlation: 0.951 p-Value:<.0001 N=9	Correlation: 0.886 p-Value:0.002 N=9
Proportion of Flu-Related Hospitalizations Among Adults (18-49 yr)	Correlation: 0.434 p-Value:0.2431 N=9	Correlation: 0.684 p-Value:0.042 N=9
Proportion of Flu-Related Hospitalizations Among Adults (50-64 yr)	Correlation: -0.165 p-Value:0.671 N=9	Correlation: 0.071 p-Value:0.857 N=9
Proportion of Flu-Related Hospitalizations Among Older Adults (65+ yr)	Correlation: -0.668 p-Value:0.050 N=9	Correlation: -0.853 p-Value:0.004 N=9

Figure 1. Percentage of State Population Represented by Participating FluSurv-NET Counties [26]



Data Table

State	% of State Population Represented	Number of Participating Counties
California	9%	3
Colorado	49%	5
Connecticut	29%	2
Georgia	39%	8
Maryland	46%	6
Michigan	13%	5
Minnesota	55%	7
New Mexico	61%	7
New York	11%	15
Ohio	18%	10
Oregon	44%	3
Tennessee	26%	8
Utah	36%	1

Figure 2. Proportion of flu among children (0-4 yr) per flu season

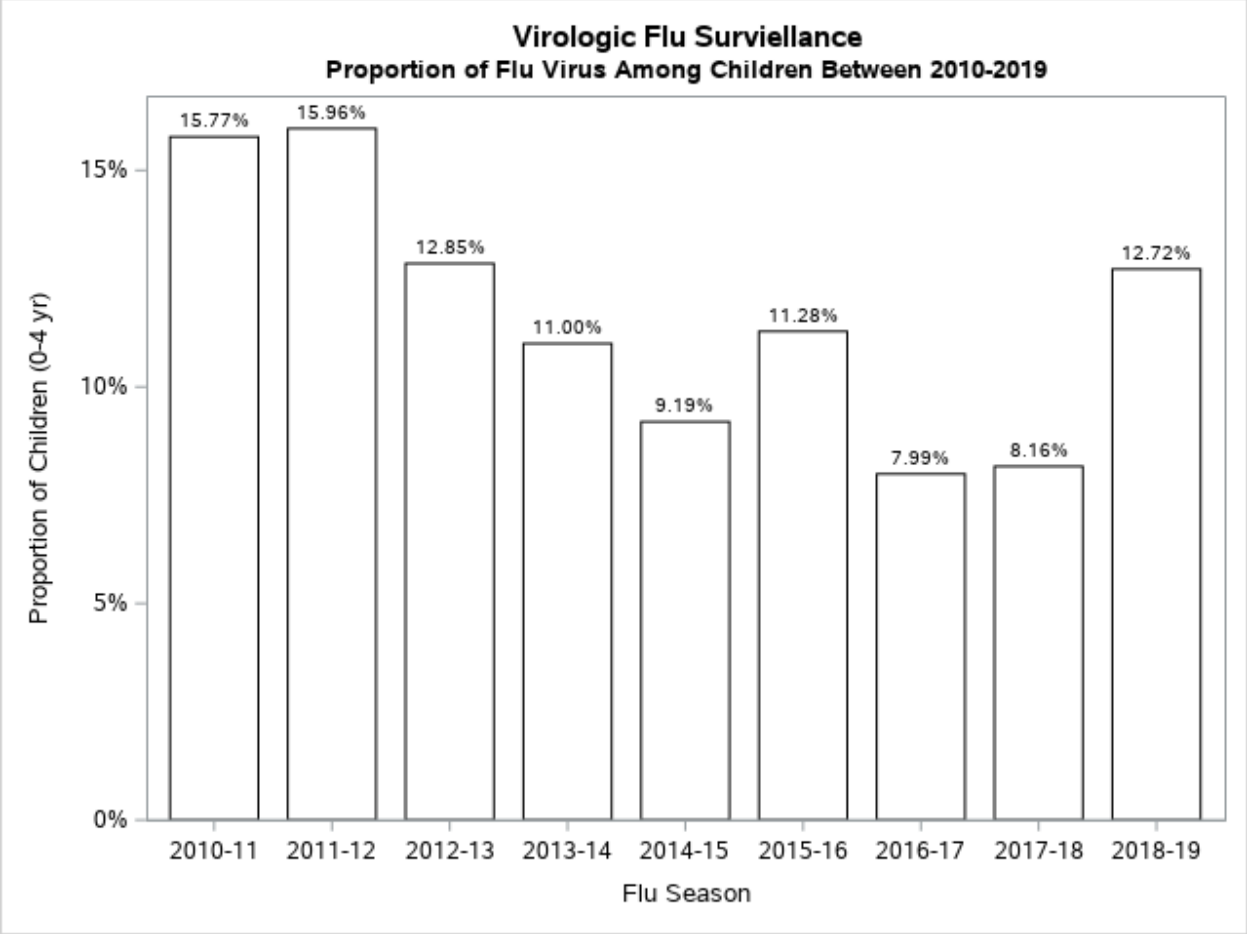


Figure 3. Proportion of flu hospitalizations among children (0-4 yr) per flu season

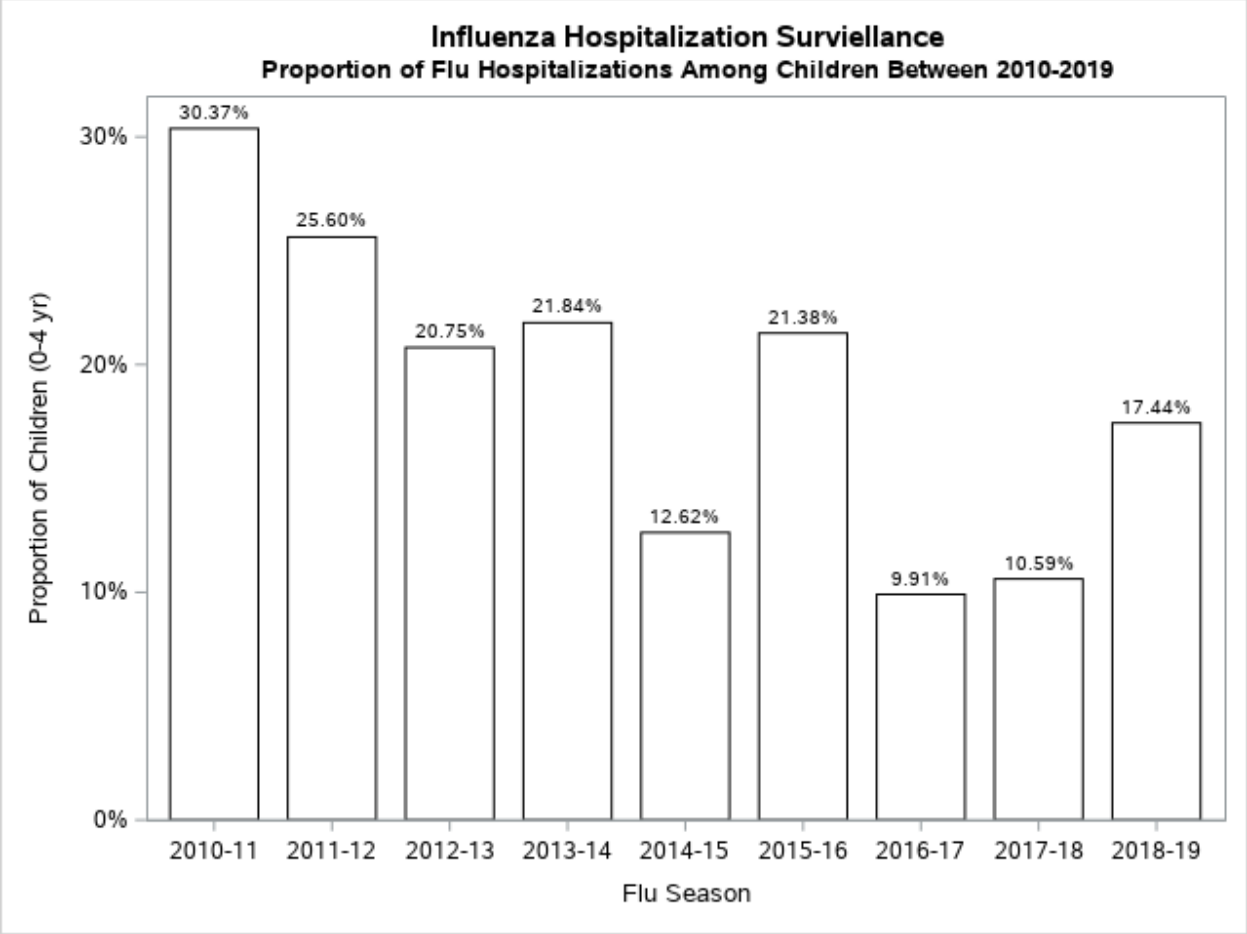


Figure 4. Proportion of flu A(H3N2) among children (0-4 yr) per flu season

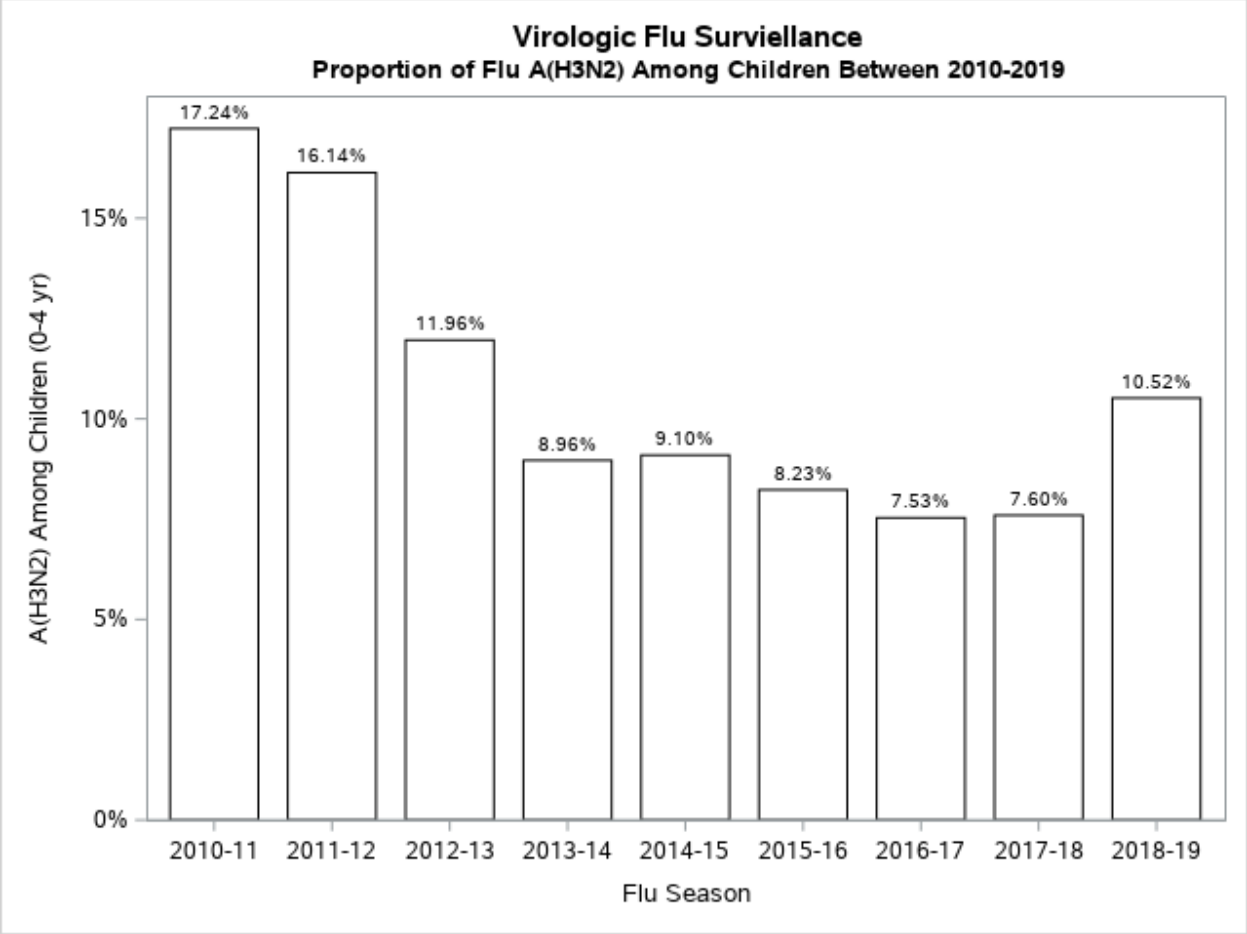


Figure 5. Proportion of flu virus among children (0-4) over time by virus type (total)

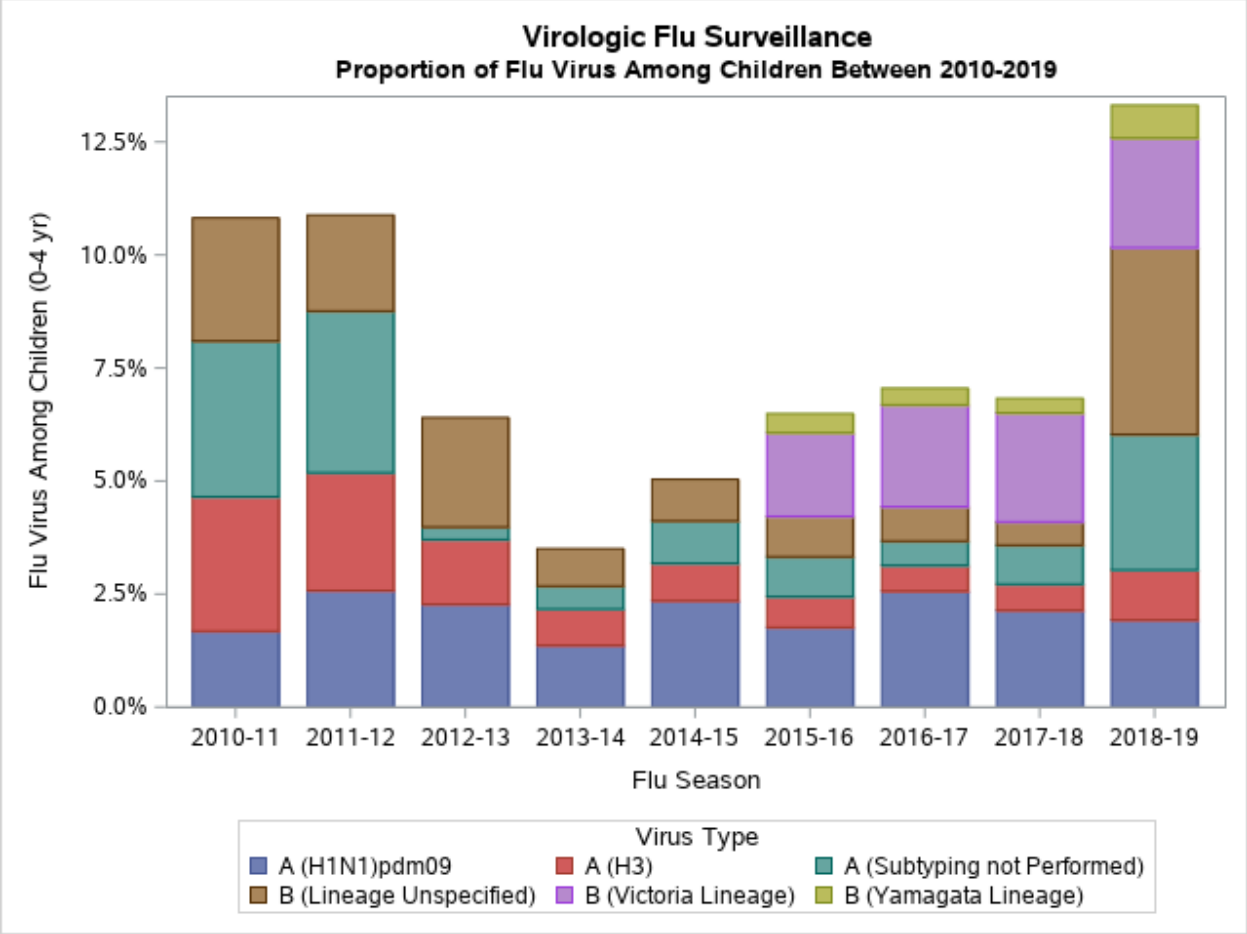
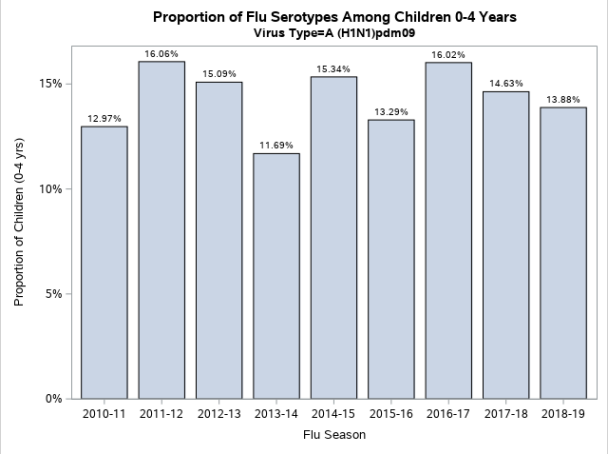
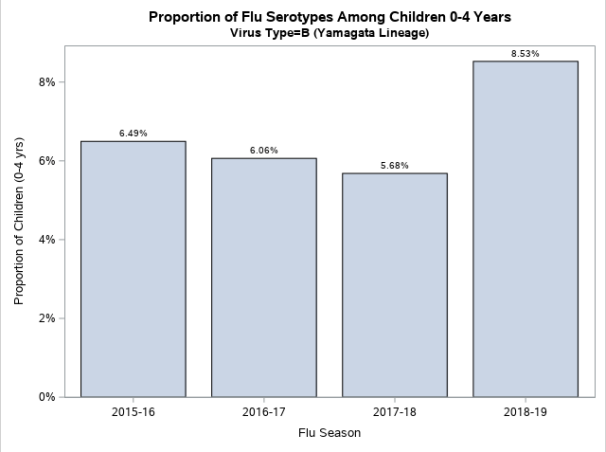
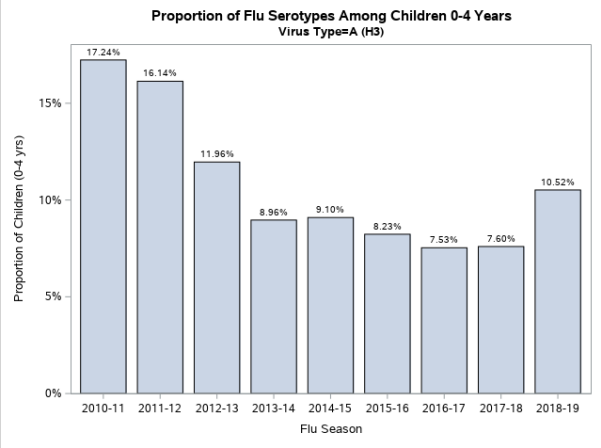
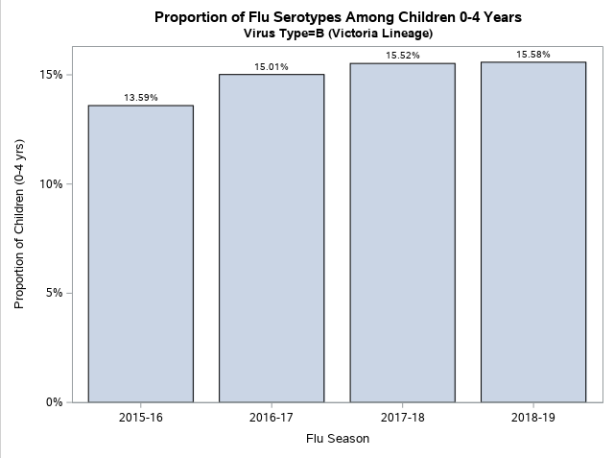


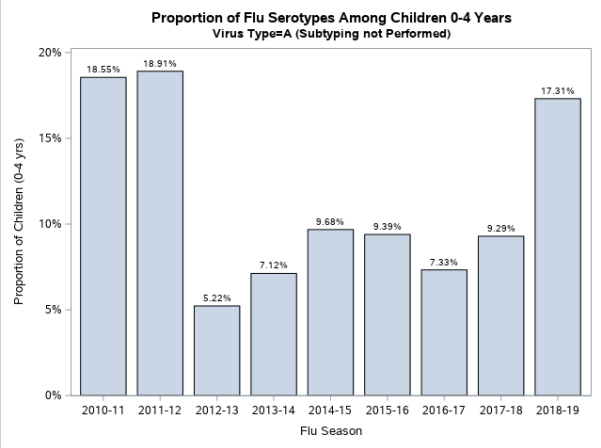
Figure 6. Proportion of flu virus types among children (0-4 yr) over time by virus type











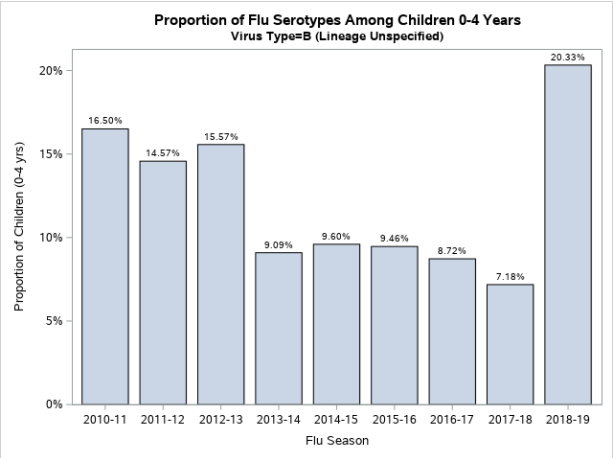


Figure 7. Total flu virus serotypes by age group over time (2010-2019)