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The Relationship Between the Severity of Influenza-Related Illness and Timing of Seasonal Influenza Vaccination in Hospitalized Children and Adults Identified Through FluSurv-NET, 2013-2017

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The Relationship Between the Severity of Influenza-Related Illness and Timing of Seasonal Influenza Vaccination in Hospitalized Children and Adults Identified Through FluSurv-NET, 2013-2017

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An abstract of

A thesis submitted to the Faculty of the

James T. Laney School of Graduate Studies of Emory University

in partial fulfilment of the requirements for the degree of

Master of Science in Clinical Research

2020

ABSTRACT

The Relationship Between the Severity of Influenza-Related Illness and Timing of Seasonal Influenza Vaccination in Hospitalized Children and Adults Identified Through FluSurv-NET, 2013-2017

By Julia C. Haston, MD

Background: The burden of influenza in the United States is substantial, and influenza vaccine is known to prevent complications of influenza. There has been growing concern that protection provided by the seasonal influenza vaccine may wane throughout an influenza season. This analysis seeks to determine whether timing of influenza vaccine is associated with odds of severe outcomes, including admission to the intensive care unit (ICU), death, pneumonia, and prolonged hospitalization among children and adults with influenza-related hospitalization.

Methods: We used data from the Influenza Hospitalization Surveillance Network (FluSurv-NET) and included patients ≥6 months of age hospitalized with laboratory-confirmed influenza during October 1-April 30 of influenza seasons 2013-14 through 2016-17 who received seasonal influenza vaccine ≥14 days prior to admission. Demographic differences among those who received vaccine early versus late were compared using Chi-square. Multivariate logistic regression was used to model the relationship between timing of vaccine and dichotomous outcomes, and Cox proportional hazard modeling was used to describe time-to-event outcomes. All analyses were stratified by age group and influenza type/subtype.

Results: Among 21,306 adults and 1,728 children, early vaccine receipt was associated with older age ($p<0.0001$), white race ($p<0.0001$), and certain medical conditions including cardiovascular disease, metabolic disorder, and kidney disease ($p<0.001$) in adults, and multiple conditions in children. Children were more likely to have ICU admission than adults (22.2% among children; 10.2% ≥85 years of age), and death increased with age among adults. Odds of ICU admission, death, and pneumonia were not increased in those with longer time between vaccination and hospitalization. Notably, odds of death decreased in adults as time since vaccination increased (aOR 0.528, 95% CI 0.369, 0.756 comparing those with ≥150 days since vaccination to those with 14-59 days). Duration of hospitalization was not associated with timing of vaccine in most groups.

Conclusion: Among influenza-vaccinated children and adults hospitalized with influenza, multiple demographic characteristics were associated with timing of influenza vaccination. However, prolonged time between vaccination and hospitalization was not associated with increased odds of death, ICU admission, pneumonia, or prolonged hospitalization. This data supports current recommendations to receive vaccine by the end of October annually.

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INTRODUCTION

Influenza is a substantial cause of morbidity and mortality in the United States, resulting in up to 810,000 hospitalizations and 61,000 deaths each year (1). Seasonal influenza vaccination is known to decrease rates of influenza-like illness (ILI) by 40-60% during seasons when the vaccine is well matched to circulating viral strains, and it is has also been shown to prevent influenza-related hospitalizations (2-4). Furthermore, receipt of seasonal influenza vaccination has been shown to attenuate severe outcomes among patients who are hospitalized with influenza despite receiving influenza vaccination in some seasons. Individuals who received influenza vaccine have been found to have lower rates of admission to the intensive care unit (ICU) and death as well as shorter duration of hospitalization (2, 3, 5-7). For these reasons, influenza vaccination recommendations in the United States currently state that all people ≥6 months of age and without contraindication should receive annual vaccination (8).

Influenza vaccine becomes available each season as early as July, and it is recommended that people be vaccinated by the end of October; however, substantial variability in the timing of influenza virus circulation exists, and influenza may still be circulating up to eight months after vaccination is received. As such, an individual vaccinated early in the season may not be exposed to the virus for several months. Recent publications have suggested that vaccine-induced protection against influenza may wane over the course of a season, as evidenced by increased odds of testing positive for influenza when presenting with influenza-like illness among those who were vaccinated early (9-13). In fact, the vaccine effectiveness may decline by >40% in some seasons (9). The impact waning protection could have on the severity of illness among individuals who are hospitalized with influenza-related illness despite receiving the influenza vaccine has not been described.

Understanding the relationship between the timing of influenza vaccination and the severity of influenza-related disease is crucial to optimizing vaccination strategies. The current recommendations for seasonal influenza vaccination include administration of the vaccine by the end of October each season (8). However, it is important to understand the full effect waning of vaccine-induced immunity may have on patient outcomes, particularly for those at highest risk of severe complications related to influenza, as

some have considered delaying vaccination due to waning protection (14-16). This analysis sought to understand how timing of seasonal influenza vaccination impacts the severity of illness observed in children and adults who are hospitalized with influenza.

To assess this relationship, demographic characteristics and patient outcomes were retrospectively evaluated across four influenza seasons (2013-2014 through 2016-2017) using data from the Influenza Hospitalization Surveillance Network (FluSurv-NET), a large surveillance network overseen by the Centers for Disease Control and Prevention (CDC). Multivariate logistic regression models as well as Cox proportional hazards models were used to determine associations between timing of vaccine receipt and odds/hazard of severe outcomes. In this analysis, waning of protection provided by the influenza vaccine was not demonstrated, as increased time since vaccination was not found to be associated with increased odds of severe outcomes. These findings support current vaccination strategies and recommendations, and we urge providers to continue administering the seasonal influenza vaccine to patients before November each season.

BACKGROUND

Influenza is a virus that circulates throughout the world annually, resulting in seasonal epidemics and, occasionally, pandemics. It has caused significant morbidity and mortality in humans for centuries, and its complications are responsible for hundreds of thousands of hospitalizations and tens of thousands of deaths each year in the United States (1). Worldwide, the mortality rate for influenza-associated respiratory disease alone is predicted to be 291,000-646,000 annually; however, the true annual mortality rate would be substantially higher when considering all complications of the disease (17). Groups at particularly increased risk for influenza-related morbidity and mortality include children <5 years of age, adults >65 years of age, pregnant women, and those with chronic medical problems (6, 18-20). These groups are often targeted by public health programs to receive influenza vaccine, but annual vaccination is currently recommended for *all* individuals ≥6 months of age in whom a contraindication does not exist (8).

The first influenza vaccines in the United States were used in the military as early as the 1940s (21). After a pandemic of influenza A(H3N2) in 1957, use was expanded to include nonmilitary individuals at high risk of complications from influenza, including those with chronic disease, pregnancy, or who were >65 years of age. Over the following decades, the list of indications for influenza vaccine receipt grew, but widespread use among all people >6 months of age was only first recommended by the Advisory Committee on Immunization Practices (ACIP) in 2010 (21, 22). Since that time, influenza vaccine has been has been shown to reduce the likelihood of medically-attended influenza illness by 40-60% during seasons when the vaccine is well matched to circulating viruses, with an average effectiveness of 45% (4). Influenza vaccination has also been shown to prevent influenza-related hospitalization even when vaccine effectiveness is estimated to be lower than expected (2, 3, 23, 24).

Furthermore, there is evidence to suggest vaccine effectiveness in preventing severe outcomes even in cases of 'vaccine failure', in which a vaccinated individual is hospitalized with influenza-related illness. Studies have found influenza vaccination to be associated with lower risk of ICU

admission and death among those hospitalized with influenza-related illness in some seasons (5-7, 25, 26). A study published in 2017 by Arriola, et al. using FluSurv-NET data demonstrated lower odds of ICU admission and death as well as shorter lengths of hospital and ICU stays in some groups of vaccinated adults with influenza-related hospitalization during an influenza A(H1N1)pdm09-dominant season (5). Another study found a 59% reduction in the odds of ICU admission among hospitalized adults who received vaccination compared to those who did not across three seasons (7). Similarly, a 2014 study suggested a 74% decrease in risk of ICU admission among children who were vaccinated compared to their unvaccinated counterparts (6). As such, it is widely accepted amongst medical providers that influenza vaccine is a life-saving public health intervention that should be offered to all who are eligible to receive it.

The influenza vaccine typically becomes available in early August with widespread vaccination efforts generally occurring in September and October. However, there is substantial variability in the circulation of influenza virus each year, ranging from November to April (27). This variability creates an important consideration in determining the optimal timing of vaccine distribution and administration from year-to-year. The ACIP and CDC currently recommend that influenza vaccination should occur by the end of October if possible and should continue throughout the influenza season for unvaccinated individuals (8). Thus, individuals may receive seasonal influenza vaccine up to 8 months prior to influenza exposure. Concern has recently arisen regarding whether seasonal influenza vaccine-induced immunity might wane over the months between influenza vaccination and virus exposure.

The antibody response to the influenza vaccine has long been regarded as a surrogate marker for protection against influenza. Antibody titers to influenza surface proteins are thought to peak around 4-6 weeks post-vaccination (28, 29). One study found that it takes, on average, >600 days to achieve a 2-fold decrease in these antibody titers, suggesting a very slow rate of decline (30), but some studies suggest that this can vary substantially by age (e.g. with titers declining more rapidly in older adults) and mode of vaccination (e.g. live attenuated influenza vaccine [LAIV] titers waning less

rapidly than inactivated influenza vaccine [IIV] titers)(31). A review of the literature published in 2008 suggested that antibody protection likely persists for at least 4 months in those who are able to mount an initial response and that the age discrepancy may not be as compelling as once thought (32). The duration of protection provided by vaccine-induced antibody production has been questioned for decades and remains somewhat unclear.

Despite inconclusive evidence regarding antibody persistence, there have been recent data to suggest declining vaccine effectiveness (VE) throughout the influenza season, particularly in those >65 years of age (9-13, 33-37). A study performed by Ferdinands, et al. including patients ≥9 years old with medically-attended acute respiratory illness described a 6-11% decrease in influenza VE per 30 days during the influenza season when considering an outcome of PCR-confirmed influenza infection. These findings were consistent for influenza A(H3N2), A(H1N1)pdm09, and B, accounting for up to a 43% total decrease in influenza VE over the course of a season in those who were vaccinated early (9). Ray, et al. found that the odds of testing positive for influenza among children and adults vaccinated >154 days prior to illness was 2.06 times the odds of those who were vaccinated 14-41 days prior to illness (12). This was consistent across seven seasons with varying dominant subtypes. Notably, several studies have specifically highlighted this waning of effectiveness among patients infected with influenza A(H3N2) or during A(H3N2)-predominant seasons (10, 33-36).

However, not all data have suggested such a strong association. In a study of hospitalized adults, there was no significant difference observed for odds of influenza-related hospitalization in those less than 65 years of age related to timing of vaccination (13). The authors of this study observed waning of protection against hospitalization to be most strongly supported in adults >65 years of age in A(H3N2)-dominant seasons. In another multicenter study performed in Europe, VE against A(H3N2) was also found to substantially decline over the course the season; however, VE against influenza A(H1N1)pdm09 remained stable in all ages throughout the duration of the season (33). Additionally, Radin, et al. found that VE across four seasons was maintained up to six months post-vaccination, arguing against rapid waning of protection (37).

These data together suggest that there may be a decline in VE related to waning immunity from influenza vaccine in some populations and in some seasons. However, studies thus far have found that results vary among patients of different age groups and also vary by influenza type/subtype. Also, studies have predominantly focused on waning immunity as it relates to ability to prevent influenza-like illness with positive influenza test. These studies are performed primarily on patients seeking medical attention for influenza symptoms, many with mild disease. To our knowledge, there are no studies that evaluate whether timing of vaccine receipt is associated with risk of severe outcomes among patients who are hospitalized with laboratory-confirmed influenza. This study sought to answer the question of whether timing of seasonal influenza vaccine receipt impacts the severity of disease among patients with 'vaccine failure'.

METHODS

Aims and Hypotheses

Aim #1: To determine whether demographic differences exist between patients who receive seasonal influenza vaccine earlier in the season and those who receive vaccine later in the season among patients who are hospitalized with influenza-related illness despite vaccination

Hypothesis: Patients with chronic medical conditions and those at the extremes of age are more likely to receive vaccine earlier in the season.

Aim #2: To determine whether time between seasonal influenza vaccination and hospitalization is associated with severe outcomes (e.g. ICU admission, death, pneumonia, and prolonged hospitalization) in patients who are hospitalized with influenza-related illness despite receiving the vaccine.

Hypothesis: Patients with longer duration between seasonal influenza vaccination and hospitalization have a longer duration of hospitalization and increased odds of other severe outcomes (ICU admission, death, pneumonia) than those with shorter duration of time since vaccination.

Study Design, Setting, and Population

The Influenza Hospitalization Surveillance Network (FluSurv-NET) is a surveillance platform through the CDC Emerging Infections Program which conducts active surveillance for influenza-related hospitalizations in acute care hospitals and laboratories. Surveillance is performed in select counties in California, Colorado, Connecticut, Georgia, Maryland, Michigan, Minnesota, Ohio, Oregon, New Mexico, New York, Tennessee, and Utah with a total catchment population of over 27 million people (~9% of the US population) (38). Upon identifying hospitalized patients, trained surveillance officers ensure that cases have laboratory-confirmed influenza (by positive rapid antigen test, reverse-transcriptase polymerase chain reaction, immunofluorescence antibody staining, serology, or viral culture), reside inside a catchment area, and were hospitalized during the influenza season (October 1 – April 30 of each

year). Demographic and clinical data is then abstracted into a standardized case report form before being uploaded to a centralized database.

This study retrospectively evaluated all influenza-infected hospitalized adults (≥18 years of age) and children (>6 months through 17 years of age) identified through FluSurv-NET during the 2013-2014 through 2016-2017 influenza seasons. We excluded unvaccinated patients, patients with incomplete vaccination data, patients with hospital-acquired influenza (test sent >3 days after admission), and patients who received vaccine <14 days prior to hospitalization, as this is generally accepted as the time required to mount an adequate immune response to the vaccine (9). We also excluded patients ≥9 years of age with multiple discrepant vaccine dates that were >6 weeks apart, as it was thought that these cases were more likely to represent receipt of two distinct vaccines rather than recall bias. For the analysis of outcomes, patients with positive tests for both influenza A and influenza B and those with unknown type of influenza were excluded in order to facilitate stratifying by subtype and controlling for subtype. Age groups for analyses were determined based upon previous epidemiologic studies describing patients at high risk of complications from influenza as well as studies evaluating waning of influenza vaccine effectiveness (9, 13).

This study was determined to be consistent with routine public health surveillance and exempt from Human Subjects Regulations by the CDC Human Research Protection Office. FluSurv-NET sites obtained human subjects and ethics approvals from their respective state health department and academic partner institutional review boards.

Influenza Vaccination Date

Vaccination criteria for inclusion in this study required documented date of influenza vaccine during the specified season via state registry, provider documentation, medical record, and/or patient interview. If date of vaccination was unknown, patients were excluded. For patients <9 years of age with multiple influenza vaccine dates recorded in a single season, vaccination date was determined by the latest of the dates, as two vaccine doses are recommended in the first season of vaccination for all

children <9 years of age. For patients ≥9 years of age with multiple influenza vaccine dates recorded, vaccination date was determined by an algorithm constructed based on reliability of source information, with the order of reliability as follows: state registry, provider documentation, medical record, and patient interview. State registry dates and provider documentation were deemed highest reliability, as these require documentation by medical providers on the date of vaccine administration. The medical record influenza vaccination date may be recorded upon administration of vaccine, or it may be recorded at time of hospital admission based on patient recall. Patient interview dates are determined solely by patient recall during interviews conducted several months following hospitalization. For dates provided by patient recall (i.e. medical record and patient interview dates), the date was recorded as the first day of the specified month if patient was able to recall only the month but not the date of vaccination. Sensitivity analyses were performed to assess the possibility of misclassification of vaccination date by the above algorithm, as described below.

Measurements – Predictor, Outcomes, and Covariates

For descriptive analyses of demographic characteristics, the primary measure was calendar date of seasonal influenza vaccine receipt. Subjects were categorized into "early vaccination" and "late vaccination" groups based on median vaccination date of the cohort for the four included seasons and typical earliest onset of influenza season. For adults, the "early vaccination" group was defined as those vaccinated prior to October 15th, and subjects in the "late vaccination" group were vaccinated on or after October 15th. For children, the "early vaccination" group was defined as those vaccinated prior to November 1st, and subjects in the "late vaccination" group were vaccinated on or after November 1st. The goal of this analysis was to determine whether differences exist among those who receive vaccine early enough to achieve an adequate immune response by the earliest likely onset of influenza season and those who receive vaccination once influenza season may have begun.

For analyses to determine relationship between vaccine timing and severe outcomes, the primary measure was duration of time between seasonal influenza vaccination and influenza-related

hospitalization. Exposure groups were created based on number of days between vaccination and hospitalization, as follows: for adults, 14-59 days, 60-89 days, 90-119 days, 120-149 days, and ≥150 days; for children, 14-89 days, 90-119 days, and ≥120 days. This approach allowed for standardization of time since vaccination among seasons regardless of peak timing of influenza circulation, which varies by season. The outcomes of interest were duration of hospitalization (in days), ICU admission at any time during hospitalization, all-cause death during hospitalization (for adults only), and pneumonia (for children only). Except for duration of hospitalization, all outcomes were described as dichotomous, categorical variables. Patients with unknown or missing outcome data for ICU admission and/or death were grouped with those who did not have the outcome of interest, in a category labeled "No/Unknown"; therefore, any misclassification of outcome would bias results toward the null hypothesis.

Additional variables were assessed for potential confounding, including age, sex, race/ethnicity, presence of preexisting/comorbid medical conditions (listed in Tables 1 and 5), state of residence, influenza type/subtype, receipt of antiviral treatment prior to hospitalization, and timing of hospitalization within the influenza season.

Influenza subtype categories included Influenza A(H1N1)pdm09, A(H3N2), and B. If type was unknown (e.g. Influenza A or B), patients were excluded. For those with influenza A for whom subtype information was not available, subtype was assigned based on predominant circulating strain during the relevant season. As such, patients with unknown influenza A subtype in 2013-2014 or 2015-2016 were assigned A(H1N1)pdm09, and patients with unknown influenza A subtype in 2014-2015 or 2016-2017 were assigned A(H3N2). Misclassification rate was estimated to be <5% for A(H1N1)pdm09-predominant seasons and <1% for A(H3N2)-predominant seasons based on distribution of subtypes in patients with known subtypes.

All analyses controlled for timing of hospitalization within the influenza season in attempt to account for variability in exposure to influenza within a season. This was done by dividing date of hospitalization into tertiles for each season for both adults and children and assigning patients to one of three groups based on peak of influenza-related hospitalizations: "pre-peak", where hospitalization date

was <=33rd percentile; “peak”, where hospitalization date >33rd and <67th percentile, and “post-peak”, where hospitalization date was ≥67th percentile.

Sample Size/Power Considerations

ICU Admission was used as a representative outcome to determine statistical power for this study. The stated hypothesis was that a higher percentage of patients are admitted to the ICU among those with longer duration since vaccination compared to those vaccinated a short time prior to hospitalization. For these sample size analyses, we use “early vaccine” and “late vaccine” based on calendar date as proxy for time since vaccination. Upon review of preliminary data from a single site within FluSurv-NET (Georgia Emerging Infections Program) for a single influenza season, 16.2% of hospitalized patients with influenza were admitted to the ICU. Similarly, Catania, et al. (2014) reported an ICU admission rate of 15.4% among influenza-related hospitalizations for patients who received seasonal influenza vaccine (39). These data were used to determine a starting benchmark for sample size calculations before our sample size was known. As such, we determined that we would have 90% statistical power to detect a 2.5% difference in proportion of patients with ICU admission between those vaccinated early and those vaccinated late given a total sample size of 9,308 (4,654 per study group if groups were equal), assuming 15% of our early vaccine patients to have ICU admission as a baseline (see table below). This was thought to be well below the numbers we anticipated for the analysis of adults. It was anticipated that we would have ~2,500 children, in which case we would have 90% power to detect a difference in proportion of ICU admissions of 5.0%. The values used for the effect size (absolute difference of 2.5% and 5.0%) were chosen to represent low yet clinically significant differences. These numbers were thought to provide adequate power to detect meaningful statistical associations.

Statistical power was calculated at 90% with a 0.05 significance level. All power calculations were performed using www.sample-size.net. Calculated variables are shaded in the table below.

α	β	Proportion with ICU Admission, Early Vaccination (P_0)	Proportion with ICU Admission, Late Vaccination (P_1)	Absolute Difference (P_1-P_0)	Total N Needed
0.05	0.1	15%	17.5%	2.5%	9,308
0.05	0.1	15%	20.0%	5.0%	2,504

Ultimately, our total sample size included 21,306 adults and 1,728 children across the four seasons. The "early vaccination" and "late vaccination" groups were not equal in size. The baseline percentage of patients admitted to the ICU (i.e. those in the "early vaccination" groups) was approximately 14% among adults and 22% among children. These numbers provided 80% power to detect a 1.4% difference in percentage of patients admitted to the ICU among adults and a 6% difference in children (see table).

Statistical power was calculated at 80% with a 0.05 significance level. All power calculations were performed using www.sample-size.net. Calculated variables are shaded in the table below.

α	β	Proportion with ICU Admission, Early Vaccination (P_0)	Proportion with ICU Admission, Late Vaccination (P_1)	Absolute Difference (P_1-P_0)	N (P_0)	N (P_1)	Total N in study
0.05	0.2	14%	15.4%	1.4%	13,157	8,149	21,306
0.05	0.2	22%	28.0%	6.0%	984	744	1,728

Because death was a substantially less common outcome, sample size calculations were also performed for this outcome in adults. With our sample size, we achieved 80% power to detect a 0.7% difference in percentage of patients with an outcome of death. The baseline outcome among those vaccinated early was 2.8%.

Analytic Plan

For all analyses, adults (≥18 years of age) and children (6 months through 17 years of age) were analyzed separately. Demographic differences between early and late vaccination groups were described as frequencies and compared using Chi-square tests of difference in proportion or Fisher's exact tests if

expected counts of the contingency table were low (≥25% cells with counts <5), as determined by analytic software. All variables in the descriptive analysis were categorical.

The relationships between time since vaccination and dichotomous severe disease outcomes (ICU admission, death, pneumonia) were described using multivariate logistic regression. First, each variable was evaluated independently using univariate logistic regression to determine unadjusted odds ratios (OR). A model was then fit containing all variables deemed significant by univariate analyses as well as those thought to be clinically significant regardless of statistical significance. Next, statistically insignificant variables (i.e. those without significant p-values in Wald Chi-Square) were sequentially removed from the model, and the difference in -2LogL was assessed as well as OR estimates for exposure of interest (time since vaccination). Variables that did not contribute significantly to the model and were not deemed clinically necessary to the model were removed. Effect modification was then assessed by including interaction terms between the exposure of interest and covariates. After the final model was obtained, stratification by both age group and influenza type/subtype was employed. This process was repeated separately for adults and children and for each outcome. Therefore, 4 unique models were created as follows: adults, ICU admission; adults, death; children, ICU admission; children, pneumonia. Reported point estimates for the outcomes were presented as adjusted OR with 95% confidence intervals. The 14-59 day groups were used as the reference groups, as it was hypothesized that these groups would have the most robust immune response (i.e. lower percentage of patients with severe outcomes) and that severe outcomes would increase with time since vaccination. Final models for the multivariate logistic regression models including covariates can be found in the Appendix.

Cox proportional hazard modeling was used to assess the relationship between time since vaccination and duration of hospitalization. The h(t) was considered to be the hazard of discharge at time (t). First, each variable was evaluated independently with ANOVA, comparing the means of number of days of hospitalization within variable groups. A model was then fit containing all variables deemed significant by ANOVA as well as those thought to be clinically significant regardless of statistical significance. Next, log-log likelihood curves were used to ensure that the proportional hazards assumption

was met for all included covariates as well as the exposure of interest. Statistically insignificant variables (i.e. those without significant Log Rank tests) were sequentially removed from the model, and the difference in -2LogL was assessed as well as hazard ratio (HR) estimates for exposure of interest (time since vaccination). Variables that did not contribute significantly to the model and were not deemed clinically necessary to the model were removed. After the final model was obtained, stratification by both age group and influenza type/subtype was employed. Adjusted hazard ratios (aHR) with 95% confidence intervals were reported, where a hazard ratio of <1 represented an increased duration of hospitalization (i.e. lower instantaneous "hazard" of discharge). Final models for the Cox proportional hazard modeling including covariates can be found in the Appendix.

Planned sensitivity analyses to assess the statistical effect of exposure misclassification included the following: (1) exclusion of those with vaccination status based on self-report (i.e. those with interview date and medical chart date); (2) exclusion of those with date of vaccination on the first of the month, as these numbers were disproportionately higher than other dates for all vaccination date categories; (3) exclusion of those with multiple vaccination dates; (4) Re-ordering vaccination date hierarchy for those with multiple vaccination dates such that provider documentation is given priority over state registry; (5) For children only, exclusion of those receiving live attenuated influenza vaccine (LAIV), due to concerns regarding effectiveness in certain seasons (of note, information regarding receipt of LAIV was only available for children <9 years of age).

All statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, North Carolina). Statistical significance was assessed at the 0.05 level.

RESULTS

Description of Cohorts and Seasons

Across these four seasons, a total of 21,306 vaccinated adults and 1,728 vaccinated children were identified after exclusion criteria were applied (Figure 1). The majority of adults were ≥65 years of age (69%), and 44% of children were between 2 and 8 years of age (Tables 1 and 5). The adult population was predominantly of white, non-Hispanic race/ethnicity (66%) while a much smaller percentage of the pediatric cohort was white, non-Hispanic (37%). Among adults, 96% had at least one chronic/comorbid condition, with cardiovascular disease (CVD), chronic metabolic disorder (CMD), and chronic lung disease (CLD) affecting the largest number of patients. Fewer children had comorbid conditions (73%), with asthma and neurologic/neuromuscular disorder most prevalent.

The most common influenza type among these hospitalized patients was influenza A. There were two Influenza A(H1N1)pdm09-dominant seasons included in this analysis (2013-2014 and 2015-2016), and two influenza A(H3N2)/B-dominant seasons (2014-2015 and 2016-2017). More adults were hospitalized in the A(H3N2)/B dominant seasons, accounting for 74% of the adult cohort, compared with 59% of the pediatric cohort. The 2013-2014 and 2014-2015 seasons experienced an early influenza circulation, with peak surveillance weeks occurring in January and December compared to February and March for the other seasons.

Timing of Vaccine Receipt Among Adults

Overall, 62% of adult patients received seasonal influenza vaccine prior to October 15th across these four seasons. Proportion of those vaccinated early increased with increasing age, as only 54% were vaccinated early among those 18-49 years of age, but 66% were vaccinated early in those ≥85 years ($p < 0.0001$) (Table 1). White, non-Hispanic patients were more likely to receive vaccine early compared to black non-Hispanic and Hispanic patients ($p<0.0001$). Among the 96% of patients found to have at least one chronic medical condition, more patients with CVD, CMD, and kidney disease were vaccinated early compared to those without the conditions, whereas lower proportions of patients with liver disease and

pregnancy were vaccinated early. Vaccine timing also varied by state of residence and season, with more Minnesotans receiving vaccine early than residents of other included states in nearly all seasons, and more patients receiving vaccine early in 2014-2015 than other seasons ($p<0.0001$).

Timing of Vaccine Receipt Among Children

Fifty-seven percent of hospitalized children received vaccine prior to November 1st (Table 5). A significantly lower proportion of those <2 years of age received vaccine early compared to older children ($p<0.0001$). Discrepancies among race/ethnicity were seen, with a higher proportion of white, non-Hispanic children receiving vaccine early compared to the other groups ($p=0.0194$). All chronic medical conditions assessed were associated with early receipt of vaccine compared to patients without the condition. Those that reached statistical significance included CMD, CLD, asthma, neurologic/neuromuscular disease, immunocompromised state, and upper airway abnormality. State of residence and sex were not associated with timing of vaccination. More children were vaccinated early in 2014-2015 compared to other seasons ($p<0.0001$).

Association Between Timing of Vaccination and Severe Outcomes Among Adults

For the analyses of severe outcomes, 138 additional patients were excluded, including 100 with both influenza A and influenza B and 38 in whom the type of influenza was unknown (Total N=21,168). Among these hospitalized adults, 14.4% were admitted to the ICU, 2.85% died, and the mean duration of hospitalization was 4.87 days (Table 2). The highest proportion of ICU admissions occurred among those 50-64 year-olds (19%), and the highest proportion of deaths occurred in patients ≥85 years of age (4.40%). Duration of hospitalization was similar for all age groups. A lower percentage of patients infected with influenza A(H3N2) were admitted to the ICU (13.3%), although the majority of patients admitted to the ICU were infected with influenza A(H3N2).

The highest percentage of patients admitted to the ICU was observed among patients in the shortest time-since-vaccination group (i.e. 14-59 days, 16.0%). Patients who received vaccine ≥150 days

prior to hospitalization were not observed to have increased odds of admission to the ICU when controlling for identified covariates (aOR 0.850, 95% CI 0.717, 1.008; Table 3). Stratification by age group revealed similar results. Patients who were 75-84 years of age and were vaccinated ≥150 days prior to hospitalization had lower odds of ICU admission (aOR 0.618, 95% CI 0.426, 0.896). The highest proportion of deaths also occurred among patients who received vaccine 14-59 days prior to hospitalization (3.31%). In multivariate analysis, odds of death decreased as time since vaccination increased, as those receiving vaccine ≥150 days prior to hospitalization had 0.528 times the odds of death compared to those who received vaccine late (95% CI 0.369, 0.756, Table 3). No age group demonstrated increased odds of death as time since vaccination increased.

The mean duration of hospitalization for all exposure groups was between 4.83 and 4.97 days. Patients who were hospitalized ≥150 days after receiving vaccination were not observed to have longer hospitalizations (aHR 1.051, 95% CI 0.989, 1.118, Table 3). Of note, an additional 26 patients were excluded from the Cox proportional hazard models due to unknown date of discharge (Total N=21,142).

When stratifying analyses by influenza type/subtype, there were no significant differences in ICU admission related to timing of vaccine receipt for any type/subtype (Table 4). Infection with Influenza A(H3N2) was associated with decreasing odds of death as time since vaccination increased, as patients who received vaccine ≥150 days had 0.504 times the odds of death compared with those who received vaccine recent to their hospitalization (95% CI 0.312, 0.816). The association between time since vaccination and duration of hospitalization did not vary by influenza type/subtype.

Association Between Timing of Vaccination and Severe Outcomes Among Children

For the analyses of severe outcomes, 26 additional patients were excluded, including 6 with both influenza A and influenza B and 20 in whom the type of influenza was unknown (total N = 1702). The proportion of children admitted to the ICU was 22.2%. Pneumonia was diagnosed in 20% of children, and the mean duration of hospitalization was 3.75 days (SD 6.79; Table 6). Children 9-17 years of age had the highest percentage of ICU admission, longest duration of hospitalization, and lowest percentage of

pneumonia compared to the other age groups. Children infected with influenza A(H1N1)pdm09 had higher proportion of pneumonia (27.5%) compared to those infected with other subtypes.

The highest proportion of ICU admissions occurred in children who received vaccine 14-59 days prior to hospitalization (25.4%), and the odds of ICU admission was not significantly different in the group vaccinated ≥120 days prior to hospitalization (aOR 0.802, 95% CI 0.556, 1.159; Table 7). This was consistent across age groups. The highest proportion of pneumonia diagnoses were also observed among children in the shortest time-since-vaccination group (22.0%). There was no association between timing of vaccine receipt and odds of pneumonia overall or for any single age group.

The mean duration of hospitalization was between 3.40 days (SD 4.16) and 4.33 days (SD 10.13; Table 7). There was no association between hazard of discharge and timing of vaccine receipt overall or for any age group.

Children who were infected with influenza B and received vaccine ≥120 days prior to hospitalization had significantly lower odds of being admitted to the ICU (Table 8). Those with A(H1N1)pdm09 had lower odds of pneumonia with longer time since vaccination, and they also had a higher hazard of discharge, signifying a shorter hospitalization. However, children with influenza A(H3N2) had increased odds of pneumonia as time since vaccination increased (aOR 2.016, 95% CI 1.024, 3.967).

Sensitivity Analyses

Sensitivity analyses were performed to assess the potential effect of exposure misclassification given the variation in reliability of vaccine information. As such, the above analyses were performed excluding all patients who received vaccine on the first day of the month; excluding those with vaccination date based on self-report (i.e. those with interview date and medical chart date); excluding those with multiple different vaccine dates; and re-arranging the algorithm of vaccine source such that provider documentation was given priority over state registry. Also, for children only, an additional analysis was performed excluding those who received LAIV.

For all sensitivity analyses, similar results were obtained (Tables 9, 10). None of the above described analyses revealed conflicting information that would substantially alter the results.

DISCUSSION

In this large, retrospective cohort study of children and adults who were hospitalized with influenza-related illness despite receiving seasonal influenza vaccine, there were demographic differences associated with variation in timing of vaccine receipt, but timing of vaccination was not found to be associated with increased odds of experiencing a severe outcome in most groups. Furthermore, evidence of waning of seasonal influenza vaccine-related immunity resulting in severe influenza-related illness was not demonstrated. Instead, receiving vaccine earlier in the season appeared to be protective against ICU admission and death among some groups of vaccinated individuals.

Older age, white race, and certain medical conditions were associated with early receipt of influenza vaccination among adults and children. A geographic disparity in vaccine timing was also observed in this cohort. Previous vaccine coverage estimates have shown that adults >65 years of age, children <5 years of age, and those with chronic medical conditions are more likely to receive influenza vaccine compared to those who are younger and healthier (5, 40), so it is unsurprising that these groups also receive influenza vaccine earlier in the season, as our analysis suggests. It is most likely that this is due to frequent healthcare encounters and targeted public health strategies in high-risk groups. The association with race, where white, non-Hispanic patients received vaccine earlier, may be related to issues with access to preventive medical care, although that was not assessed in this analysis. Very young children (<2 years of age) were less likely to be completely vaccinated early in this season, which is likely heavily influenced by the recommendation for children to receive two vaccines during the first season of vaccination, as well as the likelihood that one may become eligible for vaccine late in the influenza season. Finally, pregnant women were also less likely to receive vaccine early in the season, which is also unsurprising given that a pregnant woman may first seek care at any time during the influenza season.

Prevalence of ICU admission varied inversely with age, where children were more likely to be admitted to the ICU and adults ≥85 years of age were at lowest risk (Supplemental Tables 1 and 2). Death, however, was found to increase with age among adults, as those ≥85 years of age were at highest risk. These findings have been described in previous studies and may represent an admitting bias, where

providers are more likely to admit older adults with mild illness (20). Alternatively, this finding may be influenced by reluctance to escalate end-of-life care in older adults. In our analysis, nearly all patients had a comorbid condition, which is likely an effect of solely including hospitalized patients, as chronically ill individuals are at higher risk for more severe disease. Several comorbid conditions including CVD, CLD, kidney disease, and neurologic disorder were associated with both ICU admission and death in adults, which is consistent with previous reports (18). Similarly, asthma, neurologic disorder, and history of upper airway abnormality were associated with increased odds of ICU admission and pneumonia in children. Interestingly, immunocompromised adults had increased odds of poor outcomes, but immunocompromised children had lower odds of ICU admission and pneumonia compared to immunocompetent children. These findings are similar to those recently reported by Collins, et al., and may represent an admitting bias among providers of immunocompromised children (41, 42).

We hypothesized that we would see more patients with severe outcomes as time since vaccination increased given recent data supporting waning of immunity provided by the influenza vaccine. However, this hypothesis was not supported by our data. Several studies have suggested increased risk of infection with influenza as time since vaccination increases when considering outpatient visits for influenza-like illness (9-13, 33-37). Our findings suggest that, although individuals who are vaccinated early may be at higher risk of becoming infected with influenza, they are not likely to be at increased risk of complications related to influenza. In fact, many groups in this analysis had lower proportions of patients with severe outcomes among those with longer time since vaccination, implying that receiving vaccine early may actually be protective against severe outcomes. This relationship was most substantial amongst adults when considering odds of death. As time since vaccination increased, odds of death significantly decreased, especially among those infected with influenza A(H3N2). This suggests that receiving vaccine early in the season is protective against death from influenza among those hospitalized with influenza. Similar results were observed among children infected with influenza B who received intensive care and children infected with influenza A(H1N1)pdm09 who were diagnosed with pneumonia. Also, children infected with A(H1N1)pdm09 were found to have shorter hospitalization as time since vaccination

increased. Duration of hospitalization did not otherwise seem to be associated with time since vaccination.

The only instance of increased odds of a severe outcome with increasing time since vaccination was among children with influenza A(H3N2) who were diagnosed with pneumonia. While influenza A(H3N2) is known to cause severe illness, reasons for the isolated association with time since vaccination remain unclear.

Several theories were examined to explain these findings which are, overall, contradictory to a growing consensus supporting waning of influenza vaccine-related protection. First, we excluded those with 14 to 28 days between vaccination and hospitalization, with the concern that perhaps 14 days is insufficient to build an adequate antibody response to the vaccine in some populations. Odds of severe disease were largely unchanged for either ICU admission or death in adults (Supplemental Table 3). We also explored the data to determine whether those who received vaccine late in the season may also present to the hospital later in the course of illness, which may influence outcomes. This was done using date of symptom onset in those for whom this data was available. Patients in the shortest time since vaccination group (i.e. 14-59 days since vaccination) were found to have had symptoms for a similar number of days as the other groups at time of hospitalization. The mean number of days between symptom onset and hospital admission was 2.23 for the latest group, compared with 2.15-2.32 for other groups.

These data support current vaccination recommendations to receive vaccine by the end of October each season. Our findings suggest that receiving vaccine later in the season may actually increase the odds of death among those who become hospitalized with influenza. Several modeling studies have examined the implications of delaying influenza vaccination and have failed to produce convincing evidence that this would be beneficial (14-16, 43). Although more cases may be prevented in some groups by delaying vaccination, it is difficult to determine how the trade-off of missing vaccine opportunities may impact overall number of cases. Because of the substantial variability in influenza season timing, vaccine effectiveness by season and type/subtype, and proposed rates of waning of immunity amongst

individuals, it would be incredibly challenging to make a recommendation to delay vaccination without strong, conclusive evidence that patient outcomes would be improved. The data from this analysis do not support a delay in influenza vaccine for the prevention of severe outcomes.

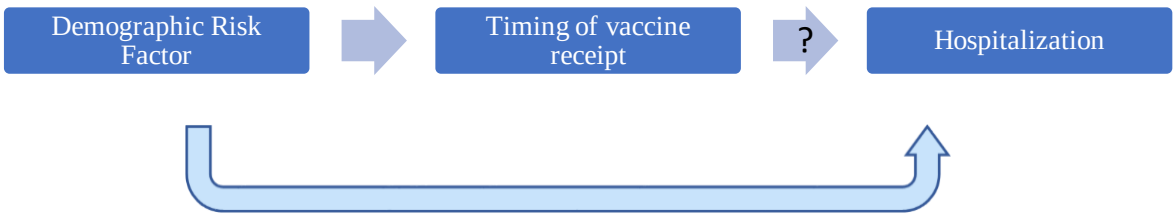
This analysis is, to our knowledge, the first to examine how waning of immunity provided by the influenza vaccine might affect patient outcomes beyond influenza-like illness. This is also one of the first analyses to assess the concept of waning immunity from the vaccine in children <9 years of age. Other major strengths of this study are the large sample size achieved by using the FluSurv-NET surveillance network as well as the quality of data provided which allowed for inclusion of many possible confounding variables. The patients included in this surveillance network are diverse in age, race/ethnicity, and geographic location, making the results applicable to many populations. Finally, the influenza seasons included were diverse in dominant type/subtypes as well as timing of peak circulation, allowing for generalizability among seasons.

Despite the above strengths, there are several limitations to this study. This analysis only included hospitalized individuals who were more likely to have severe outcomes such as ICU admission and death compared to those with less severe illness who did not require hospitalization. As such, the results of this study are not generalizable to those who are not hospitalized with influenza-related illness. Also, clinical practice may vary by a number of factors – geographic location, institution, provider, or patient characteristics. This variation in clinical practice may result in different thresholds for hospital admission, ICU admission, influenza testing, and antiviral prescribing. Discrepancies in the true date of vaccination as described in the methods may have introduced misclassification of the exposure; however, we attempted to address this by using categorical exposure variables rather than a continuous variable for time-since-vaccination, as it was thought that misclassification would be less likely among groups. Also, we performed multiple sensitivity analyses to examine this possibility, none which changed the results. We know that timing of vaccine receipt is influenced by several factors for children, including age and prior vaccinations. As we did not have access to previous years' vaccination records, it was impossible to know whether one or two vaccines were indicated for children <9 years of age, so some patients may

have been incorrectly grouped. Finally, it is impossible to eliminate unmeasured/unknown confounders when using a retrospective design with observational data.

It is possible that the relationship between demographic risk factors and timing of vaccine receipt may represent conditioning on a collider, as all patients in this analysis were hospitalized. The directed acyclic graph below represents a possible explanation for the relationship between demographic characteristics assessed in Tables 1 and 5 and timing of vaccine receipt, with hospitalization as a collider. In this case, it would be impossible to determine whether specific demographic characteristics are truly associated with the timing of vaccine receipt, as hospitalization may be causally influenced by both.

Another possible relationship between demographic characteristics, timing of vaccine receipt, and hospitalization with influenza-related illness is depicted below in the causal diagram. In this diagram, demographic risk factors are directly, independently associated with hospitalization, which is known from prior studies (18-20). As described in Tables 1 and 5 and by previous studies, these risk factors also influence timing of vaccine receipt (5). It is unknown whether timing of vaccine receipt is independently associated with hospitalization when controlling for such risk factors. This is a gap that currently remains in the literature and is unanswerable with the FluSurv-NET database. However, the results of this analysis suggest that timing of vaccine receipt is not related to severe outcomes among hospitalized individuals when controlling for demographic risk factors.



Henceforth, the next step in determining who is at highest risk from waning of influenza-related immunity and whether public health intervention is required may be to determine whether the waning

observed in studies assessing influenza-like illness is also seen when assessing risk of influenza-related hospitalization. Because hospitalization is, in itself, a poor outcome irrespective of ICU admission, death, and pneumonia, it is important to understand how waning may be affecting risk of hospitalization among vaccinated individuals throughout a season. If earlier vaccine receipt is associated with increased risk of hospitalization from influenza, this may warrant additional consideration of current vaccine recommendations.

In conclusion, the differences described in timing of seasonal influenza vaccination amongst patients in our study cohort did not impact the severity of influenza-related illness. This is encouraging, given that current guidelines recommend that all eligible individuals receive vaccine by the end of October annually. Given this information, we would not recommend a change in current vaccination strategies but instead would continue to urge providers to administer influenza vaccine to those at highest risk of severe outcomes as early as possible and certainly by the end of October each season.

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TABLES/FIGURES

FIGURE 1: Flowchart of included/excluded cases of patients hospitalized with influenza in the United States identified through FluSurv-NET, 2013-2017

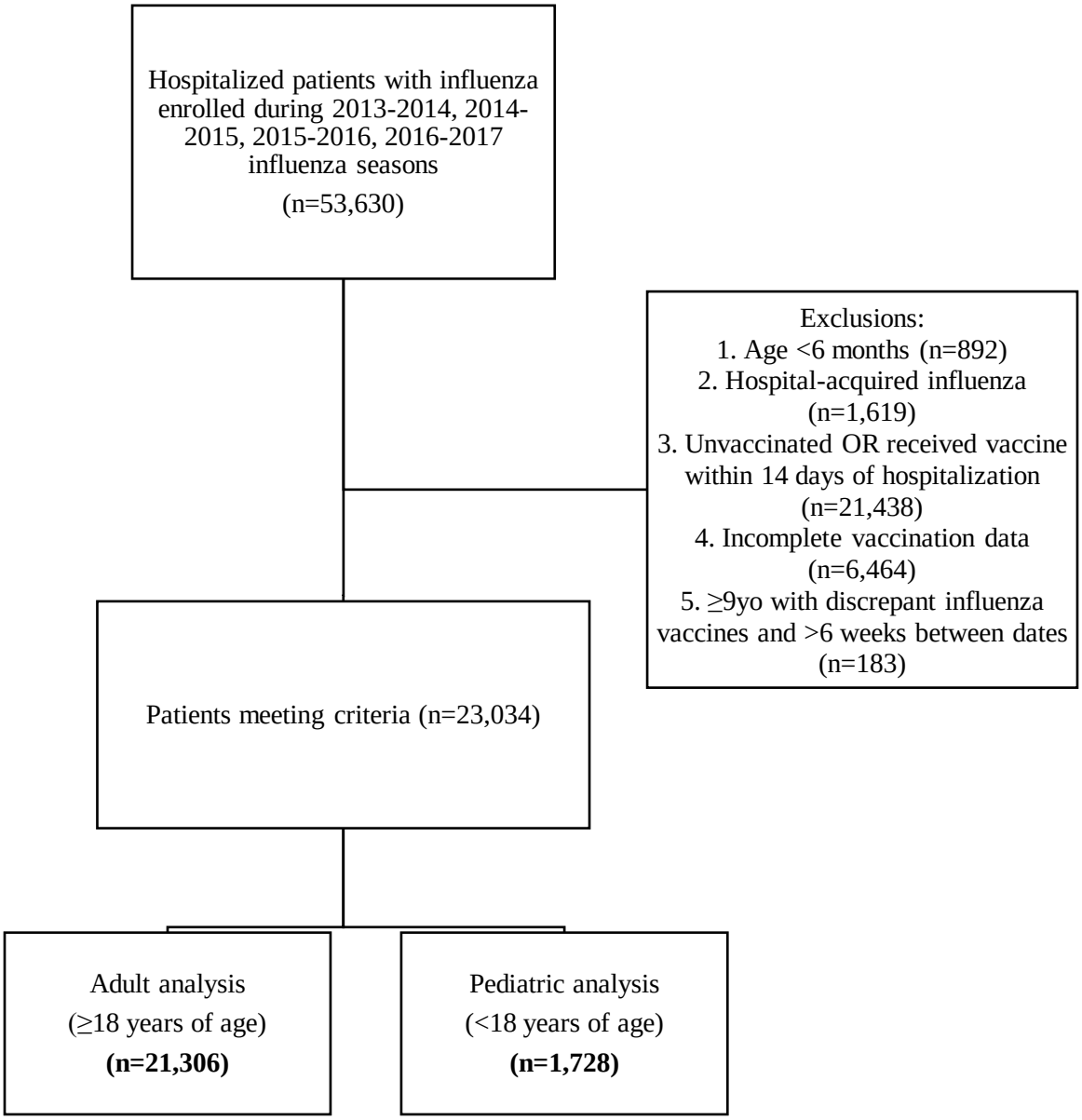

TABLE 1: Characteristics of adults hospitalized with influenza-related illness during the 2013-2014 through 2016-2017 influenza seasons, by timing of vaccine administration

Demographic and Clinical Characteristics*	Total†	Early vaccine†§	Late vaccine†§	p-value
Total	21306	13157 (62)	8149 (38)	
Age groups n (%)				**<0.0001**
18 – 49 years	2295 (11)	1234 (54)	1061 (46)	
50 – 64 years	4183 (20)	2489 (60)	1694 (40)	
65 – 74 years	4353 (20)	2635 (61)	1718 (39)	
75 - 84 years	5217 (24)	3351 (64)	1866 (36)	
≥ 85 years	5258 (25)	3448 (66)	1810 (34)	
Sex, n (%)				0.4072
Male	9426 (44)	5850 (62)	3576 (38)	
Female	11880 (56)	7307 (62)	4573 (38)	
Race/Ethnicity, n (%)				**<0.0001**
White, Non-Hispanic	13988 (66)	8841 (63)	5147 (37)	
Black, Non-Hispanic	2865 (13)	1597 (56)	1268 (44)	
Hispanic or Latino	1232 (6)	672 (55)	560 (45)	
Unknown/Other	3221 (15)	2047 (64)	1174 (36)	
Pre-existing medical conditions, n (%)				
Any chronic condition	20462 (96)	12650 (62)	7812 (38)	0.305
No/Unknown	844 (4)	507 (60)	337 (40)	
Cardiovascular Disease	11856 (56)	7490 (63)	4366 (37)	**<0.0001**
No/Unknown	9450 (44)	5667 (60)	3783 (40)	
Chronic Metabolic Disorder	10265 (48)	6470 (63)	3795 (37)	**0.0002**
No/Unknown	11041 (52)	6687 (61)	4354 (39)	
Chronic Lung Disease¶	5469 (26)	3437 (63)	2032 (37)	0.0538
No/Unknown	15837 (74)	9720 (61)	6117 (39)	
Asthma	4178 (20)	2557 (61)	1621 (39)	0.4137
No/Unknown	17128 (80)	10600 (62)	6528 (38)	
Neurologic/Neuromuscular Disease	6122 (29)	3786 (62)	2336 (38)	0.8638
No/Unknown	15184 (71)	9371 (62)	5813 (38)	
Kidney Disease	5316 (25)	3460 (65)	1856 (35)	**<0.0001**
No/Unknown	15990 (75)	9697 (61)	6293 (39)	
Immunocompromised**	4247 (20)	2608 (61)	1639 (39)	0.6057
No/Unknown	17059 (80)	10549 (62)	6510 (38)	
Cancer	1160 (5)	753 (65)	407 (35)	**0.0227**
No/Unknown	20146 (95)	12404 (62)	7742 (38)	
HIV	432 (2)	221 (51)	211 (49)	**<0.0001**
No/Unknown	20874 (98)	12936 (62)	7938 (38)	
Liver Disease	872 (4)	500 (57)	372 (43)	**0.0062**
No/Unknown	20434 (96)	12657 (62)	7777 (38)	
Pregnancy††	346 (3)	174 (50)	172 (50)	**<0.0001**
No/Unknown	11534 (97)	7133 (62)	4401 (38)	
State, n (%)				**<0.0001**
California	2250 (11)	1340 (60)	910 (40)	
Colorado	2166 (10)	1355 (63)	811 (37)	
Connecticut	1665 (8)	872 (52)	793 (48)	
Georgia	1260 (6)	779 (62)	481 (38)	
Maryland	2316 (11)	1416 (61)	900 (39)	
Michigan	352 (2)	194 (55)	158 (45)	

Minnesota	2924 (14)	1977 (68)	947 (32)	
New Mexico	648 (3)	410 (63)	238 (37)	
New York - Albany	1265 (6)	818 (65)	447 (35)	
New York - Rochester	1777 (8)	1139 (64)	638 (36)	
Ohio	1395 (7)	879 (63)	516 (37)	
Oregon	1556 (7)	926 (60)	630 (40)	
Tennessee	932 (4)	558 (60)	374 (40)	
Utah	800 (4)	494 (62)	306 (38)	
Influenza type, n (%)				**0.0002**
A	17692 (83)	11033 (62)	6659 (38)	
B	3476 (16)	2035 (59)	1441 (41)	
A&B	100 (0)	62 (62)	38 (38)	
Unknown	38 (0)	27 (71)	11 (29)	
Influenza Season, n (%)				**<0.0001**
2013-2014	2656 (12)	1645 (62)	1011 (38)	
2014-2015	7925 (37)	5149 (65)	2776 (35)	
2015-2016	2914 (14)	1708 (59)	1206 (41)	
2016-2017	7811 (37)	4655 (60)	3156 (40)	

*All variables were categorical and were compared using Chi-square test of difference in proportion. Significance level: 0.05

† Percentages for the "Total" column represent column percent. For the comparison of early and late vaccine, percentages represent row percent.

§ Early vaccine defined as those receiving vaccine prior to October 15th of each season. Late vaccine defined as those receiving vaccine on or after October 15th

¶ Chronic Lung Disease category does not include asthma

** Immunocompromised includes cancer, HIV, immunoglobulin deficiency, organ/stem cell transplant, immunosuppressive therapy, steroid therapy, and CVID

††Pregnancy analysis includes females only

TABLE 2: Prevalence of ICU admission and death and mean duration of hospitalization among adults with influenza-related hospitalization, by age group and influenza type/subtype

		Total N (%)	Outcome		
			ICU Admission, n (%)	Death, n (%)	Duration of hospitalization (days), Mean (SD)
Total		21,168	3056 (14.4)	603 (2.85)	4.87 (5.40)
Age Group	18-49 yo	2277 (11)	355 (15.6)	23 (1.01)	4.73 (6.30)
	50-64 yo	4151 (20)	790 (19.0)	85 (2.05)	4.85 (5.88)
	65-74 yo	4326 (20)	700 (16.2)	108 (2.50)	4.85 (5.44)
	75-84 yo	5186 (24)	680 (13.1)	157 (3.03)	4.83 (5.32)
	≥85 yo	5228 (25)	531 (10.2)	230 (4.40)	5.02 (4.55)
Influenza Type/ Subtype	A	4009 (19)	752 (18.8)	100 (2.49)	5.12 (5.91)
	A (H3N2)	13683 (65)	1819 (13.3)	407 (2.97)	4.80 (5.21)
	B	3476 (16)	485 (14.0)	96 (2.76)	4.90 (5.51)

TABLE 3: Relationship between time since vaccination and severe outcomes in adults hospitalized with influenza-related illness, overall and by age group

Outcome	Time Between Vaccination and Hospitalization (Days)	Prevalence of outcome, n (%)	aOR of ICU Admission and Death (95% CI)					
			Overall	**18-49 yo**	**50-64 yo**	**65-74 yo**	**75-84 yo**	**>=85 yo**
ICU Admission*	14-59	**405/2534 (16.0)**	Ref	Ref	Ref	Ref	Ref	Ref
	60-89	617/4498 (13.7)	0.886 (0.771, 1.018)	0.721 (0.482, 1.078)	0.948 (0.707, 1.272)	0.962 (0.716, 1.294)	**0.738 (0.552, 0.987)**	0.985 (0.712, 1.363)
	90-119	744/5294 (14.1)	0.882 (0.768, 1.012)	0.900 (0.617, 1.313)	1.099 (0.826, 1.462)	1.011 (0.754, 1.355)	**0.657 (0.490, 0.881)**	0.779 (0.556, 1.091)
	120-149	597/4129 (14.5)	0.873 (0.748, 1.019)	0.782 (0.504, 1.212)	1.136 (0.832, 1.550)	0.838 (0.600, 1.169)	0.775 (0.560, 1.071)	0.749 (0.509, 1.103)
	≥150	693/4713 (14.7)	0.850 (0.717, 1.008)	0.949 (0.601, 1.497)	0.968 (0.687, 1.365)	0.914 (0.638, 1.309)	**0.618 (0.426, 0.896)**	0.820 (0.529, 1.270)
Death†	14-59	**84/2534 (3.31)**	Ref	Ref	Ref	Ref	Ref	Ref
	60-89	144/4498 (3.20)	0.868 (0.658, 1.145)	**0.105 (0.013, 0.863)**	0.756 (0.355, 1.610)	1.437 (0.711, 2.904)	0.740 (0.444, 1.232)	1.033 (0.631, 1.689)
	90-119	136/5294 (2.57)	**0.637 (0.478, 0.849)**	0.389 (0.116, 1.311)	1.212 (0.599, 2.453)	1.118, 0.551, 2.266)	**0.357 (0.202, 0.631)**	0.640 (0.380, 1.077)
	120-149	115/4129 (2.79)	**0.638 (0.464, 0.879)**	0.503 (0.125, 2.023)	0.610 (0.258, 1.443)	0.637 (0.281, 1.443)	**0.422 (0.230, 0.777)**	0.942 (0.537, 1.652)
	≥150	124/4713 (2.63)	**0.528 (0.369, 0.756)**	0.648 (0.146, 2.883)	0.544 (0.214, 1.382)	0.535 (0.229, 1.251)	**0.349 (0.176, 0.693)**	0.767 (0.401, 1.466)
Duration of Hospitalizations§		**Duration of Hospitalization (days), Mean (SD)**	**aHR of Hospital Discharge (95% CI)**					
	14-59	4.74 (4.85)	Ref	Ref	Ref	Ref	Ref	Ref
	60-89	4.85 (5.71)	1.005 (0.956, 1.056)	0.999 (0.869, 1.148)	0.978 (0.872, 1.096)	1.021 (0.912, 1.142)	1.079 (0.975, 1.194)	0.966 (0.869, 1.072)
	90-119	4.97 (5.79)	0.998 (0.950, 1.048)	0.961 (0.839, 1.100)	0.911 (0.814, 1.019)	0.944 (0.846, 1.054)	**1.121 (1.013, 1.242)**	1.040 (0.934, 1.157)
	120-149	4.83 (4.95)	1.040 (0.984, 1.099)	1.070 (0.919, 1.245)	0.937 (0.830, 1.058)	1.019 (0.902, 1.151)	**1.152 (1.026, 1.294)**	1.033 (0.913, 1.169)
	≥150	4.90 (5.30)	1.051 (0.989, 1.118)	1.055 (0.896, 1.241)	0.941 (0.825, 1.074)	1.024 (0.896, 1.169)	**1.178 (1.034, 1.342)**	1.039 (0.903, 1.194)

Abbreviations: aOR=Adjusted Odds Ratio, ICU=Intensive Care Unit; CI=Confidence Interval

*Controlling for age (in years), season, subtype, sex, race/ethnicity, state, CVD, CMD, CLD, Asthma, Neurologic disease, renal disease, immunosuppression, pregnancy, timing of hospitalization in the season (peak), and antiviral receipt

† Controlling for age (years), season, subtype, sex, race/ethnicity, state, CVD, CLD, Asthma, Neurologic disease, renal disease, immunosuppression, liver disease, timing of hospitalization in the season (peak), and antiviral receipt

§ Controlling for age (years), season, subtype, sex, race/ethnicity, state, CVD, CMD, CLD, Neurologic disease, renal disease, immunosuppression, pregnancy, timing of hospitalization in the season (peak), and antiviral receipt (N=21,142)

TABLE 4: Relationship between time since vaccination and risk of ICU admission and death in adults hospitalized with influenza-related illness, by influenza type/subtype

Outcome	Time Between Vaccination and Hospitalization (Days)	aOR of ICU Admission and Death (95% CI)			
		Overall	**A (H1N1)pdm09**	**A (H3N2)**	**B**
ICU Admission*	14-59	Ref	Ref	Ref	Ref
	60-89	0.886 (0.771, 1.018)	0.837 (0.607, 1.153)	0.898 (0.762, 1.057)	0.951 (0.580, 1.557)
	90-119	0.882 (0.768, 1.012)	0.898 (0.666, 1.210)	0.884 (0.748, 1.045)	0.894 (0.562, 1.422)
	120-149	0.873 (0.748, 1.019)	1.083 (0.790, 1.483)	0.820 (0.672, 1.001)	0.786 (0.502, 1.231)
	≥150	0.850 (0.717, 1.008)	0.919 (0.648, 1.303)	0.943 (0.746, 1.192)	0.670 (0.431, 1.041)
Death†	14-59	Ref	Ref	Ref	Ref
	60-89	0.868 (0.658, 1.145)	0.523 (0.220, 1.239)	0.898 (0.660, 1.220)	1.140 (0.389, 3.345)
	90-119	**0.637 (0.478, 0.849)**	**0.427 (0.194, 0.938)**	**0.614 (0.441, 0.855)**	1.590 (0.602, 4.198)
	120-149	**0.638 (0.464, 0.879)**	0.659 (0.307, 1.419)	**0.636 (0.431, 0.939)**	0.734 (0.269, 1.999)
	≥150	**0.528 (0.369, 0.756)**	0.607 (0.266, 1.389)	**0.504 (0.312, 0.816)**	0.631 (0.235, 1.690)
		aHR of Hospital Discharge (95% CI)			
Duration of Hospitalizations§	14-59	Ref	Ref	Ref	Ref
	60-89	1.005 (0.956, 1.056)	1.057 (0.931, 1.199)	1.000 (0.945, 1.058)	0.963 (0.798, 1.162)
	90-119	0.998 (0.950, 1.048)	1.017 (0.904, 1.144)	1.000 (0.944, 1.060)	0.919 (0.772, 1.095)
	120-149	1.040 (0.984, 1.099)	0.994 (0.877, 1.127)	1.035 (0.966, 1.108)	1.072 (0.906, 1.268)
	≥150	1.051 (0.989, 1.118)	1.046 (0.912, 1.200)	1.043 (0.961, 1.132)	1.033 (0.876, 1.219)

Abbreviations: aOR=adjusted odds ratio; ICU=Intensive Care Unit; CI=confidence interval; aHR = adjusted hazard ratio
*Controlling for age (years), season, sex, race/ethnicity, state, CVD, CMD, CLD, Asthma, Neurologic disease, renal disease, immunosuppression, pregnancy, timing of hospitalization in the season (peak), and antiviral receipt
† Controlling for age (years), season, sex, race/ethnicity, state, CVD, CLD, Asthma, Neurologic disease, renal disease, immunosuppression, liver disease, timing of hospitalization in the season (peak), and antiviral receipt
§ Controlling for age (years), season, sex, race/ethnicity, state, CVD, CMD, CLD, Neurologic disease, renal disease, immunosuppression, pregnancy, timing of hospitalization in the season (peak), and antiviral receipt (N=21,142)

TABLE 5: Characteristics of children hospitalized with influenza-related illness during the 2013-2014 through 2016-2017 influenza seasons, by timing of vaccine administration

Demographic and Clinical Characteristics*	Total†	Early vaccine†§	Late vaccine†§	p-value
Total	1728	984 (57)	744 (43)	
Age groups n (%)				**<0.0001**
6 - 23 months	533 (31)	182 (34)	351 (66)	
2 - 8 years	760 (44)	507 (67)	253 (33)	
9-17 years	435 (25)	295 (68)	140 (32)	
Sex, n (%)				0.1032
Male	960 (56)	530 (55)	430 (45)	
Female	768 (44)	454 (59)	314 (41)	
Race/Ethnicity, n (%)				**0.0194**
White, Non-Hispanic	642 (37)	396 (62)	246 (38)	
Black, Non-Hispanic	415 (24)	225 (54)	190 (46)	
Hispanic or Latino	335 (19)	186 (56)	149 (44)	
Unknown/Other	336 (19)	177 (53)	159 (47)	
Pre-existing medical condition, n (%)				
Any chronic condition	1258 (73)	762 (61)	496 (39)	**<0.0001**
No chronic condition	470 (27)	222 (47)	248 (53)	
Cardiovascular Disease¶	219 (13)	135 (62)	84 (38)	0.1328
No/Unknown	1509 (87)	849 (56)	660 (44)	
Congenital heart disease	69 (4)	42 (61)	27 (39)	0.5016
No/Unknown	1659 (96)	942 (57)	717 (43)	
Chronic Metabolic Disorder	121 (7)	83 (69)	38 (31)	**0.0073**
No/Unknown	1607 (93)	901 (56)	706 (44)	
Chronic Lung Disease**	136 (8)	92 (68)	44 (32)	**0.0086**
No/Unknown	1592 (92)	892 (56)	700 (44)	
Asthma	571 (33)	345 (60)	226 (40)	**0.0404**
No/Unknown	1157 (67)	639 (55)	518 (45)	
Neurologic/Neuromuscular Disease	424 (25)	272 (64)	152 (36)	**0.0006**
No/Unknown	1304 (75)	712 (55)	592 (45)	
History of Febrile Seizure	42 (2)	28 (67)	14 (33)	0.1977
No/Unknown	1686 (98)	956 (57)	730 (43)	
Kidney Disease	58 (3)	39 (67)	19 (33)	0.1072
No/Unknown	1670 (97)	945 (57)	725 (43)	
Immunocompromised††	247 (14)	169 (68)	78 (32)	**<0.0001**
No/Unknown	1481 (86)	815 (55)	666 (45)	
Cancer	67 (4)	57 (85)	10 (15)	**<0.0001**
No/Unknown	1661 (96)	927 (56)	734 (44)	
Prematurity§§	103 (19)	42 (41)	61 (59)	0.1141
No/Unknown	430 (81)	140 (33)	290 (67)	
Upper Airway Abnormality	97 (6)	66 (68)	31 (32)	**0.0231**
No/Unknown	1631 (94)	918 (56)	713 (44)	
State, n (%)				0.2228
California	128 (7)	70 (55)	58 (45)	
Colorado	294 (17)	170 (58)	124 (42)	
Connecticut	71 (4)	39 (55)	32 (45)	
Georgia	185 (11)	121 (65)	64 (35)	
Maryland	201 (12)	109 (54)	92 (46)	
Michigan	70 (4)	36 (51)	34 (49)	

Minnesota	228 (13)	137 (60)	91 (40)	
New Mexico	101 (6)	50 (50)	51 (50)	
New York - Albany	74 (4)	37 (50)	37 (50)	
New York - Rochester	64 (4)	32 (50)	32 (50)	
Ohio	123 (7)	77 (63)	46 (37)	
Oregon	38 (2)	23 (61)	15 (39)	
Tennessee	56 (3)	34 (61)	22 (39)	
Utah	95 (5)	49 (52)	46 (48)	
Influenza type, n (%)				0.2224*
A	1279 (74)	746 (58)	533 (42)	
B	423 (24)	223 (53)	200 (47)	
A&B	6 (0)	4 (67)	2 (33)	
Unknown	20 (1)	11 (55)	9 (45)	
Influenza Season, n (%)				**<0.0001**
2013-2014	349 (20)	207 (59)	142 (41)	
2014-2015	547 (32)	361 (66)	186 (34)	
2015-2016	370 (21)	179 (48)	191 (52)	
2016-2017	462 (27)	237 (51)	225 (49)	

*All variables were categorical and were compared using Chi-square test of difference in proportion or Fisher's exact test where sample size is small (Fisher's exact test used for influenza type only). Significance level: 0.05.

† Percentages for the "Total" column represent column percent. For the comparison of early and late vaccine, percentages represent row percent.

§ Early vaccine defined as those receiving vaccine prior to November 1st of each season. Late vaccine defined as those receiving vaccine on or after November 1st.

¶ Cardiovascular Disease category includes Congenital heart disease

** Chronic Lung Disease category does not include asthma

†† Immunocompromised includes cancer, HIV, immunoglobulin deficiency, organ/stem cell transplant, immunosuppressive therapy, steroid therapy, and CVID

§§ Prematurity analysis only includes patients <2 years of age who were <37 weeks gestation at birth

TABLE 6: Prevalence of ICU admission and pneumonia and mean duration of hospitalization among children with influenza-related hospitalization, by age group and influenza type/subtype

		Total N (%)	Outcome		
			ICU Admission, n (%)	Pneumonia, n (%)	Duration of hospitalization (days), Mean (SD)
Total		**1702**	**378 (22.2)**	**340 (20.0)**	**3.75 (6.79)**
Age Group	6-23 mo	529 (31)	112 (21.2)	102 (19.3)	3.21 (3.85)
	2-8 yo	744 (44)	166 (22.3)	164 (22.0)	3.56 (4.63)
	9-17 yo	429 (25)	100 (23.3)	74 (17.2)	4.75 (11.25)
Influenza Type/ Subtype	A	531 (31)	125 (23.5)	146 (27.5)	3.66 (4.39)
	A (H3N2)	748 (44)	162 (21.7)	126 (16.8)	3.49 (4.84)
	B	423 (25)	91 (21.5)	68 (16.1)	4.31 (10.95)

TABLE 7: Relationship between time since vaccination and severe outcomes in children hospitalized with influenza-related illness, overall and by age group

Outcome	Time Between Vaccination and Hospitalization (Days)	Prevalence of outcome, n (%)	aOR of ICU Admission and Pneumonia (95% CI)			
			Overall	6-23 months	2-8 yo	9-17 yo
ICU Admission*	14-59	**106/418 (25.4)**	Ref	Ref	Ref	Ref
	60-119	132/682 (19.4)	**0.644 (0.472, 0.880)**	**0.571 (0.327, 0.996)**	0.613 (0.359, 1.048)	0.548 (0.266, 1.130)
	≥120	140/602 (23.3)	0.802 (0.556, 1.159)	0.948 (0.469, 1.914)	0.905 (0.492, 1.666)	0.428 (0.172, 1.069)
Pneumonia*	14-59	**92/418 (22.0)**	Ref	Ref	Ref	Ref
	60-119	142/682 (20.8)	0.944 (0.689, 1.294)	0.569 (0.323, 1.000)	0.912 (0.541, 1.537)	1.180 (0.500, 2.784)
	≥120	106/602 (17.6)	0.757 (0.514, 1.114)	0.642 (0.308, 1.339)	0.644 (0.345, 1.204)	0.746 (0.258, 2.158)
Duration of Hospitalization*		**Duration of Hospitalization (days), Mean (SD)**	**aHR of Hospital Discharge (95% CI)**			
	14-59	3.40 (4.16)	Ref	Ref	Ref	Ref
	60-119	3.45 (3.70)	1.029 (0.906, 1.170)	1.000 (0.803, 1.246)	1.009 (0.808, 1.260)	1.073 (0.794, 1.450)
	≥120	4.33 (10.13)	1.064 (0.913, 1.240)	1.180 (0.883, 1.576)	0.997 (0.770, 1.290)	1.165 (0.793, 1.710)

Abbreviations: aOR=Adjusted Odds Ratio, ICU=Intensive Care Unit; CI=Confidence Interval
*Controlling for age (years), season, subtype, sex, race/ethnicity, state, CVD, CLD, Asthma, Neurologic disease, immunosuppression, and timing of hospitalization in the season

TABLE 8: Relationship between time since vaccination and risk of ICU admission and pneumonia in children hospitalized with influenza-related illness, by influenza type/subtype

Outcome	Time Between Vaccination and Hospitalization (Days)	aOR of ICU Admission and Pneumonia (95% CI)			
		Overall	**A (H1N1)pdm09**	**A (H3N2)**	**B**
ICU Admission*	14-59	Ref	Ref	Ref	Ref
	60-119	**0.644 (0.472, 0.880)**	**0.549 (0.311, 0.969)**	0.883 (0.563, 1.385)	**0.347 (0.147, 0.820)**
	≥120	0.802 (0.556, 1.159)	0.804 (0.428, 1.510)	1.375 (0.735, 2.572)	**0.351 (0.153, 0.804)**
Pneumonia*	14-59	Ref	Ref	Ref	Ref
	60-119	0.944 (0.689, 1.294)	0.727 (0.445, 1.187)	1.165 (0.701, 1.937)	1.066 (0.431, 2.639)
	≥120	0.757 (0.514, 1.114)	**0.375 (0.204, 0.691)**	2.016 (1.024, 3.967)	0.626 (0.248, 1.582)
Duration of Hospitalization*		**aHR of Hospital Discharge (95% CI)**			
	14-59	Ref	Ref	Ref	Ref
	60-119	1.029 (0.906, 1.170)	**1.305 (1.036, 1.643)**	0.867 (0.724, 1.040)	1.156 (0.820, 1.628)
	≥120	1.064 (0.913, 1.240)	**1.371 (1.051, 1.788)**	0.925 (0.719, 1.190)	1.113 (0.786, 1.577)

Abbreviations: aOR=adjusted odds ratio; ICU=Intensive Care Unit; CI=confidence interval; aHR = adjusted hazard ratio
*Controlling for age (years), season, subtype, sex, race/ethnicity, state, CVD, CLD, Asthma, Neurologic disease, immunosuppression, and timing of hospitalization in the season

TABLE 9: Sensitivity analyses for adults to assess misclassification of exposure

Outcome	Time Between Vaccination and Hospitalization (Days)	aOR of ICU Admission and Death (95% CI)				
		Reported	Removing those with vaccine on the 1st of the month (N=16940)	Removing those with self-reported vaccine dates (N=9517)	Removing those with multiple vaccine dates (N=20304)	Prioritizing PCP date over Registry date
ICU Admission*	14-59	Ref	Ref	Ref	Ref	Ref
	60-89	0.886 (0.771, 1.018)	0.913 (0.784, 1.062)	1.011 (0.821, 1.245)	0.872 (0.757, 1.005)	0.886 (0.771, 1.018)
	90-119	0.882 (0.768, 1.012)	0.920 (0.790, 1.072)	1.042 (0.844, 1.287)	0.877 (0.762, 1.010)	0.882 (0.768, 1.012)
	120-149	0.873 (0.748, 1.019)	0.888 (0.747, 1.056)	1.068 (0.842, 1.354)	**0.852 (0.728, 0.998)**	0.872 (0.747, 1.018)
	>=150	0.850 (0.717, 1.008)	0.855 (0.706, 1.036)	0.958 (0.737, 1.246)	**0.834 (0.701, 0.992)**	0.850 (0.716, 1.008)
Death†	14-59	Ref	Ref	Ref	Ref	Ref
	60-89	0.868 (0.658, 1.145)	0.908 (0.675, 1.220)	1.138 (0.779, 1.796)	0.869 (0.656, 1.151)	0.867 (0.657, 1.143)
	90-119	**0.637 (0.478, 0.849)**	**0.703 (0.517, 0.957)**	0.772 (0.495, 1.202)	**0.639 (0.477, 0.855)**	**0.637 (0.478, 0.849)**
	120-149	**0.638 (0.464, 0.879)**	**0.661 (0.466, 0.937)**	0.804 (0.491, 1.315)	**0.648 (0.468, 0.896)**	**0.637 (0.463, 0.878)**
	>=150	**0.528 (0.369, 0.756)**	**0.514 (0.346, 0.765)**	0.603 (0.347, 1.048)	**0.542 (0.377, 0.779)**	**0.527 (0.369, 0.755)**
		aHR of Hospital Discharge (95% CI)				
Duration of Hospitalization§	14-59	Ref	Ref	Ref	Ref	Ref
	60-89	1.005 (0.956, 1.056)	0.991 (0.938, 1.046)	0.994 (0.922, 1.071)	1.012 (0.962, 1.065)	1.005 (0.956, 1.056)
	90-119	0.998 (0.950, 1.048)	0.995 (0.942, 1.050)	0.952 (0.882, 1.027)	1.004 (0.955, 1.056)	0.998 (0.950, 1.049)
	120-149	1.040 (0.984, 1.099)	1.031 (0.969, 1.096)	0.993 (0.911, 1.082)	1.047 (0.989, 1.108)	1.040 (0.984, 1.099)
	>=150	1.051 (0.989, 1.118)	1.049 (0.979, 1.124)	1.011 (0.921, 1.111)	1.054 (0.991, 1.122)	1.051 (0.989, 1.118)

Abbreviations: aOR=adjusted odds ratio; ICU=Intensive Care Unit; CI=confidence interval; aHR = adjusted hazard ratio

*Controlling for age (years), season, sex, race/ethnicity, state, CVD, CMD, CLD, Asthma, Neurologic disease, renal disease, immunosuppression, pregnancy, timing of hospitalization in the season (peak), and antiviral receipt

† Controlling for age (years), season, sex, race/ethnicity, state, CVD, CLD, Asthma, Neurologic disease, renal disease, immunosuppression, liver disease, timing of hospitalization in the season (peak), and antiviral receipt

§ Controlling for age (years), season, sex, race/ethnicity, state, CVD, CMD, CLD, Neurologic disease, renal disease, immunosuppression, pregnancy, timing of hospitalization in the season (peak), and antiviral receipt

TABLE 10: Sensitivity analyses for children to assess misclassification of exposure

Outcome	Time Between Vaccination and Hospitalization (Days)	aOR of ICU Admission and Death (95% CI)					
		Reported	**Removing those with vaccine on the 1st of the month (n=1555)**	**Removing those with self-reported vaccine dates (n=981)**	**Removing those with multiple vaccine dates (n=1473)**	**Prioritizing PCP date over registry date**	**Removing LAIV (n=1630)**
ICU Admission*	14-59	Ref	Ref	Ref	Ref	Ref	Ref
	60-119	**0.644 (0.472, 0.880)**	**0.635 (0.459, 0.879)**	0.839 (0.558, 1.260)	**0.527 (0.373, 0.744)**	**0.644 (0.472, 0.880)**	**0.630 (0.457, 0.868)**
	>=120	0.802 (0.556, 1.159)	0.835 (0.567, 1.230)	1.253 (0.768, 2.045)	**0.652 (0.435, 0.976)**	0.802 (0.556, 1.159)	0.778 (0.534, 1.135)
Pneumonia*	14-59	Ref	Ref	Ref	Ref	Ref	
	60-119	0.944 (0.689, 1.294)	0.891 (0.641, 1.237)	0.977 (0.655, 1.458)	0.972 (0.685, 1.380)	0.944 (0.689, 1.294)	0.883 (0.639, 1.219)
	>=120	0.757 (0.514, 1.114)	0.734 (0.490, 1.099)	0.836 (0.503, 1.387)	0.761 (0.498, 1.163)	0.757 (0.514, 1.114)	0.731 (0.492, 1.087)
Duration of Hospitalization*		**aHR of Hospital Discharge (95% CI)**					
	14-59	Ref	Ref	Ref	Ref	Ref	
	60-119	1.029 (0.906, 1.170)	1.037 (0.907, 1.186)	0.968 (0.821, 1.140)	1.074 (0.932, 1.237)	1.029 (0.906, 1.170)	1.063 (0.933, 1.212)
	>=120	1.064 (0.913, 1.240)	1.064 (0.906, 1.250)	1.006 (0.822, 1.229)	1.103 (0.932, 1.305)	1.064 (0.913, 1.240)	1.082 (0.925, 1.265)

Abbreviations: aOR=adjusted odds ratio; ICU=Intensive Care Unit; CI=confidence interval; aHR = adjusted hazard ratio
*Controlling for age (years), season, subtype, sex, race/ethnicity, state, CVD, CLD, Asthma, Neurologic disease, immunosuppression, and timing of hospitalization in the season

SUPPLEMENTAL TABLE 1: Association between patient characteristics and severe outcomes among adults hospitalized with laboratory-confirmed influenza during the 2013-2014 through 2016-2017 influenza seasons

	Outcome							
	ICU admission			Death			Duration of hospitalization*	
	Yes, n (%)	No/Unknown, n (%)	OR (95% CI) †	Yes, n (%)	No/Unknown, n (%)	OR (95% CI) †	Mean (SD)	p-value†
Total	3090 (14.5)	18216 (85.5)		611 (2.87)	20695 (97.13)			
Time between vaccination and hospitalization								0.4892
14-59 days	411 (16.1)	2146 (83.9)	Reference	85 (3.32)	2472 (96.68)	Reference	4.75 (4.85)	
60-89 days	624 (13.8)	3899 (86.2)	**0.836 (0.730, 0.957)**	146 (3.23)	4377 (96.77)	0.970 (0.739, 1.273)	4.87 (5.73)	
90-119 days	752 (14.1)	4572 (85.9)	**0.859 (0.754, 0.979)**	138 (2.59)	5186 (97.41)	0.774 (0.588, 1.018)	4.97 (5.78)	
120-149 days	602 (14.5)	3556 (85.5)	0.884 (0.771, 1.013)	116 (2.79)	4042 (97.21)	0.835 (0.628, 1.109)	4.83 (4.96)	
≥150 days	701 (14.8)	4043 (85.2)	0.905 (0.793, 1.034)	126 (2.66)	4618 (97.34)	0.793 (0.600, 1.049)	4.91 (5.31)	
Age groups								0.2284
18 – 49 years	358 (15.6)	1937 (84.4)	Reference	24 (1.05)	2271 (98.95)	Reference	4.73 (6.29)	
50 – 64 years	802 (19.2)	3381 (81.8)	**1.283 (1.120, 1.471)**	86 (2.06)	4097 (97.94)	**1.986 (1.260, 3.132)**	4.87 (5.91)	
65 – 74 years	708 (16.3)	3645 (83.7)	1.051 (0.915, 1.207)	108 (2.48)	4245 (97.52)	**2.407 (1.542, 3.758)**	4.86 (5.45)	
75 – 84 years	687 (13.2)	4530 (86.8)	**0.821 (0.714, 0.942)**	158 (3.03)	5059 (96.97)	**2.955 (1.918, 4.553)**	4.84 (5.33)	
≥ 85 years	535 (10.2)	4723 (89.8)	**0.613 (0.531, 0.708)**	235 (4.47)	5023 (95.53)	**4.427 (2.900, 6.757)**	5.02 (4.54)	
Sex								0.4450
Male	1522 (16.2)	7904 (83.9)	Reference	270 (2.86)	9156 (97.14)	Reference	4.91 (5.64)	
Female	1568 (13.2)	10312 (86.8)	**0.790 (0.732, 0.852)**	341 (2.87)	11539 (97.13)	1.002 (0.852, 1.178)	4.86 (5.21)	
Race/Ethnicity								**<0.0001**
White, Non-Hispanic	2058 (14.7)	11930 (85.3)	Reference	458 (3.27)	13530 (96.73)	Reference	4.96 (5.32)	
Black, Non-Hispanic	462 (16.1)	2403 (83.9)	1.115 (0.998, 1.244)	54 (1.88)	2811 (98.12)	**0.568 (0.427, 0.755)**	5.18 (6.13)	
Hispanic or Latino	151 (12.3)	1081 (87.7)	**0.810 (0.679, 0.966)**	23 (1.87)	1209 (98.13)	**0.562 (0.368, 0.858)**	4.32 (5.84)	
Unknown/Other	419 (13.0)	2802 (87.0)	**0.867 (0.774, 0.970)**	76 (2.36)	3145 (97.64)	**0.714 (0.558, 0.913)**	4.49 (4.84)	
Pre-existing medical conditions								
Any chronic condition	3033 (14.8)	17429 (85.2)	**2.402 (1.831, 3.152)**	598 (2.92)	19864 (97.08)	**1.924 (1.106, 3.348)**	4.95 (5.47)	**<0.0001**
No/Unknown	57 (6.8)	787 (93.2)	Reference	13 (1.54)	831 (98.46)	Reference	3.17 (2.81)	

Cardiovascular Disease	1879 (15.9)	9977 (84.2)	**1.281 (1.185, 1.385)**	425 (3.58)	11431 (96.42)	**1.852 (1.555, 2.205)**	5.29 (5.78)	**<0.0001**
No/Unknown	1211 (12.8)	8239 (87.2)	Reference	186 (1.97)	9264 (98.03)	Reference	4.37 (4.85)	
Chronic Metabolic Disorder	1597 (15.6)	8668 (84.4)	**1.178 (1.092, 1.272)**	316 (3.08)	9949 (96.92)	1.157 (0.985, 1.359)	5.09 (5.70)	**<0.0001**
No/Unknown	1493 (13.5)	9548 (86.5)	Reference	295 (2.67)	10746 (97.33)	Reference	4.69 (5.11)	
Chronic Lung Diseases	1114 (20.4)	4355 (79.6)	**1.794 (1.655, 1.946)**	188 (3.44)	5281 (96.56)	**1.297 (1.090, 1.545)**	5.51 (5.73)	**<0.0001**
No/Unknown	1976 (12.5)	13861 (87.5)	Reference	423 (2.67)	15414 (97.33)	Reference	4.67 (5.27)	
Asthma	570 (13.6)	3608 (86.4)	0.916 (0.830, 1.010)	78 (1.87)	4100 (98.13)	0.592 (0.466, 0.753)	4.64 (5.09)	**0.0011**
No/Unknown	2520 (14.7)	14608 (85.3)	Reference	533 (3.11)	16595 (96.89)	Reference	4.94 (5.48)	
Neurologic/Neuromuscular Disease	934 (15.3)	5188 (84.7)	**1.088 (1.001, 1.182)**	235 (3.84)	5887 (96.16)	**1.572 (1.332, 1.856)**	5.55 (5.72)	**<0.0001**
No/Unknown	2156 (14.2)	13028 (85.8)	Reference	376 (2.48)	14808 (97.52)	Reference	4.61 (5.25)	
Kidney Disease	854 (16.1)	4462 (83.9)	**1.177 (1.081, 1.283)**	215 (4.04)	5101 (95.96)	**1.660 (1.402, 1.965)**	5.39 (6.11)	**<0.0001**
No/Unknown	2236 (14.0)	13754 (86.0)	Reference	396 (2.48)	15594 (97.52)	Reference	4.71 (5.14)	
Immunocompromised	737 (17.4)	3510 (82.7)	**1.312 (1.199, 1.437)**	139 (3.27)	4108 (96.73)	1.189 (0.981, 1.441)	5.34 (5.97)	**<0.0001**
No/Unknown	2353 (13.8)	14706 (86.2)	Reference	472 (2.77)	16587 (97.23)	Reference	4.77 (5.25)	
HIV	75 (17.4)	357 (82.6)	1.245 (0.967, 1.601)	8 (1.85)	424 (98.15)	0.634 (0.314, 1.283)	4.65 (5.64)	0.3579
No/Unknown	3015 (14.4)	17859 (85.6)	Reference	603 (2.89)	20271 (97.11)	Reference	4.89 (5.40)	
Cancer	182 (15.7)	978 (84.3)	1.103 (0.937, 1.298)	48 (4.14)	1112 (95.86)	**1.501 (1.111, 2.028)**	5.42 (5.57)	**0.0005**
No/Unknown	2908 (14.4)	17238 (85.6)	Reference	563 (2.79)	19583 (97.21)	Reference	4.85 (5.39)	
Liver Disease	151 (17.3)	721 (82.7)	**1.247 (1.042, 1.492)**	29 (3.33)	843 (96.67)	1.173 (0.803, 1.715)	5.22 (5.42)	0.0623
No/Unknown	2939 (14.4)	17495 (85.6)	Reference	582 (2.85)	19852 (97.15)	Reference	4.87 (5.41)	
Pregnancy¶	12 (3.5)	334 (96.5)	**0.230 (0.129, 0.411)**	1 (0.29)	345 (99.71)	**0.095 (0.013, 0.681)**	2.77 (2.99)	**<0.0001**
No/Unknown	1556 (13.5)	9978 (86.5)	Reference	340 (2.95)	11194 (97.05)	Reference	4.92 (5.25)	
State								**<0.0001**
California	337 (15.0)	1913 (85.0)	**1.313 (1.117, 1.542)**	79 (3.51)	2171 (96.49)	1.294 (0.943, 1.774)	4.70 (5.50)	
Colorado	374 (17.3)	1792 (82.7)	**1.555 (1.328, 1.821)**	45 (2.08)	2121 (97.92)	0.754 (0.521, 1.091)	4.41 (4.91)	
Connecticut	216 (13.0)	1449 (87.0)	1.111 (0.926, 1.332)	41 (2.46)	1624 (97.54)	0.898 (0.613, 1.314)	5.16 (5.71)	
Georgia	173 (13.7)	1087 (86.3)	1.186 (0.975, 1.442)	29 (2.30)	1231 (97.70)	0.837 (0.545, 1.288)	5.04 (5.49)	
Maryland	364 (15.7)	1952 (84.3)	**1.389 (1.186, 1.628)**	77 (3.32)	2239 (96.68)	1.223 (0.890, 1.680)	5.16 (5.23)	
Michigan	45 (12.8)	307 (87.2)	1.092 (0.783, 1.523)	9 (2.56)	343 (97.44)	0.933 (0.464, 1.875)	5.38 (4.83)	
Minnesota	346 (11.8)	2578 (88.2)	Reference	80 (2.74)	2844 (97.26)	Reference	4.46 (4.47)	
New Mexico	84 (13.0)	564 (87.0)	1.110 (0.860, 1.432)	17 (2.62)	631 (97.38)	0.958 (0.563, 1.628)	4.90 (5.88)	
New York – Albany	187 (14.8)	1078 (85.2)	**1.292 (1.067, 1.565)**	45 (3.56)	1220 (96.44)	1.311 (0.905, 1.901)	5.69 (6.18)	
New York – Rochester	201 (11.3)	1576 (88.7)	0.950 (0.790, 1.143)	57 (3.21)	1720 (96.79)	1.178 (0.834, 1.663)	5.73 (7.04)	
Ohio	269 (19.3)	1126 (80.7)	**1.780 (1.496, 2.118)**	47 (3.37)	1348 (96.63)	1.240 (0.860, 1.787)	5.18 (6.01)	
Oregon	211 (13.6)	1345 (86.4)	1.169 (0.973, 1.404)	52 (3.34)	1504 (96.66)	1.229 (0.862, 1.752)	4.69 (5.05)	
Tennessee	151 (16.2)	781 (83.8)	**1.441 (1.171, 1.772)**	12 (1.29)	920 (98.71)	0.464 (0.252, 0.855)	4.55 (4.16)	
Utah	132 (16.5)	668 (83.5)	**1.472 (1.184, 1.831)**	21 (2.63)	779 (97.38)	0.958 (0.589, 1.560)	3.44 (3.56)	
Influenza type, n (%)								**0.0299**
A	2571 (14.5)	15121 (85.5)	Reference	507 (2.87)	17185 (97.13)	Reference	4.87 (5.38)	
B	485 (14.0)	2991 (86.1)	0.954 (0.859, 1.059)	96 (2.76)	3380 (97.24)	0.963 (0.772, 1.201)	4.90 (5.51)	
A&B	27 (27.0)	73 (73.0)	**2.175 (1.396, 3.389)**	8 (8.00)	92 (92.00)	**2.947 (1.423, 6.103)**	6.49 (6.57)	

Unknown	7 (18.4)	31 (81.6)	1.328 (0.584, 3.019)	0 (0)	38 (100)	0	4.87 (4.51)	
Influenza Season								**0.0263**
2013-2014	490 (18.5)	2166 (81.6)	Reference	69 (2.60)	2587 (97.40)	Reference	4.99 (5.57)	
2014-2015	1026 (13.0)	6899 (87.1)	**0.657 (0.584, 0.739)**	246 (3.10)	7679 (96.90)	1.201 (0.916, 1.574)	4.95 (5.33)	
2015-2016	501 (17.2)	2413 (82.8)	0.918 (0.800, 1.053)	86 (2.95)	2828 (97.05)	1.140 (0.827, 1.572)	5.00 (5.83)	
2016-2017	1073 (13.7)	6738 (86.3)	**0.704 (0.626, 0.791)**	210 (2.69)	7601 (97.31)	1.036 (0.786, 1.365)	4.74 (5.26)	
Antiviral treatment Prior to Admission								<0.0001
Yes	65 (8.1)	738 (91.9)	**0.509 (0.394, 0.658)**	15 (1.87)	788 (98.13)	0.636 (0.379, 1.067)	3.93 (4.03)	
No/Unknown	3025 (14.8)	17478 (85.2)	Reference	596 (2.91)	19907 (97.09)	Reference	4.92 (5.45)	

Abbreviations: ICU=intensive care unit, OR=unadjusted odds ratio of outcome, CI=Confidence Interval, SD=Standard Deviation
All percentages represent row percent.
* 26 individuals were excluded from the Duration analysis due to missing information regarding either admission date or discharge date
† Odds ratios for categorical outcomes were determined using univariate logistic regression. Means were compared using analysis of variance (ANOVA).
§ Chronic Lung Disease category does not include asthma
¶ Pregnancy analysis includes females only

SUPPLEMENTAL TABLE 2: Association between patient characteristics and severe outcomes among children hospitalized with laboratory-confirmed influenza during the 2013-2014 through 2016-2017 influenza seasons

	Outcome							
	ICU admission			Pneumonia			Duration of hospitalization	
	Yes, n (%)	No, n (%)	OR (95% CI)*	Yes, n (%)	No, n (%)	OR (95% CI)*	Mean (SD)	p-value*
Total	380 (22.0)	1348 (78.0)		346 (20.0)	1382 (80.0)			
Time between vaccination and hospitalization								**0.0388**
14-59 days	107 (25.0)	321 (75.0)	Reference	94 (22.0)	334 (78.0)	Reference	3.40 (4.13)	
60-119 days	133 (19.3)	558 (80.8)	**0.715 (0.535, 0.955)**	145 (21.0)	546 (79.0)	0.944 (0.704, 1.265)	3.45 (3.70)	
≥120 days	140 (23.0)	469 (77.0)	0.896 (0.671, 1.196)	107 (17.6)	502 (82.4)	0.757 (0.556, 1.032)	4.30 (10.07)	
Age groups, n (%)								**0.0010**
6 - 23 months	112 (21.0)	421 (79.0)	Reference	103 (19.3)	430 (80.7)	Reference	3.21 (3.84)	
2 - 8 years	168 (22.1)	592 (77.9)	1.067 (0.814, 1.397)	169 (22.2)	591 (77.8)	1.194 (0.907, 1.571)	3.53 (4.59)	
9-17 years	100 (23.0)	335 (77.0)	1.122 (0.827, 1.523)	74 (17.0)	361 (83.0)	0.856 (0.615, 1.190)	4.75 (11.19)	
Sex, n (Row %)								0.5477
Male	207 (21.6)	753 (78.4)	Reference	195 (20.3)	765 (79.7)	Reference	3.65 (5.31)	
Female	173 (22.5)	595 (77.5)	1.058 (0.841, 1.330)	151 (19.7)	617 (80.3)	0.960 (0.757, 1.217)	3.85 (8.21)	
Race/Ethnicity, n (%)								0.4339
White, Non-Hispanic	145 (22.6)	497 (77.4)	Reference	117 (18.2)	525 (81.8)	Reference	3.56 (5.38)	
Black, Non-Hispanic	99 (23.9)	316 (76.1)	1.074 (0.802, 1.438)	78 (18.8)	337 (81.2)	1.039 (0.756, 1.427)	3.47 (4.08)	
Hispanic or Latino	76 (22.7)	259 (77.3)	1.006 (0.734, 1.379)	79 (23.6)	256 (76.4)	**1.385 (1.003, 1.911)**	4.09 (5.00)	
Unknown/Other	60 (17.9)	276 (82.1)	0.745 (0.533, 1.042)	72 (21.4)	264 (78.6)	1.224 (0.881, 1.700)	4.06 (11.56)	
Pre-existing medical conditions, n (%)								
Any chronic condition	288 (22.9)	970 (77.1)	1.220 (0.938, 1.587)	239 (19.0)	1019 (81.0)	0.796 (0.615, 1.029)	4.10 (7.62)	**0.0002**
No/Unknown	92 (19.6)	378 (80.4)	Reference	107 (22.8)	363 (77.2)	Reference	2.77 (3.29)	
Cardiovascular Disease†	55 (25.1)	164 (74.9)	1.222 (0.879, 1.698)	40 (18.3)	179 (81.7)	0.879 (0.610, 1.266)	4.10 (3.84)	0.4020
No/Unknown	325 (21.5)	1184 (78.5)	Reference	306 (20.3)	1203 (79.7)	Reference	3.69 (7.08)	
Congenital heart disease	22 (31.9)	47 (68.1)	**1.701 (1.012, 2.860)**	16 (23.2)	53 (76.8)	1.216 (0.686, 2.154)	4.35 (3.79)	0.4444
No/Unknown	358 (21.6)	1301 (78.4)	Reference	330 (19.9)	1329 (80.1)	Reference	3.71 (6.85)	
Chronic Metabolic Disorder	29 (24.0)	92 (76.0)	1.128 (0.731, 1.741)	17 (14.1)	104 (85.0)	0.635 (0.375, 1.075)	5.02 (7.04)	**0.0297**
No/Unknown	351 (21.8)	1256 (78.2)	Reference	329 (20.5)	1278 (79.5)	Reference	3.64 (6.72)	
Chronic Lung Diseases§	39 (28.7)	97 (71.3)	1.475 (0.999, 2.180)	40 (29.4)	96 (70.6)	**1.751 (1.186, 2.585)**	6.40 (9.97)	**<0.0001**
No/Unknown	341 (21.4)	1251 (78.6)	Reference	306 (19.2)	1286 (80.8)	Reference	3.51 (6.46)	
Asthma	155 (27.2)	416 (72.9)	**1.544 (1.220, 1.952)**	130 (22.8)	441 (77.2)	**1.284 (1.005, 1.641)**	4.02 (9.09)	0.2161
No/Unknown	225 (19.5)	932 (80.6)	Reference	216 (18.7)	941 (81.3)	Reference	3.60 (5.23)	
Neurologic/Neuromuscular Disease	143 (33.7)	281 (66.3)	**2.291 (1.792, 2.929)**	103 (24.3)	321 (75.7)	**1.401 (1.078, 1.821)**	5.21 (7.40)	**<0.0001**
No/Unknown	237 (18.2)	1067 (81.8)	Reference	243 (18.6)	1061 (81.4)	Reference	3.26 (6.46)	

History of Febrile Seizure	11 (26.2)	31 (73.8)	1.267 (0.631, 2.544)	3 (7.1)	39 (92.9)	**0.302 (0.093, 0.981)**	2.26 (1.50)	0.1514
No/Unknown	369 (21.9)	1317 (78.1)	Reference	343 (20.3)	1343 (79.7)	Reference	3.78 (6.83)	
Kidney Disease	10 (17.2)	48 (82.8)	0.732 (0.367, 1.461)	8 (13.8)	50 (86.2)	0.631 (0.296, 1.343)	3.91 (5.52)	0.8506
No/Unknown	370 (22.2)	1300 (77.8)	Reference	338 (20.2)	1332 (79.8)	Reference	3.73 (6.79)	
Immunocompromised	42 (17.0)	205 (83.0)	**0.693 (0.487, 0.987)**	33 (13.4)	214 (86.6)	**0.575 (0.391, 0.848)**	5.28 (14.29)	**<0.0001**
No/Unknown	338 (22.8)	1143 (77.2)	Reference	313 (21.1)	1168 (78.9)	Reference	3.48 (4.34)	
Cancer	3 (4.5)	64 (95.5)	**0.160 (0.050, 0.511)**	3 (4.5)	64 (95.5)	**0.180 (0.056, 0.577)**	5.42 (8.40)	**0.0378**
No/Unknown	377 (22.7)	1284 (77.3)	Reference	343 (20.7)	1318 (79.4)	Reference	3.67 (6.67)	
Prematurity¶	28 (27.2)	75 (72.8)	1.538 (0.937, 2.524)	19 (18.5)	84 (81.6)	0.932 (0.536, 1.618)	3.61 (3.28)	0.8949
No/Unknown	84 (19.5)	346 (80.5)	Reference	84 (19.5)	346 (80.47)	Reference	3.54 (5.35)	
Upper Airway Abnormality	30 (30.9)	67 (69.1)	**1.640 (1.049, 2.563)**	28 (28.9)	69 (71.1)	**1.676 (1.062, 2.643)**	5.18 (6.73)	**0.0310**
No/Unknown	350 (21.5)	1281 (78.5)	Reference	318 (19.5)	1313 (80.5)	Reference	3.65 (6.75)	
State								0.4129
California	25 (19.5)	103 (80.5)	0.628 (0.378, 1.041)	28 (21.9)	100 (78.1)	0.775 (0.474, 1.269)	4.41 (4.56)	
Colorado	82 (27.9)	212 (72.1)	Reference	78 (26.5)	216 (73.5)	Reference	4.29 (11.73)	
Connecticut	15 (21.1)	56 (78.9)	0.693 (0.371, 1.293)	5 (7.0)	66 (93.0)	**0.210 (0.082, 0.540)**	4.29 (3.30)	
Georgia	33 (17.8)	152 (82.2)	**0.561 (0.356, 0.884)**	30 (16.2)	155 (83.8)	**0.536 (0.335, 0.857)**	4.12 (6.95)	
Maryland	53 (26.4)	148 (73.6)	0.926 (0.618, 1.387)	38 (18.9)	163 (81.1)	0.646 (0.417, 1.000)	3.02 (2.78)	
Michigan	13 (18.6)	57 (81.4)	0.590 (0.307, 1.134)	15 (21.4)	55 (78.6)	0.755 (0.403, 1.414)	2.66 (2.04)	
Minnesota	37 (16.2)	191 (83.8)	**0.501 (0.324, 0.773)**	40 (17.5)	188 (82.5)	**0.589 (0.384, 0.904)**	3.75 (6.15)	
New Mexico	13 (12.9)	88 (87.1)	**0.382 (0.202, 0.721)**	24 (23.8)	77 (76.2)	0.863 (0.510, 1.461)	4.32 (7.05)	
New York - Albany	11 (14.9)	63 (85.1)	**0.451 (0.227, 0.899)**	6 (8.1)	79 (91.9)	**0.244 (0.102, 0.586)**	2.65 (2.71)	
New York - Rochester	19 (29.7)	45 (70.3)	1.092 (0.603, 1.977)	12 (18.8)	52 (81.3)	0.639 (0.324, 1.260)	4.06 (8.27)	
Ohio	40 (32.5)	83 (67.5)	1.246 (0.790, 1.964)	30 (24.4)	93 (75.6)	0.893 (0.549, 1.453)	4.04 (4.00)	
Oregon	9 (23.7)	29 (76.3)	0.802 (0.364, 1.768)	9 (23.7)	29 (76.3)	0.859 (0.389, 1.896)	3.97 (6.86)	
Tennessee	9 (16.1)	47 (83.9)	0.495 (0.232, 1.056)	12 (21.4)	44 (78.6)	0.755 (0.379, 1.504)	3.45 (3.75)	
Utah	21 (22.1)	74 (77.9)	0.734 (0.424, 1.269)	19 (20.0)	76 (80.0)	0.692 (0.393, 1.219)	2.76 (3.01)	
Influenza type, n (%)								0.2205
A	287 (22.4)	992 (77.6)	Reference	272 (21.3)	1007 (78.7)	Reference	3.56 (4.66)	
B	91 (21.5)	332 (78.5)	0.947 (0.726, 1.237)	68 (16.1)	355 (83.9)	**0.709 (0.530, 0.950)**	4.31 (10.95)	
A&B	0 (0)	6 (100)	0	3 (50.0)	3 (50.0)	3.702 (0.743, 18.446)	4.17 (3.06)	
Other	2 (10.0)	18 (90.0)	0.384 (0.089, 1.665)	3 (15.0)	17 (85.0)	0.653 (0.190, 2.246)	2.75 (2.90)	
Influenza Season								0.2336
2013-2014	74 (21.2)	275 (78.8)	Reference	96 (27.5)	253 (72.5)	Reference	3.49 (3.48)	
2014-2015	128 (23.4)	419 (76.6)	1.135 (0.821, 1.570)	97 (17.7)	450 (82.3)	**0.568 (0.412, 0.783)**	3.44 (4.37)	
2015-2016	80 (21.6)	290 (78.4)	1.025 (0.718, 1.464)	79 (21.4)	291 (78.7)	0.715 (0.508, 1.007)	3.78 (4.90)	
2016-2017	98 (21.2)	364 (78.8)	1.001 (0.712, 1.406)	74 (16.0)	388 (84.0)	**0.503 (0.357, 0.708)**	4.25 (10.93)	
Antiviral treatment Prior to Admission								0.0003
Yes	7 (15.2)	39 (84.8)	0.631 (0.280, 1.421)	12 (26.1)	34 (73.9)	1.425 (0.730, 2.781)	7.30 (28.00)	
No/Unknown	373 (22.2)	1309 (77.8)	Reference	334 (19.9)	1348 (80.1)	Reference	3.64 (5.05)	

Abbreviations: ICU=intensive care unit, OR=unadjusted odds ratio of outcome, CI=Confidence Interval, SD=Standard Deviation

All percentages represent row percent.
* Odds ratios for categorical outcomes were determined using univariate logistic regression. Means were compared using analysis of variance (ANOVA).
† Cardiovascular Disease category includes Congenital heart disease
§ Chronic Lung Disease category does not include asthma
¶ Prematurity analysis only includes patients <2 years of age

SUPPLEMENTAL TABLE 3: Examining changes in odds of ICU admission and death in adults, excluding patients with <28 days between vaccination and hospitalization

Time between vaccination and hospitalization	ICU Admission - Reported		ICU Admission – Excluding those 14-28 days	
	Number admitted to ICU, n (%)	Adjusted OR (95% CI)*	Number admitted to ICU, n (%)	Adjusted OR (95% CI)*
14-59 days; 28-59 days	405/2534 (16.0)	Reference	319/2050 (15.6)	Reference
60-89 days	617/4498 (13.7)	0.886 (0.771, 1.018)	617/4498 (13.7)	0.909 (0.783, 1.056)
90-119 days	744/5294 (14.1)	0.882 (0.768, 1.012)	744/5294 (14.1)	0.909 (0.784, 1.056)
120-149 days	597/4129 (14.5)	0.873 (0.748, 1.019)	597/4129 (14.5)	0.904 (0.766, 1.066)
≥150 days	693/4713 (14.7)	0.850 (0.717, 1.008)	693/4713 (14.7)	0.878 (0.733, 1.052)
	Death – Reported		**Death – Excluding those 14-28 days**	
	Number of Deaths, n (%)	Adjusted OR (95% CI)	Number of Deaths, n (%)†	Adjusted OR (95% CI) †
14-59 days; 28-59 days	84/2534 (3.31)	Reference	66/2050 (3.22)	Reference
60-89 days	144/4498 (3.20)	0.868 (0.658, 1.145)	144/4498 (3.20)	0.901 (0.668, 1.215)
90-119 days	136/5294 (2.57)	0.637 (0.478, 0.849)	136/5294 (2.57)	0.664 (0.487, 0.905)
120-149 days	115/4129 (2.79)	0.638 (0.464, 0.879)	115/4129 (2.79)	0.669 (0.475, 0.940)
≥150 days	124/4713 (2.63)	0.528 (0.369, 0.756)	124/4713 (2.63)	0.553 (0.378, 0.808)

Abbreviations: OR= odds ratio; ICU=Intensive Care Unit; CI=confidence interval

Red values represent changes after removing excluded patients. 484 patients excluded using new criteria.

*Controlling for age (years), season, sex, race/ethnicity, state, CVD, CMD, CLD, Asthma, Neurologic disease, renal disease, immunosuppression, pregnancy, timing of hospitalization in the season (peak), and antiviral receipt

† Controlling for age (years), season, sex, race/ethnicity, state, CVD, CLD, Asthma, Neurologic disease, renal disease, immunosuppression, liver disease, timing of hospitalization in the season (peak), and antiviral receipt

APPENDIX

1. **Adults, ICU Admission**

   Logit (p-hat) = β_0 + β_1(Timegroup1) + β_2(Timegroup2) + β_3(Timegroup3)+ β_4(Timegroup4) + β_5(ageyears) + β_6(season2) + β_7(season3) + β_8(season4) + β_9(sex) + β_{10}(race black)+ β_{11}(race hisp) + β_{12}(race other) + β_{13}(state2) + β_{14}(state3) + β_{15}(state4) + β_{16}(state5) + β_{17}(state6)+ β_{18}(state7) + β_{19}(state8) + β_{20}(state9) + β_{21}(state10) + β_{22}(state11) + β_{23}(state12) + β_{24}(state13)+ β_{25}(state14)+ β_{26}(flutype2) + β_{27}(flutype3) + β_{28} (cvd) + β_{29}(cmd) + β_{30}(cld) + β_{31}(asthma)+ β_{32}(neuro) + β_{33}(renal) + β_{34}(immunosup) + β_{35}(pregnancy) + β_{36}(peak1) + β_{37}(peak2) + β_{38}(antiviral)

   Where:
   p = probability of ICU admission
   Timegroup: Time between vaccine receipt and hospitalization (primary exposure)
   Age (years): continuous
   Season: Influenza season; reference = 2013-2014
   Sex: reference = male
   Race: reference = white, non-Hispanic
   State: reference = Minnesota
   Flu type: 3 influenza types included, as above; reference = A(H1N1)pdm09
   CVD (cardiovascular disease), CMD (chronic metabolic disorder), CLD (chronic lung disease), Asthma, Neuro (neurologic/neuromuscular disease), Renal disease, Immunosuppressed, Pregnancy: reference = no/unknown
   Peak: Timing of hospitalization within the season; reference = pre-peak
   Antiviral: reference = no/unknown

2. **Adults, Death**

   Logit (p-hat) = β_0 + β_1(Timegroup1) + β_2(Timegroup2) + β_3(Timegroup3)+ β_4(Timegroup4) + β_5(ageyears) + β_6(season2) + β_7(season3) + β_8(season4) + β_9(sex) + β_{10}(race black)+ β_{11}(race hisp) + β_{12}(race other) + β_{13}(state2) + β_{14}(state3) + β_{15}(state4) + β_{16}(state5) + β_{17}(state6)+ β_{18}(state7) + β_{19}(state8) + β_{20}(state9) + β_{21}(state10) + β_{22}(state11) + β_{23}(state12) + β_{24}(state13)+ β_{25}(state14)+ β_{26}(flutype2) + β_{27}(flutype3) + β_{28} (cvd) + β_{29}(liver) + β_{30}(cld) + β_{31}(asthma)+ β_{32}(neuro) + β_{33}(renal) + β_{34}(immunosup) + β_{35}(peak1) + β_{36}(peak2) + β_{37}(antiviral)

   Where:
   p = probability of death
   Liver disease: reference = no/unknown
   Other variables as described above

3. **Children, ICU Admission**

   Logit (p-hat) = β_0 + β_1(Timegroup1) + β_2(Timegroup2) + β_3(Timegroup3)+ β_4(Timegroup4) + β_5(ageyears) + β_6(season2) + β_7(season3) + β_8(season4) + β_9(sex) + β_{10}(race black)+ β_{11}(race hisp) + β_{12}(race other) + β_{13}(state2) + β_{14}(state3) + β_{15}(state4) + β_{16}(state5) + β_{17}(state6)+ β_{18}(state7) + β_{19}(state8) + β_{20}(state9) + β_{21}(state10) + β_{22}(state11) + β_{23}(state12) + β_{24}(state13)+ β_{25}(state14)+ β_{26}(flutype2) + β_{27}(flutype3) + β_{28} (cvd) + β_{29}(cld) + β_{30}(asthma)+ β_{31}(neuro) + β_{32}(immunosup) + β_{33} (peak1) + β_{34}(peak2)

   Where:
   p = probability of ICU admission
   State: reference = Colorado

Other variables as described above

4. **Children, Pneumonia**

Logit (p-hat) = β_0 + β_1(Timegroup1) + β_2(Timegroup2) + β_3(Timegroup3)+ β_4(Timegroup4) + β_5(ageyears) + β_6(season2) + β_7(season3) + β_8(season4) + β_9(sex) + β_{10}(race black)+ β_{11}(race hisp) + β_{12}(race other) + β_{13}(state2) + β_{14}(state3) + β_{15}(state4) + β_{16}(state5) + β_{17}(state6)+ β_{18}(state7) + β_{19}(state8) + β_{20}(state9) + β_{21}(state10) + β_{22}(state11) + β_{23}(state12) + β_{24}(state13)+ β_{25}(state14)+ β_{26}(flutype2) + β_{27}(flutype3) + β_{28} (cvd) + β_{29}(cld) + β_{30}(asthma)+ β_{31}(neuro) + β_{32}(immunosup) + β_{33} (peak1) + β_{34}(peak2)

Where:
p = probability of pneumonia
Other variables as described above

5. **Adults, Duration of Hospitalization**

H(t) = h0(t) exp [β_1(Timegroup1) + β_2(Timegroup2) + β_3(Timegroup3)+ β_4(Timegroup4) + β_5(ageyears) + β_6(season2) + β_7(season3) + β_8(season4) + β_9(sex) + β_{10}(race black)+ β_{11}(race hisp) + β_{12}(race other) + β_{13}(state2) + β_{14}(state3) + β_{15}(state4) + β_{16}(state5) + β_{17}(state6)+ β_{18}(state7) + β_{19}(state8) + β_{20}(state9) + β_{21}(state10) + β_{22}(state11) + β_{23}(state12) + β_{24}(state13)+ β_{25}(state14)+ β_{26}(flutype2) + β_{27}(flutype3) + β_{28} (cvd) + β_{29}(cmd) + β_{30}(cld) + β_{31}(neuro)+ β_{32}(renal) + β_{33}(immunosup) + β_{34}(pregnancy) + β_{35}(peak1) + β_{36}(peak2) + β_{37}(antiviral)]

Where H(t) = hazard of being discharged at time t
Other variables as described above

6. **Children, Duration of Hospitalization**

H(t) = h0(t) exp [β_1(Timegroup1) + β_2(Timegroup2) + β_3(Timegroup3)+ β_4(Timegroup4) + β_5(ageyears) + β_6(season2) + β_7(season3) + β_8(season4) + β_9(sex) + β_{10}(race black)+ β_{11}(race hisp) + β_{12}(race other) + β_{13}(state2) + β_{14}(state3) + β_{15}(state4) + β_{16}(state5) + β_{17}(state6)+ β_{18}(state7) + β_{19}(state8) + β_{20}(state9) + β_{21}(state10) + β_{22}(state11) + β_{23}(state12) + β_{24}(state13)+ β_{25}(state14)+ β_{26}(flutype2) + β_{27}(flutype3) + β_{28} (cvd) + β_{29}(cld) + β_{30}(asthma)+ β_{31}(neuro) + β_{32}(immunosup) + β_{33} (peak1) + β_{34}(peak2)]

Where H(t) = hazard of being discharged at time t
Other variables as described above