学位論文

Epidemiology, Clinical Characteristics, and Outcomes of Influenza-Associated Hospitalizations in U.S. Children Over 9 Seasons Following the 2009 H1N1 Pandemic

新型インフルエンザ（H1N1）パンデミック以後９年間における米国での小児インフルエンザに関連した入院の疫学的推移、臨床的特徴、および転帰に関する研究

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Contents

ABSTRACT

Introduction

Recent population-based data are limited regarding influenza-associated hospitalizations in U.S. children.

Methods

I identified children <18 years hospitalized with laboratory-confirmed influenza during 2010–2019 seasons through CDC's Influenza Hospitalization Surveillance Network. Adjusted hospitalization and in-hospital mortality rates were calculated, and multivariable logistic regression was conducted to evaluate risk factors for pneumonia, intensive care unit (ICU) admission, mechanical ventilation, and death.

Results

Over 9 seasons, adjusted influenza-associated hospitalization incidence rates ranged from 10–375 per 100,000 persons each season and were highest among infants <6 months. Rates decreased with increasing age. The highest in-hospital mortality rates were observed in children <6 months (0.73 per 100,000 persons). Over time, antiviral treatment significantly increased from 56% to 85% ($P < .001$) and influenza vaccination rates increased from 33% to 44% ($P = .003$). Among the 13,235 hospitalized children, 2,676 (20%) of hospitalized children were admitted to the ICU, 2,262 (17%) had pneumonia, 690 (5%) required mechanical ventilation, and 72 (0.5%) died during hospitalization. As compared with those <6 months of age, hospitalized children ≥13 years had higher odds of pneumonia (adjusted odds ratios [aOR], 2.7; 95% confidence interval [CI], 2.1–3.4), ICU admission (aOR, 1.6; 95% CI, 1.3–1.9), mechanical ventilation (aOR, 1.6; 95% CI, 1.1–2.2), and death (aOR, 3.3; 95% CI, 1.2–9.3).

Conclusions

Hospitalization and death rates were greatest in younger children at the population level. Among hospitalized children, however, older children had a higher risk of severe outcomes. Continued efforts to prevent and attenuate influenza in children are needed.

INTRODUCTION

Influenza causes significant morbidity and mortality in children, particularly among infants and young children.[1-5] Since the 2009 H1N1 influenza pandemic, advances have been made in diagnostic, treatment, and prevention strategies. For example, the use of molecular influenza testing, which is more sensitive and specific than rapid antigen detection tests, has increased.[6-8] Increased use of antiviral agents occurred during and after the 2009 H1N1 pandemic, and the US Food and Drug Administration (FDA) approved oseltamivir for treatment of influenza in patients >2 weeks of age in 2012.[6, 9] Maternal influenza vaccination is effective in preventing influenza-related illness among infants <6 months of age who are too young to be eligible for influenza vaccination.[10, 11] Although estimated influenza vaccination coverage among US pregnant women was consistently low (~15%) before 2009, it increased substantially following the 2009 H1N1 pandemic to 54% in the 2018–2019 season.[12-15] Similarly, influenza vaccination among vaccine-eligible infants increased from below 23% in the 2005–2006 season to 47% in the 2017–2018 season.[16-18]

Although data through the 2009 influenza pandemic have been published, recent population-based data on the burden of influenza-associated hospitalizations in children are limited.[6, 19, 20] Therefore, I conducted surveillance for influenza-associated hospitalizations through the US Influenza Hospitalization Surveillance Network (FluSurv-NET) to evaluate the epidemiology, clinical presentation, and outcomes of children hospitalized with influenza over 9 seasons following the 2009 H1N1 pandemic. This doctoral dissertation is based on the findings which were published in the following paper:

Kamidani S, Garg S, Rolfes MA, et al. Epidemiology, Clinical Characteristics, and Outcomes of Influenza-Associated Hospitalizations in U.S. Children Over 9 Seasons Following the 2009 H1N1 Pandemic. Clin Infect Dis. 2022 Apr 19:ciac296. doi: 10.1093/cid/ciac296. Epub ahead of print. PMID: 35438769.

METHODS

Study Design and Population

I conducted this cross-sectional study of children <18 years of age hospitalized with laboratory-confirmed, community-acquired influenza at 14 FluSurv-NET sites during the 2010–2011 through 2018–2019 seasons (defined as October 1–April 30). FluSurv-NET conducts prospective, population-based surveillance for hospitalized cases of laboratory-confirmed influenza through a network of acute-care hospitals in select counties within California, Colorado, Connecticut, Georgia, Maryland, Michigan, Minnesota, New Mexico, New York, Ohio, Oregon, Tennessee, and Utah, with a total catchment population of >27 million people (~9% of the US population).[21] Children residing within the catchment area were included if they had a positive influenza test within 14 days before or within 3 days after hospitalization during each influenza season. Laboratory-confirmed influenza was defined as ≥1 positive influenza test (rapid influenza diagnostic test [RIDT], real-time reverse transcription-polymerase chain reaction [RT-PCR], direct or indirect fluorescent antibody staining [DFA], or culture). Laboratory testing was ordered at the discretion of the clinician providing care. Trends in use of each influenza test type by season were evaluated. Trained surveillance staff abstracted data on demographic characteristics, medical history, current season influenza vaccination status, antiviral therapy, and outcomes from medical records using standardized case reporting forms.

Variables

I categorized children into age groups of 0–<6 months, 6 months–<2 years, 2–4 years, 5–8 years, 9–12 years, and 13–17 years. Age-group-specific population denominators for the FluSurv-NET catchment area were obtained from the National Centers for Health Statistics (NCHS).[22] Data on symptoms at hospital admission were collected by FluSurv-NET during the 2014–2015 to 2018–2019 influenza. Antiviral treatment was defined as receipt of influenza antiviral medication (e.g., oseltamivir, peramivir, or zanamivir) at any time during course of illness. Since data about prior seasonal influenza vaccination were not reliably available, I considered patients ≥6 months of age who received at least one dose of seasonal influenza vaccine ≥2 weeks before admission as vaccinated regardless of age. I used influenza season as a proxy for seasonal variation in the predominant circulating influenza virus subtype, since data were incomplete for influenza A subtype. Primary outcomes were all-cause in-hospital mortality, intensive care unit (ICU) admission, mechanical ventilation, and pneumonia. I used a standardized FluSurv-NET definition of pneumonia, which included a combination of radiographic findings of bronchopneumonia, air space opacity, consolidation, lobar or interstitial infiltrate within 3 days of hospital admission, and either an ICD coded discharge diagnosis of pneumonia or documentation of pneumonia on hospital discharge summary.[23-25]

Statistical Methods

Due to changes in the use of influenza diagnostic testing over the surveillance period, rates of influenza-associated hospitalizations were adjusted for influenza testing practices using a multiplier approach.[26] Briefly, FluSurv-NET sites took a stratified random sample of acute respiratory hospitalizations in each season within broad age groups and recorded the frequency of influenza testing and assay type. Adjustment multipliers, the inverse of the frequency times the average sensitivity of the assays, were calculated for each season using testing data from hospitalizations in each age group.[27] Because of small numbers, limited data were available on types of influenza assays used for the 13–17 year age group during the 2011–2012 season; therefore, the assay and its sensitivity were assumed to be the same as for the 9–12 year old group. Since data on testing practices during the 2018–2019 season were not yet available, the most conservative multiplier in an age group from any season between 2010–2011 and 2017–2018 was used for the 2018–2019 adjustment. Uncertainty in the adjusted rates was estimated using 5,000 Monte Carlo simulations, assuming a Poisson distribution for number of hospitalizations and beta distributions for frequency of influenza testing and average assay sensitivity. Adjusted rates are presented per 100,000 population with 95% uncertainty intervals (using the lower and upper 2.5th percentile of the resulting distribution). The same multiplier approach was used to evaluate mean mortality rates per 100,000 persons by age using population denominators from NCHS.

I evaluated differences in demographic and clinical characteristics by age group among patients hospitalized with influenza using the Cochran-Armitage chi-square test for trend. Trends in antiviral treatment and influenza vaccination coverage by season were also evaluated. I assessed the association of each covariate with each outcome in bivariate analyses using the chi-square test or the Fisher exact test for categorical covariates. I used multivariable logistic regression to evaluate the association of demographic factors, preexisting medical conditions, and other covariates with each outcome. Variables considered for inclusion in the final models included age group, sex, race/ethnicity, influenza type, season, surveillance site, antiviral treatment prior to hospitalization, and chronic underlying conditions.[28, 29] The majority of children (95.4%) received antiviral treatment beginning on the day of or after hospitalization (data not shown). Therefore, in order to best evaluate the impact of antiviral use on outcomes, I included antiviral treatment received only prior to hospitalization as a covariate in models. Vaccination (in those ≥6 months of age) and prematurity <37 weeks (in those <2 years of age) were not included in models since all age groups needed to be evaluated. Due to the small numbers of in-hospital deaths, variables considered for inclusion in the final model for all-cause in-hospital mortality included age group, sex, race/ethnicity, and the presence of any underlying condition. An indicator variable was used for the missing/unknown category in all models. Statistical analyses were performed using SAS version 9.4 software (SAS Institute Inc. Cary, NC) and P-values <0.05 were considered statistically significant.

FluSurv-NET sites obtained human subjects and ethics approvals from their respective state health department and academic partner Institutional Review Boards (IRBs) as needed. CDC determined this activity met the requirement for public health surveillance; therefore, CDC IRB approval was not required.

RESULTS

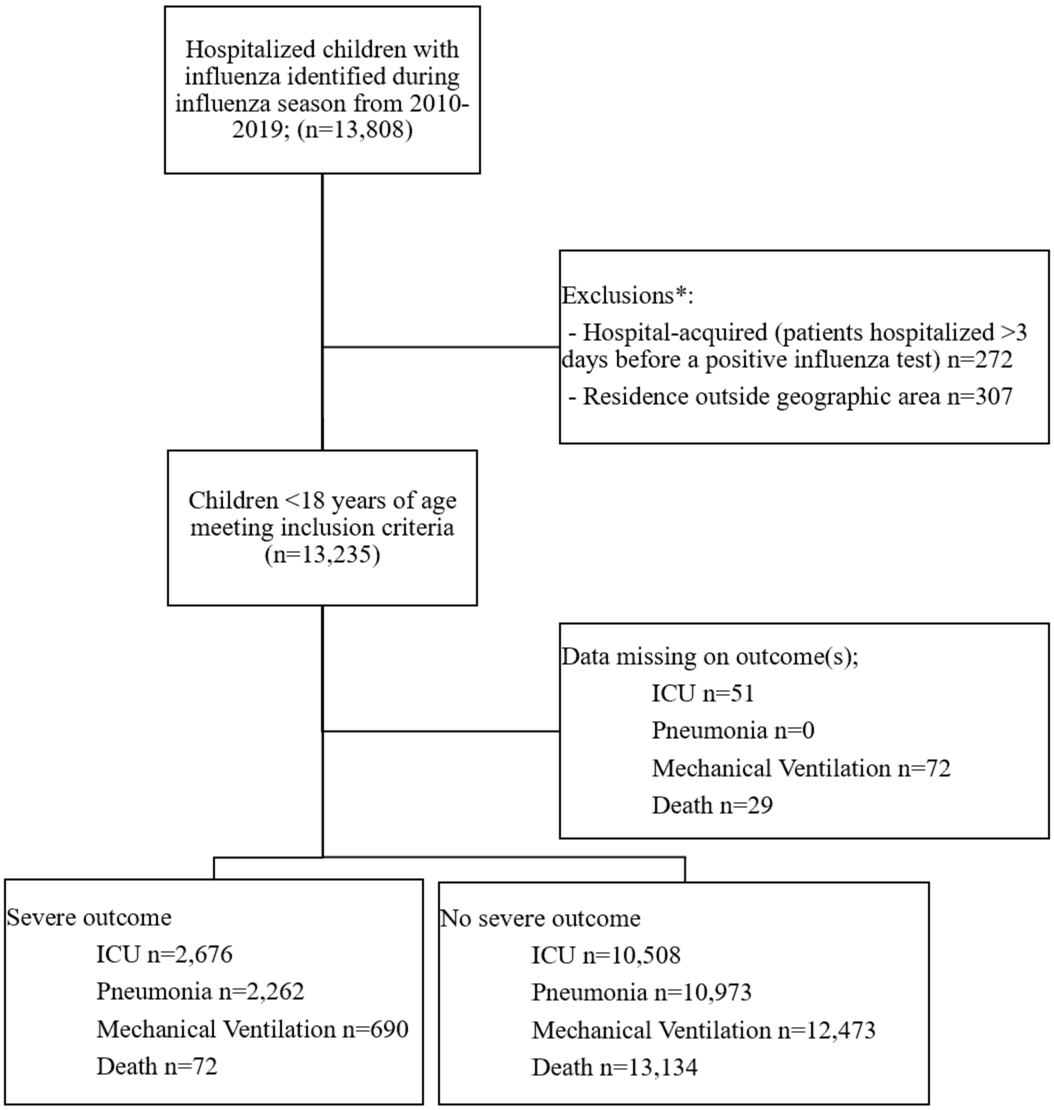
Hospitalization and Mortality Rates

Among 13,808 children <18 years of age with an influenza-associated hospitalization identified from the 2010–2011 through 2018–2019 influenza seasons, 13,235 (96%) children met the inclusion criteria (**Supplementary Figure 1**).

Overall, there were decreases in estimated hospitalization rates with increasing age across influenza seasons (**Figure 1**). The highest adjusted hospitalization rates were demonstrated in infants <6 months, ranging from 125–375 per 100,000 persons, whereas rates among children 13–17 years ranged from 17.2–48.6 per 100,000 persons (**Supplementary Table 1**).

In-hospital mortality and hospitalization rates by age group were shown in **Figure 2**. The highest adjusted in-hospital mortality rates were also observed among children <6 months of age. Whereas the adjusted hospitalization rates decreased substantially with increasing age (until age 9), the mortality rates remained similar in age groups ≥2 year of age, ranging from 0.23–0.26 per 100,000 persons.

Supplementary Figure 1. Flow Chart of Hospitalized Patients with Laboratory-Confirmed Influenza included in this analysis, FluSurv-NET, 2010 – 2019.



*Some cases met more than one exclusion criterion.

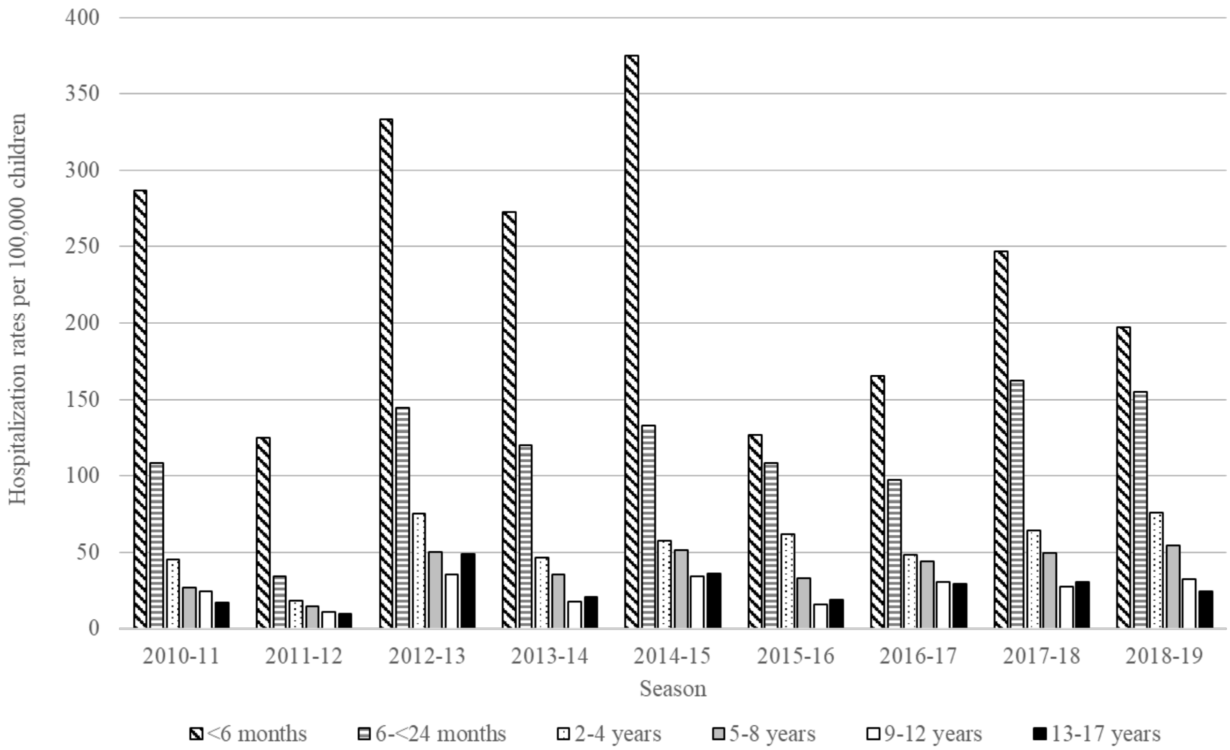


Figure 1. Adjusted influenza-associated hospitalization rates among children <18 years, by influenza season and age group, FluSurv-NET, 2010-2019.

Supplementary Table 1. Adjusted Influenza-associated Hospitalization Rates with 95% Confidence Interval (CI) among Children <18 Years, by Influenza Season and Age Group, FluSurv-NET, 2010-2019.*

	<6 months		6–<2 years		2–4 Years		5–8 Years		9–12 Years		13–17 Years	
Season	Rates	95% CI	Rates	95% CI	Rates	95% CI	Rates	95% CI	Rates	95% CI	Rates	95% CI
2010–2011	287	179–736	108	67–299	45	25–234	27	19–43	25	20–30	17	14–21
2011–2012	125	101–150	34	21–135	18	11–42	15	9–66	11	8–14	10	5–68
2012–2013	334	228–985	145	106–288	76	53–136	50	41–68	35	23–73	49	41–56
2013–2014	273	189–489	120	89–194	47	31–92	36	31–41	18	14–21	21	13–42
2014–2015	375	245–816	133	100–191	57	42–96	51	46–57	34	25–58	36	31–41
2015–2016	127	89–253	108	72–253	62	40–133	33	22–74	16	13–19	19	12–35
2016–2017	165	113–439	97	65–232	48	29–144	44	29–103	31	20–61	29	19–60
2017–2018	247	176–506	162	124–274	64	48–128	50	40–69	27	21–40	31	24–43
2018–2019	197	141–397	155	117–254	76	58–154	54	43–75	33	25–48	25	19–34
2010–2019 (Mean Rates)	237	NA	118	NA	55	NA	40	NA	25	NA	26	NA

*Rates per 100,000 children, Abbreviation: N.A., not applicable

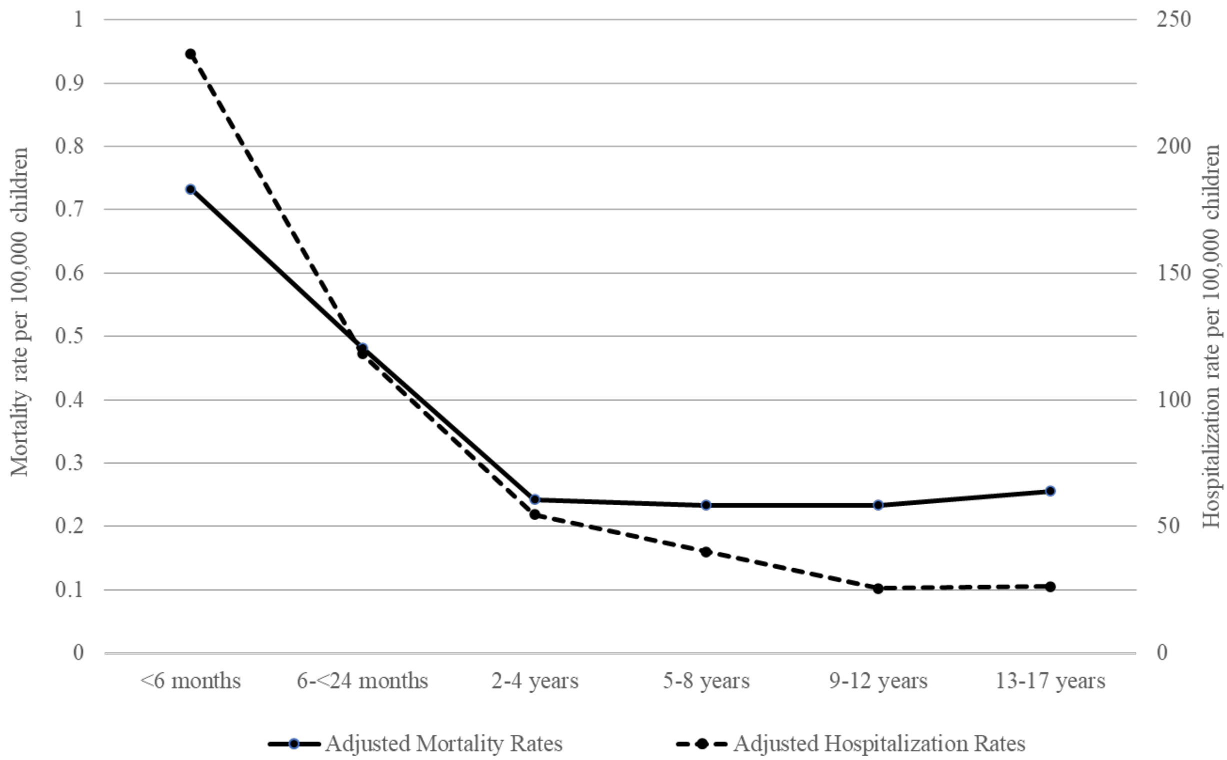


Figure 2. Adjusted Influenza-associated In-Hospital Mortality and Hospitalization Rates among Children <18 years, by Age Group, FluSurv-NET, 2010-2019.

Characteristics and Interventions among Hospitalized Children

Overall, 56% of children hospitalized with influenza were male, 34% were non-Hispanic White, and 55% had ≥1 preexisting medical condition (**Table 1**). Fever or chills was the most common symptom reported (84.3%), followed by cough (77.8%). The frequency of reported chest pain, myalgia, sore throat, and headache increased with increasing age ($P < .001$). Most documented symptoms were less frequently observed in infants <6 months of age, compared with older age groups. Influenza type A predominated among hospitalized children each season (**Supplementary Figure 2**). Influenza B accounted for 24% of the total cases but ranged seasonally from 4% to 42% of all hospitalizations.

Between 2010–2011 and 2018–2019, use of antiviral treatment significantly increased from 56% to 85% ($P < .001$), and influenza vaccination coverage among hospitalized children increased from 33% to 44% (P = .003) (**Supplementary Figure 3**). Infants <6 months of age and children 13–17 years of age were more frequently treated with antiviral agents than all other age groups (**Table 1**). Influenza vaccination was highest among children 6 months to <2 years of age (45%). Use of RT-PCR substantially increased from 49% to 81%, while all other testing methods decreased substantially over time (RIDT 27% to 19%, DFA 20% to 0%, and culture 5% to 0.1%, serology 0% to 0% [<1% in the 2011–2012 and 2012–2013 seasons], from the 2010–2011 to 2018–2019 seasons, respectively) (**Supplementary Figure 4**).

Table 1. Characteristics and Outcome of Children <18 Years of Age Hospitalized with Laboratory-Confirmed Influenza by Age Group, FluSurv-NET, 2010-2019.

Demographic characteristics	<6 months	6 months – <2 years	2–4 years	5–8 years	9–12 years	13–17 years	Total
	n = 2029 (15.3%)	n = 3040 (23.0%)	n = 2791 (21.1%)	n = 2633 (19.9%)	n = 1366 (10.3%)	n = 1376 (10.4%)	n = 13235
	no. (%)	no. (%)	no. (%)	no. (%)	no. (%)	no. (%)	no. (%)
Sex							
Male	1176 (58.0)	1717 (56.5)	1571 (56.3)	1527 (58.0)	774 (56.7)	699 (50.8)	7464 (56.4)
Female	853 (42.0)	1323 (43.5)	1220 (43.7)	1106 (42.0)	592 (43.3)	677 (49.2)	5771 (43.6)
Race							
Non-Hispanic White	654 (32.2)	865 (28.5)	920 (33.0)	995 (37.8)	514 (37.6)	555 (40.3)	4503 (34.0)
Non-Hispanic Black	484 (23.9)	785 (25.8)	792 (28.4)	746 (28.3)	381 (27.9)	383 (27.8)	3571 (27.0)
Hispanic	494 (24.4)	748 (24.6)	598 (21.4)	487 (18.5)	255 (18.7)	253 (18.4)	2835 (21.4)
Other[a]	161 (7.9)	331 (10.9)	226 (8.1)	183 (7.0)	92 (6.7)	79 (5.7)	1072 (8.1)
Unknown	236 (11.6)	311 (10.2)	255 (9.1)	222 (8.4)	124 (9.1)	106 (7.7)	1254 (9.5)
Preexisting medical conditions							
Prematurity <37 weeks[b]	336 (16.6)	514 (16.9)	NA	NA	NA	NA	850 (16.8)
Abnormality of upper airway	25 (1.2)	99 (3.3)	90 (3.2)	79 (3.0)	42 (3.1)	41 (3.0)	376 (2.8)
Asthma	17 (0.8)	352 (11.6)	753 (27.0)	998 (37.9)	562 (41.1)	551 (40.0)	3233 (24.4)
Cystic fibrosis	4 (0.2)	8 (0.3)	7 (0.3)	14 (0.5)	19 (1.4)	29 (2.1)	81 (0.6)
Congenital heart disease	37 (1.8)	111 (3.7)	71 (2.5)	59 (2.2)	32 (2.3)	22 (1.6)	332 (2.5)

Chronic kidney disease	18 (0.9)	29 (1.0)	56 (2.0)	61 (2.3)	48 (3.5)	55 (4.0)	267 (2.0)
Neurologic disease	58 (2.9)	282 (9.3)	458 (16.4)	467 (17.7)	294 (21.5)	284 (20.6)	1843 (13.9)
Neuromuscular disorder	11 (0.5)	57 (1.9)	83 (3.0)	88 (3.3)	57 (4.2)	75 (5.5)	371 (2.8)
Chronic liver disease	1 (0.0)	11 (0.4)	10 (0.4)	16 (0.6)	8 (0.6)	12 (0.9)	58 (0.4)
Diabetes	0 (0.0)	5 (0.2)	13 (0.5)	30 (1.1)	46 (3.4)	77 (5.6)	171 (1.3)
Sickle cell disease	23 (1.1)	90 (3.0)	87 (3.1)	156 (5.9)	108 (7.9)	102 (7.4)	566 (4.3)
Immunocompromising status	10 (0.5)	123 (4.1)	201 (7.2)	293 (11.1)	177 (13.0)	235 (17.1)	1039 (7.9)
Any chronic condition above	531 (26.2)	1342 (44.1)	1574 (56.4)	1748 (66.4)	1035 (75.8)	1079 (78.4)	7309 (55.2)
Presenting sign/symptom[c]							
Fever/Chills	843 (76.1)	1705 (88.0)	1595 (87.7)	1587 (87.2)	772 (80.6)	742 (78.5)	7244 (84.3)
Cough	746 (67.3)	1600 (82.6)	1460 (80.3)	1416 (77.8)	744 (77.7)	713 (75.5)	6679 (77.8)
Dyspnea	385 (34.8)	927 (47.8)	711 (39.1)	652 (35.8)	381 (39.8)	359 (38.0)	3415 (39.8)
Wheeze	104 (9.4)	413 (21.3)	327 (18.0)	346 (19.0)	206 (21.5)	154 (16.3)	1550 (18.0)
Nasal congestion/Runny nose	750 (67.7)	1419 (73.2)	1138 (62.6)	999 (54.9)	467 (48.8)	490 (51.9)	5263 (61.3)
GI symptoms[d]	245 (27.5)	641 (44.2)	548 (42.3)	581 (43.0)	292 (41.5)	340 (45.5)	2647 (41.1)
Chest pain	NA	NA	NA	90 (6.7)	90 (12.8)	166 (22.2)	381 (5.9)
Myalgia	NA	NA	NA	223 (16.5)	125 (17.8)	198 (26.5)	657 (10.2)
Sore throat	NA	NA	NA	346 (19.0)	268 (28.0)	315 (33.3)	1114 (13.0)
Headache	NA	NA	NA	231 (17.1)	150 (21.3)	222 (29.7)	675 (10.5)
Febrile or respiratory symptoms[e]	1061 (95.8)	1907 (98.4)	1772 (97.4)	1774 (97.4)	926 (96.7)	897 (94.9)	8337 (97.1)
Influenza type							
A	1675 (82.6)	2348 (77.2)	2104 (75.4)	1836 (69.7)	986 (72.2)	1000 (72.7)	9949 (75.2)
B	318 (15.7)	647 (21.3)	641 (23.0)	762 (28.9)	363 (26.6)	359 (26.1)	3090 (23.3)
A and B	19 (0.9)	18 (0.6)	16 (0.6)	14 (0.5)	3 (0.2)	5 (0.4)	75 (0.6)

Unknown	17 (0.8)	27 (0.9)	30 (1.1)	21 (0.8)	14 (1.0)	12 (0.9)	121 (0.9)
Influenza Vaccination							
Yes	NA	1374 (45.2)	958 (34.3)	928 (35.2)	541 (39.6)	473 (34.4)	4274 (38.1)
No	NA	1476 (48.6)	1602 (57.4)	1464 (55.6)	709 (51.9)	761 (55.3)	6012 (53.6)
Unknown	NA	190 (6.3)	231 (8.3)	241 (9.2)	116 (8.5)	142 (10.3)	920 (8.2)
Antiviral treatment							
Yes	1638 (80.7)	2333 (76.7)	2145 (76.9)	1976 (75.0)	1067 (78.1)	1126 (81.8)	10285 (77.7)
Antivirals <=2 days after symptom onset[f]							
Yes	832 (46.7)	865 (31.3)	772 (30.7)	802 (34.0)	450 (36.5)	461 (37.7)	4182 (35.2)
Antivirals <=2 days after admission, n (%)[g]							
Yes	1598 (79.5)	2238 (74.7)	2047 (74.3)	1900 (73.2)	1016 (75.2)	1079 (79.3)	9878 (75.6)
ICU Admission[h]							
Yes	308 (15.2)	623 (20.5)	550 (19.7)	499 (19.0)	336 (24.6)	360 (26.2)	2676 (20.2)
Death[h]							
Yes	6 (0.3)	14 (0.5)	13 (0.5)	15 (0.6)	13 (1.0)	11 (0.8)	72 (0.5)
Mechanical Ventilation[h]							
Yes	83 (4.1)	154 (5.1)	152 (5.5)	120 (4.6)	89 (6.5)	92 (6.7)	690 (5.2)
Pneumonia[h]							
Yes	133 (6.6)	559 (18.4)	623 (22.3)	481 (18.3)	252 (18.5)	214 (15.6)	2262 (17.1)

[a]Other races include Asian, Pacific islander, American Indian, Alaska Native, and multiracial.

[b]Number of patients <2 years of age without prematurity or with unknown data: (n=4219).

[c]Total numbers of each age group in the seasons 2014-2019; <6 months (n=1108), 6 months–<2 years (n=1938), 2–4 years (n=1819), 5–8 years (n=1821), 9–12 years (n=958), and 13–17 years of age (n=945). Analysis of self-reported symptoms was restricted to children ≥5 years of age.

[d]Nausea/vomiting, or diarrhea

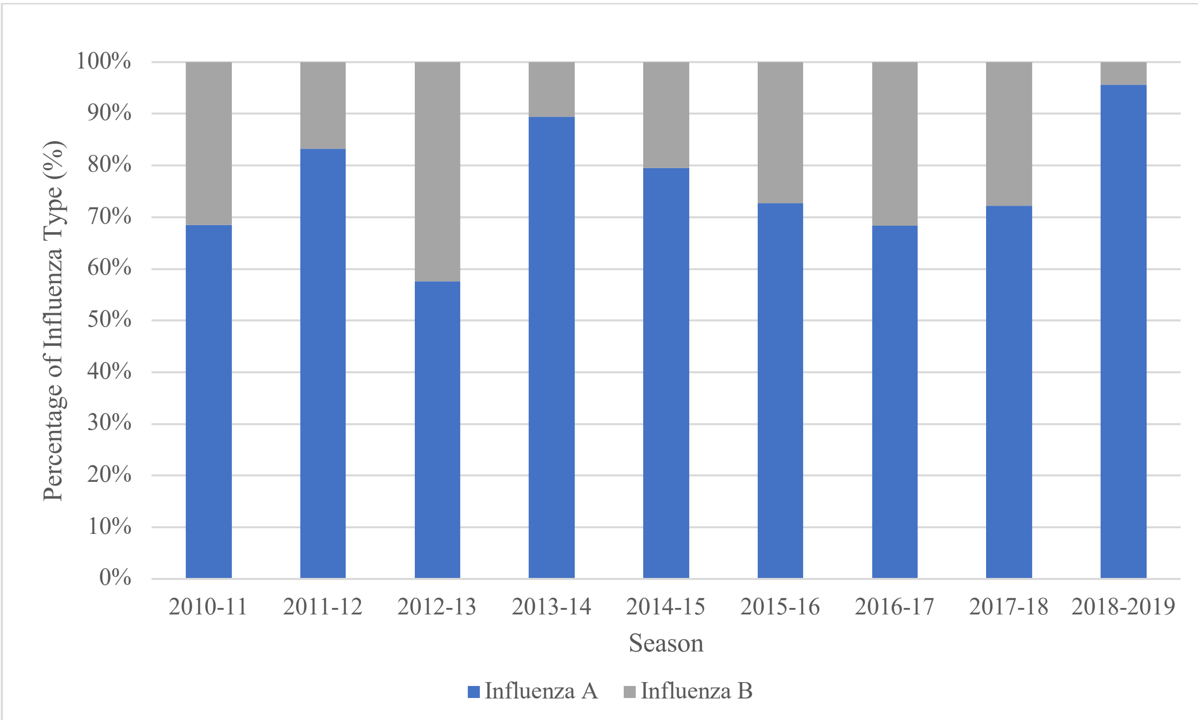
[e]Defined as fever, cough, shortness of breath, sore throat, runny nose/congestion, and/or wheezing

[f]Among children (n= 11,876) with data on antiviral timing relative to symptom onset.

[g]Among children (n= 13,067) with data on antiviral timing relative to admission.

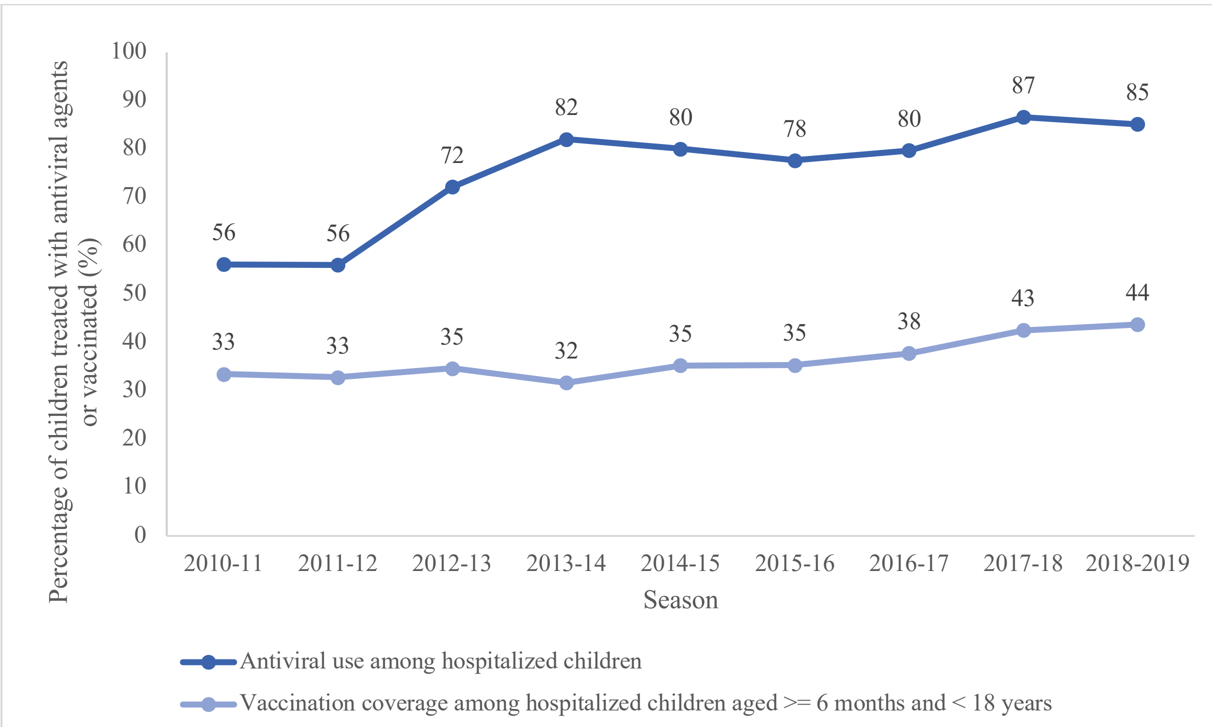
[h]Number with missing data: ICU admission (51), Death (29), Mechanical ventilation (72), Pneumonia (0).

Supplementary Figure 2. Distribution of Influenza Type among Children <18 years Hospitalized with Laboratory-Confirmed Influenza, by Influenza Season, FluSurv-NET, 2010-2019.*

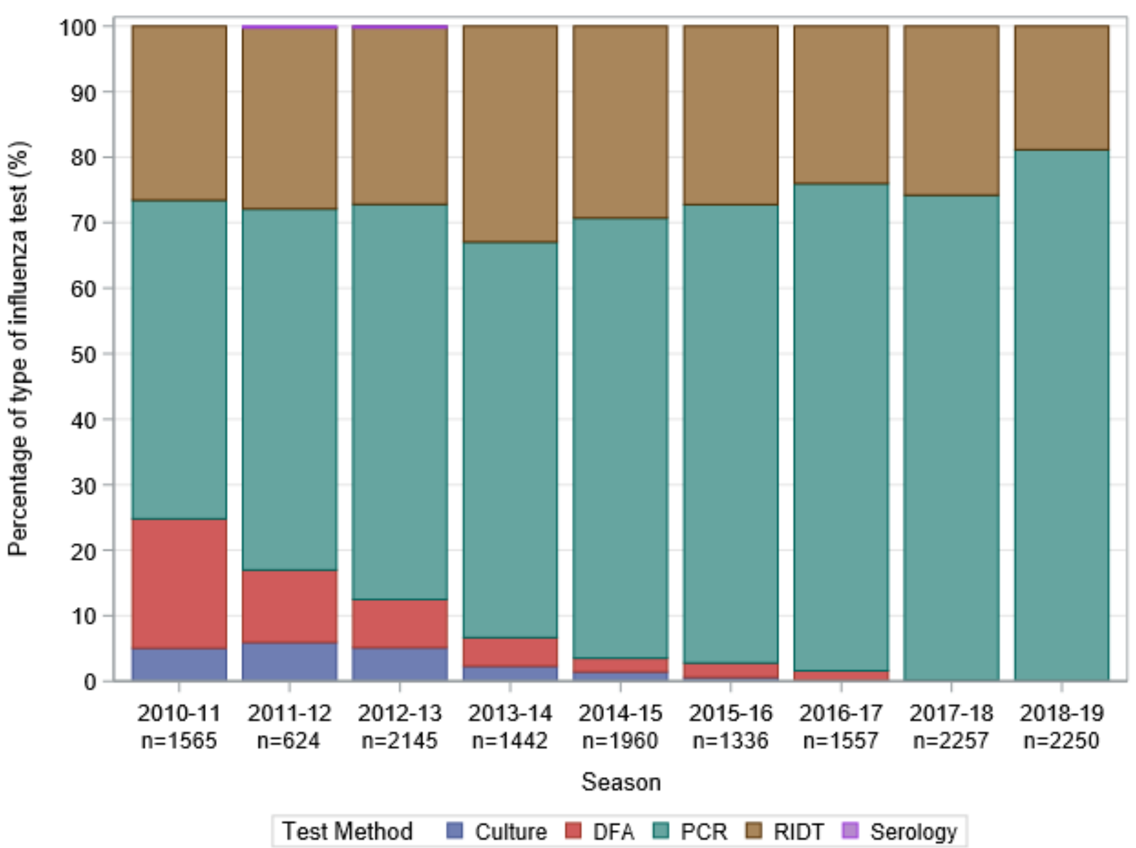


*Among children with data available on influenza type (those with positive both A and B [75 cases] were excluded).

Supplementary Figure 3. Antiviral Treatment and Influenza Vaccination Coverage among Children <18 years Hospitalized with Laboratory-Confirmed Influenza, by Season, FluSurv-NET, 2010-2019.



Supplementary Figure 4. Distribution of Hospitalizations among Children <18 years, by Influenza Testing Type and Season, FluSurv-NET, 2010-2019.*



*More than one influenza test was performed in some individuals, and denominators are the total number of influenza tests performed each season among people with laboratory-confirmed influenza.

Abbreviations: RIDT, rapid influenza diagnostic test; RT-PCR, real-time reverse transcription polymerase chain reaction; DFA, direct or indirect fluorescent antibody staining.

Severe Outcomes among Hospitalized Children

Among 13,235 hospitalized children with influenza, 2,676 (20%) were admitted to ICU, 2,262 (17%) had pneumonia, 690 (5%) required mechanical ventilation, and 72 (0.5%) died during hospitalization (**Table 1**). Among children admitted to ICU, 1194 (45%) either had pneumonia or required mechanical ventilation. The distribution of severe outcomes differed by age group (ICU admission: *P*<.001, mechanical ventilation: *P*=.001, pneumonia: *P*<.001, and in-hospital death: *P*=.007) (statistical data not shown in Table 1). The frequency of severe outcomes among hospitalized children with influenza varied somewhat by season (**Supplementary Table 2**). While the highest ICU admission rates were observed in the 2017–2018 season, the highest mortality rates were observed in the 2014–2015 season. In the multivariable models, the odds of each severe outcome were higher among older children 13–17 years of age (pneumonia: adjusted OR [aOR], 2.7; 95% CI, 2.1–3.4, ICU admission: aOR 1.6; 95% CI, 1.3–1.9, mechanical ventilation: aOR, 1.6; 95% CI, 1.1–2.2, all-cause in-hospital mortality: aOR, 3.3; 95% CI, 1.2–9.1), compared with children <6 months of age (**Table 2, 3**). Children 9–12 years of age also had similar odds of each severe outcome compared to those 13–17 years of age. Furthermore, a variety of underlying conditions were associated or inversely associated with each severe outcome (**Table 2**). Of these, conditions including abnormal upper airway, neurologic disease, or neuromuscular disease were associated with ICU admission and mechanical ventilation, while sickle cell disease was inversely associated with all severe outcomes.

Supplementary Table 2. Frequency of Severe Outcomes among Children <18 Years Hospitalized with Laboratory-Confirmed Influenza, by Influenza Season, FluSurv-NET, 2010-2019.

Season	2010–2011	2011–2012	2012–2013	2013–2014	2014–2015	2015–2016	2016–2017	2017–2018	2018–2019
Pneumonia, n (%)	164 (14.0)	73 (16.0)	274 (15.0)	280 (23.0)	254 (15.0)	229 (20.0)	204 (15.0)	387 (18.0)	397 (18.0)
ICU admission, n (%)	187 (15.8)	89 (19.2)	311 (17.7)	247 (20.2)	371 (21.6)	231 (19.8)	310 (22.2)	484 (22.8)	446 (20.8)
Mechanical ventilation, n (%)	70 (5.9)	18 (3.9)	91 (5.2)	68 (5.6)	97 (5.7)	50 (4.3)	79 (5.7)	109 (5.1)	108 (5.0)
Death, n (%)	4 (0.3)	0 (0.0)	15 (0.8)	3 (0.2)	17 (1.0)	5 (0.4)	5 (0.4)	13 (0.6)	10 (0.5)

Table 2. Adjusted Odds Ratios for ICU Admission, Mechanical Ventilation, and Pneumonia among Children Hospitalized with Laboratory-Confirmed Influenza, FluSurv-NET, 2010-2019.

	Pneumonia[a]			ICU Admission[b]			Mechanical Ventilation[c]		
	Multivariable Analysis			Multivariable Analysis			Multivariable Analysis		
	aOR	95% CI		aOR	95% CI		aOR	95% CI	
Age, years									
<6 months	reference			reference			reference		
6–<24 months	**3.18**[e]	**2.60**	**3.89**	**1.29**	**1.11**	**1.51**	1.16	0.88	1.53
2–4 years	**3.91**	**3.19**	**4.79**	1.09	0.93	1.28	1.20	0.90	1.60
5–8 years	**3.20**	**2.59**	**3.95**	1.03	0.87	1.22	1.03	0.76	1.39
9–12 years	**3.33**	**2.63**	**4.21**	**1.42**	**1.17**	**1.71**	**1.49**	**1.07**	**2.07**

13–17 years	**2.70**	**2.12**	**3.44**	**1.56**	**1.29**	**1.88**	**1.56**	**1.13**	**2.17**
Sex									
Male	reference			reference			reference		
Female	1.08	0.98	1.18	1.01	0.93	1.11	1.07	0.92	1.26
Race/Ethnicity, n (%)									
Non-Hispanic White	reference			reference			reference		
Non-Hispanic Black	1.03	0.90	1.17	**1.17**	**1.03**	**1.32**	1.12	0.90	1.38
Hispanic	1.08	0.95	1.24	0.95	0.83	1.08	0.89	0.71	1.12
Other	1.12	0.94	1.34	1.07	0.90	1.27	1.17	0.88	1.56
Unknown	**0.81**	**0.67**	**0.97**	0.86	0.72	1.02	0.77	0.55	1.07
Preexisting medical conditions[d]									
Abnormality of upper airway	1.16	0.89	1.51	**1.71**	**1.35**	**2.17**	**1.82**	**1.29**	**2.56**
Asthma	**1.33**	**1.20**	**1.49**	**1.44**	**1.30**	**1.61**	**0.80**	**0.66**	**0.98**
Cystic fibrosis	1.08	0.60	1.95	**0.14**	**0.05**	**0.39**	0.20	0.03	1.45
Congenital heart disease	0.89	0.66	1.20	**1.48**	**1.15**	**1.90**	1.44	0.99	2.09
Chronic kidney disease	0.73	0.50	1.06	**0.68**	**0.48**	**0.95**	1.16	0.72	1.87
Neurologic disease	1.13	0.99	1.30	**1.79**	**1.58**	**2.02**	**2.24**	**1.83**	**2.72**
Neuromuscular disorder	**1.42**	**1.10**	**1.84**	**1.48**	**1.16**	**1.87**	**1.64**	**1.17**	**2.29**
Chronic liver disease	**0.28**	**0.09**	**0.89**	1.29	0.69	2.43	2.01	0.87	4.63
Diabetes	**0.50**	**0.30**	**0.83**	**2.90**	**2.10**	**4.02**	0.67	0.31	1.45
Sickle cell disease	**0.29**	**0.20**	**0.42**	**0.16**	**0.11**	**0.24**	**0.16**	**0.07**	**0.40**
Immunocompromising status	**0.68**	**0.56**	**0.82**	**0.67**	**0.56**	**0.81**	0.82	0.60	1.11
Influenza type									
A	reference			reference			reference		

B	**0.83**	**0.74**	**0.94**	0.90	0.81	1.01	1.13	0.93	1.36
A&B	**1.75**	**1.02**	**3.01**	0.91	0.50	1.66	1.20	0.43	3.34
Unknown	1.12	0.71	1.76	0.60	0.36	1.02	0.67	0.24	1.85
Antiviral use before admission									
No	reference			reference			reference		
Yes	**1.54**	**1.23**	**1.93**	0.88	0.69	1.12	0.98	0.64	1.52
Unknown	0.87	0.56	1.34	0.81	0.51	1.27	0.90	0.39	2.06
Influenza Season									
2010-2011	reference			reference			reference		
2011-2012	1.12	0.83	1.53	1.15	0.87	1.54	**0.56**	**0.32**	**0.95**
2012-2013	1.14	0.92	1.42	1.04	0.84	1.27	**0.67**	**0.48**	**0.93**
2013-2014	**1.76**	**1.41**	**2.19**	1.15	0.93	1.43	0.78	0.55	1.11
2014-2015	1.04	0.84	1.29	**1.28**	**1.05**	**1.56**	0.80	0.58	1.11
2015-2016	**1.43**	**1.15**	**1.80**	1.14	0.92	1.42	**0.57**	**0.39**	**0.84**
2016-2017	1.02	0.81	1.28	**1.27**	**1.03**	**1.57**	0.72	0.51	1.01
2017-2018	**1.26**	**1.03**	**1.55**	**1.34**	**1.10**	**1.62**	**0.66**	**0.48**	**0.90**
2018-2019	1.22	0.99	1.50	1.18	0.97	1.44	**0.68**	**0.49**	**0.94**

[a]For the multivariable analysis, 2262 cases with pneumonia (n = 13235). The multivariable analysis included adjustment for study site.

[b]For the multivariable analysis, 2676 cases with ICU admission (n = 13184). The multivariable analysis included adjustment for study site.

[c]For the multivariable analysis, 690 cases with mechanical ventilation (n = 13163). The multivariable analysis included adjustment for study site.

[d]References of each preexisting medical condition were no/unknown.

[e]Bolded numbers are statistically significant.

Table 3. Adjusted Odds Ratios for All-cause In-hospital Mortality among Children Hospitalized with Laboratory-confirmed Influenza, FluSurv-NET, 2010-2019

	In-hospital Mortality		
	aOR	95% CI	
Age, years			
<6 months	reference		
6–<24 months	1.62	0.62	4.23
2–4 years	1.75	0.66	4.65
5–8 years	2.26	0.86	5.95
9–12 years	**3.93**[a]	**1.44**	**10.69**
13–17 years	**3.31**	**1.18**	**9.29**
Sex			
Male	reference		
Female	1.26	0.79	2.01
Race/Ethnicity			
Non-Hispanic White	reference		
Non-Hispanic Black	0.90	0.48	1.68
Hispanic	0.79	0.40	1.57
Other	1.94	0.95	3.96
Unknown	0.89	0.37	2.18
Any chronic medical conditions	0.67	0.41	1.11

[a]Bolded numbers are statistically significant.

DISCUSSION

In this large population-based analysis of U.S. children hospitalized with influenza during 9 recent influenza seasons, I found that influenza resulted in a substantial burden of hospitalizations among children. In my analysis, approximately 1 to 4 out of every 1,000 infants were hospitalized with influenza each year during the study period. Over time, the use of molecular testing increased to 81% which likely led to improved influenza detection among children in more recent seasons. Among hospitalized children, 20% received ICU care, 17%

developed pneumonia, 5% required mechanical ventilation, and deaths were rare; older age was the strongest risk factor for severe outcome among hospitalized children. While use of antivirals and influenza vaccination improved over time, vaccination coverage remained low among hospitalized children of all ages with influenza.

While international data suggest a lower burden of influenza-related deaths and pneumonia,[30, 31] US data identify influenza as one of the most commonly identified viral pathogens in children with pneumonia.[32] My data suggest a substantial burden of both pneumonic and non-pneumonic influenza-related disease in children. Population-based rates of in-hospital all-cause mortality were highest among infants <6 months of age. While mortality rates decreased and plateaued at ≥2 years of age, influenza-associated hospitalization rates continued to decrease until ≥9 years of age. However, among hospitalized children, severe in-hospital outcomes were more common among older children compared with younger children. These trends in severe outcomes across age remained after accounting for comorbidities and other factors. My findings are consistent with a large national surveillance study in Australia that reported children 5–14 years of age hospitalized with influenza were more likely than children under 5 years of age to have ICU admission, mechanical ventilation, and death due to severe influenza complications.[33] These findings may in part be explained by a lower threshold for admitting younger children with influenza for monitoring, leading to more frequent hospitalization of mild cases in younger children (i.e., admission bias).[34]

I observed the highest hospitalization rates among infants <6 months of age. Similar patterns of hospitalization rates by age were observed in a population-based study in Norway.[35] Infants <6 months of age are ineligible for influenza vaccination but can be protected by transfer of maternal antibodies from vaccinated pregnant women.[10, 11] Vaccination coverage among U.S. pregnant women has increased substantially to 61% during the 2019–2020 season.[14, 15] While I could not assess the impact of the improved maternal vaccination coverage through my analysis, as FluSurv-NET does not collect data on maternal vaccination status, ecologic analyses are needed to determine whether population-level vaccine coverage in pregnant women is associated with decreased rates of hospitalization among infants.

Important risk factors for severe outcomes were identified. Children with abnormal upper airway, neurologic disease, or neuromuscular disease were more likely to be admitted to the ICU and require mechanical ventilation. This is consistent with prior data that suggest that neurologic disease and neuromuscular disease are risk factors for severe outcomes of influenza and pneumonia.[36-39] Although asthma was a risk factor for ICU admission and pneumonia, it was less likely to be associated with intubation, perhaps attributable to physicians' practice (e.g., higher threshold for intubation in children with asthma, or use of noninvasive positive pressure ventilation). Similarly, children with diabetes may have been more likely to be admitted to the ICU for glucose control. Diabetes in children is predominantly type 1 and often requires intensive insulin management during acute infection, which may have led to higher rates of ICU admission, not necessarily due to acute respiratory failure or pneumonia. Of interest, hospitalized children with sickle cell disease and immunocompromising status were less likely to have severe outcomes. Collins et al, showed that immunocompromised children hospitalized with influenza were less likely to be admitted to the ICU.[34] I suspect that this could be explained by the heterogenicity of the immunocompromised group as well as possible admission practice bias. The admission practice bias may explain counterintuitive protective effects of other underlying diseases demonstrated in my study.[40]

I saw a substantial shift in influenza testing practices since 2009 towards molecular tests (>80% in the 2018–2019 season) which should have improved the sensitivity and specificity of influenza diagnostic results.[41] I also showed a significant increase in use of antiviral agents over time. However, among hospitalized children younger than 5 years, early antiviral treatment (≤2 days after symptom onset) was suboptimal (31–47%), despite the CDC recommendation for early empiric antiviral treatment in this high risk age group with suspected influenza.[42] This may be due in part to delays in healthcare seeking and low clinical suspicion for influenza among outpatient providers. Although overall use of antiviral agents improved over time, early antiviral treatment could maximize the benefits and potentially prevent some of these adverse outcomes.[43, 44]

Influenza vaccination coverage among hospitalized children over time was suboptimal despite my use of an inclusive definition (≥1 dose of influenza vaccine). I used this definition due to the inability to verify prior influenza seasonal vaccination history (1 or 2 doses). This overestimates the number of children with immunological protection against influenza since two doses are thought to be needed in the first year of influenza vaccination receipt. As expected, vaccination coverage was consistently lower than the national average of US influenza vaccination rates (≥1 dose) in each season (51.0–62.6%).[45] Given that vaccination coverage rates among children were below 50% across all age groups, there is clearly room for improvement, which could improve outcomes and decrease the risk of hospitalization. Additionally, identifying more effective influenza vaccine strategies, including development of new influenza vaccines, could improve influenza prevention in children.[46]

There are several important limitations. First, decisions about influenza testing and hospital admissions were made at the discretion of treating healthcare providers which may have led to under-detection of influenza among hospitalized children as well as admission biases that could not be accounted for in my multivariable models. Provider decisions might have been influenced by the patient's age or comorbidities. Second, although I estimated the burden of influenza by adjusting for influenza testing and test sensitivity, I had limited age-specific data to inform testing practices, particularly in certain seasons. This could have resulted in under or over-adjustment of rates in some influenza seasons. Third, the FluSurv-NET catchment population covers approximately 9% of the U.S. population and findings may not be nationally representative. Finally, while almost all children (97%) had one or more febrile or respiratory symptoms with laboratory-confirmed influenza, I could not exclude other potential reasons for admission (e.g., co-infection) as such data were not available in FluSurv-NET. In addition, the clinical severity of ICU patients was likely heterogenous across institutions within the catchment area, and data on the reason for ICU admission was not available.

In conclusion, there continues to be a substantial burden of influenza-related hospitalizations in all children after the 2009 H1N1 pandemic. Given suboptimal vaccine coverage and low rates of early antiviral use, improved influenza vaccination in children and early antiviral use could improve influenza-associated outcomes in children hospitalized with influenza.

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