Influenza Antiviral Treatment and Length of Stay

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abstract

BACKGROUND: Antiviral treatment is recommended for hospitalized patients with suspected and confirmed influenza, but evidence is limited among children. We evaluated the effect of antiviral treatment on hospital length of stay (LOS) among children hospitalized with influenza.

METHODS: We included children <18 years hospitalized with laboratory-confirmed influenza in the US Influenza Hospitalization Surveillance Network. We collected data for 2 cohorts: 1 with underlying medical conditions not admitted to the ICU ($n = 309$, 2012–2013) and an ICU cohort (including children with and without underlying conditions; $n = 299$, 2010–2011 to 2012–2013). We used a Cox model with antiviral receipt as a time-dependent variable to estimate hazard of discharge and a Kaplan–Meier survival analysis to determine LOS.

RESULTS: Compared with those not receiving antiviral agents, LOS was shorter for those treated ≤2 days after illness onset in both the medical conditions (adjusted hazard ratio: 1.37, $P = .02$) and ICU (adjusted hazard ratio: 1.46, $P = .007$) cohorts, corresponding to 37% and 46% increases in daily discharge probability, respectively. Treatment ≥3 days after illness onset had no significant effect in either cohort. In the medical conditions cohort, median LOS was 3 days for those not treated versus 2 days for those treated ≤2 days after symptom onset ($P = .005$).

CONCLUSIONS: Early antiviral treatment was associated with significantly shorter hospitalizations in children with laboratory-confirmed influenza and high-risk medical conditions or children treated in the ICU. These results support Centers for Disease Control and Prevention recommendations for prompt empiric antiviral treatment in hospitalized patients with suspected or confirmed influenza.

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Dr Campbell conceptualized and designed the study, designed data collection instruments, supervised data collection nationally, provided substantial contributions to analysis and interpretation of the data, drafted the initial manuscript, and critically reviewed and revised the manuscript; Drs Tokars and Reynolds performed analyses of the data, provided substantial contribution to interpretation of data, and critically reviewed and revised the manuscript; Dr Garg conceptualized and designed the study, supervised data collection nationally, provided substantial contributions to analysis and interpretation of the data, and critically reviewed and

WHAT'S KNOWN ON THIS SUBJECT: Antiviral treatment is recommended for hospitalized patients with suspected and confirmed influenza. Because evidence for antiviral treatment in hospitalized children is limited, we evaluated effectiveness of influenza antiviral treatment to reduce length of hospitalization among children with influenza.

WHAT THIS STUDY ADDS: Among children with laboratory-confirmed influenza and underlying medical conditions and children treated in the ICU, early antiviral treatment with oseltamivir within 2 days of symptom onset was associated with a shortened hospital length of stay compared with no or later treatment.

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Influenza causes thousands of hospitalizations and deaths every season in the United States, with children representing a substantial portion of influenza-associated hospitalization burden.[1–4] Influenza antiviral treatment has been recommended for hospitalized patients of all ages with suspected and confirmed influenza since 2009.[5–8] Guidance for antiviral use among children is based on evidence from randomized placebo-controlled trials of treatment of uncomplicated outpatients and observational studies in hospitalized children. Meta-analyses of individual patient data from randomized placebo-controlled trials among outpatient adults[9] and children[10] have revealed that early neuraminidase inhibitor (NAI) treatment (participants randomly assigned within 36–48 hours of symptom onset) reduced duration of illness in treated patients, as well as risk of otitis media in children and hospitalization for any cause in adults. Authors of a meta-analysis of observational data in high-risk adults and children found that NAI treatment of outpatients with influenza A(H1N1)pdm09 reduced the likelihood of hospitalization.[11]

In hospitalized patients, a meta-analysis of data from observational studies revealed a significant reduction in mortality among adults with influenza A(H1N1)pdm09 treated with antiviral agents within 2 days of symptom onset, although treatment was not associated with reduction in mortality in children <16 years.[12] Another study of adults with influenza revealed that oseltamivir treatment received within 6 hours of hospitalization was associated with shorter length of stay (LOS) compared with later treatment.[13]

Despite these studies composed mostly of outpatients or adults, evidence to support antiviral treatment in hospitalized children is limited.[14–16] Therefore, our objective was to evaluate the effectiveness of treatment with NAIs as recommended for hospitalized patients to reduce LOS in hospitalized children with influenza-associated illnesses and comorbidities or severe illness. We used the Influenza Hospitalization Surveillance Network (FluSurv-NET) to identify 2 cohorts for our study: (1) children with underlying medical conditions and (2) children treated in the ICU.

METHODS

Study Setting

FluSurv-NET is a large population-based surveillance network for laboratory-confirmed influenza-associated hospitalizations.[17–19] During the study period, FluSurv-NET included select counties within 10 Emerging Infections Program states (California, Colorado, Connecticut, Georgia, Maryland, Minnesota, New Mexico, New York, Oregon, and Tennessee)[18] and 5 Influenza Hospitalization Surveillance Project states (Iowa, Michigan, Ohio, Rhode Island, and Utah). Influenza cases in FluSurv-NET were defined as residents of a catchment area hospitalized ≤14 days after a positive influenza test result.[17,18] Influenza testing was performed at clinician discretion by rapid influenza diagnostic test, culture, fluorescent antibody staining, and/or molecular assays.[17,18]

Study Population

We a priori limited our study to 2 cohorts of children <18 years: (1) the medical conditions cohort: children with underlying medical conditions and not admitted or transferred to the ICU, and (2) the ICU cohort: children admitted or transferred to the ICU (including those with and without underlying conditions). Although the original protocol included the 2012–2013 season for both cohorts, to improve sample size we added 2010–2011 and 2011–2012 to the ICU cohort. In all 3 US influenza seasons, influenza A(H3N2) viruses were predominant overall, but influenza B viruses and influenza A(H1N1)pdm09 viruses also circulated.[20] Because we had data for the start date but not specific time of initiation of antiviral treatment or discharge, we chose these cohorts to evaluate children most likely to have severe illness and therefore sufficiently long hospitalizations to assess antiviral effect.

Exclusion criteria included missing data on receipt of antiviral treatment or symptom onset, symptom onset after or ≥3 days before admission, LOS <1 day, and surveillance officer report of antiviral treatment before symptom onset or hospitalization (patients initiating treatment in the emergency department may not have been excluded; therefore, 7 patients with recorded antiviral start 1 day before admission were included on the basis of reviewer determination). Because unpublished data from FluSurv-NET revealed that median length of hospitalization for children with asthma was short (2 days) compared with children with other underlying conditions (4 days), we excluded children with asthma alone from the medical conditions cohort. Because of the short LOS, we did not think we would be able to discern a significant difference in days of hospitalization.

FluSurv-NET surveillance activities and this study were considered consistent with routine public health surveillance by the Human Research Protection Office at the Centers for Disease Control and Prevention (CDC). FluSurv-NET sites obtained human subjects and ethics approvals

from state health department and academic partner institutional review boards as indicated.

Data Collection

For all children, surveillance officers routinely performed retrospective medical record review to obtain information about demographics including race and ethnicity, vaccination history, medical conditions, testing results, hospital course, admission and discharge diagnoses, and antiviral treatment (Supplemental Fig 3). For reason for admission, surveillance officers were instructed to select categories that applied on the basis of diagnoses in the chart (Supplemental Fig 3). For these cohorts during the study period, routine surveillance data were augmented by retrospective chart abstraction to a supplemental case report form (Supplemental Fig 4) including details regarding antiviral treatment before admission, additional underlying medical conditions, clinical signs and symptoms of respiratory distress and mental status change, and additional interventions during hospitalization.

Statistical Analysis

We explored categorical variables with percentages and continuous variables with medians and ranges. We assessed the hazard of discharge using the Cox proportional hazard model with antiviral receipt analyzed as a time-dependent variable. Antiviral was coded as "no" for all days up to the day antiviral was started (or for all days if antiviral agents were never started) and "yes" on all subsequent days until discharge. We categorized antiviral receipt by number of days after symptom onset; after exploratory analyses, we grouped antiviral receipt as started 0 to 2 days versus ≥3 days after symptom onset. The primary analysis included children with LOS ≥2 days and assumed that antiviral effect began on day after antiviral start. Because of the latter assumption, those started on antiviral agents on day of discharge were analyzed as not receiving antiviral agents. For the ICU cohort, we treated deaths as a competing event; no deaths occurred in the medical conditions cohort.

We evaluated individual effects of potentially confounding variables (ie, patient characteristics and clinical findings) in single-variable Cox models. We then evaluated the effect of antiviral receipt in multivariable models. We considered variables with $P < .2$ in single-variable models and retained them in the multivariable model if $P < .1$. We assessed the proportional hazards assumption by including an interaction term between hospital day and antiviral receipt. We performed supplementary analyses including children hospitalized for ≥1 day; and including surveillance site as a random effect.

Because mean and median LOS cannot be determined in models with time-dependent covariates, for the medical conditions cohort, we used Kaplan–Meier survival analysis to determine these values by treatment group. We created a data set in which antiviral receipt could be validly evaluated as a time-invariate variable. The treated group included children who had been started on antiviral agents on or before day of admission and ≤2 days after illness onset. The untreated group included those never started on antiviral agents, started only on day of discharge, and started during admission (these were censored on day after antiviral start). The number needed to treat for 1 additional patient to be discharged by hospital day 3 was calculated as $1/(S3u - S3t)$, where the probabilities of continued hospital stay at 3 days = S3u (untreated) and S3t (treated).

Data were missing more often for the ICU cohort. To facilitate multivariable analysis of ICU cohort data, we used multiple imputation of missing values, generated 100 imputed data sets, and created a summary of analysis of the 100 (Supplemental Information). We performed all analyses using SAS version 9.4 (SAS Institute, Cary, NC), using the phreg procedure for Cox models, the mi and mianalyze procedures for multiple imputation and summarization, and the lifetest procedure for Kaplan–Meier analyses.

RESULTS

Medical Conditions Cohort

During the 2012–2013 season, there were 1924 influenza-associated hospitalizations among children <18 years (Fig 1A). Of the 1924 hospitalizations, 1039 (54%) patients had ≥1 underlying medical condition. After applying exclusions, 309 patients from 52 centers (range 1–30 per center) met criteria for analysis. Median time from symptom onset to admission was 1 day (range 0–2 days) and median LOS was 3 days (range 2–22 days). Among 252 (82%) receiving antiviral agents, all received oseltamivir; median (range) time from symptom onset to antiviral start was 2 (0–10) days and from admission to antiviral start was 1 (−1 to 10) days. No children in this cohort died.

Among the 309 children, most were 5 to 17 years old (51%), admitted for acute respiratory illness (74%, Table 1) and had an abnormal chest radiograph (54%, Table 2). In univariable Cox models, LOS was significantly longer for children with chronic lung disease (hazard ratio [HR] of discharge 0.59, Table 1),

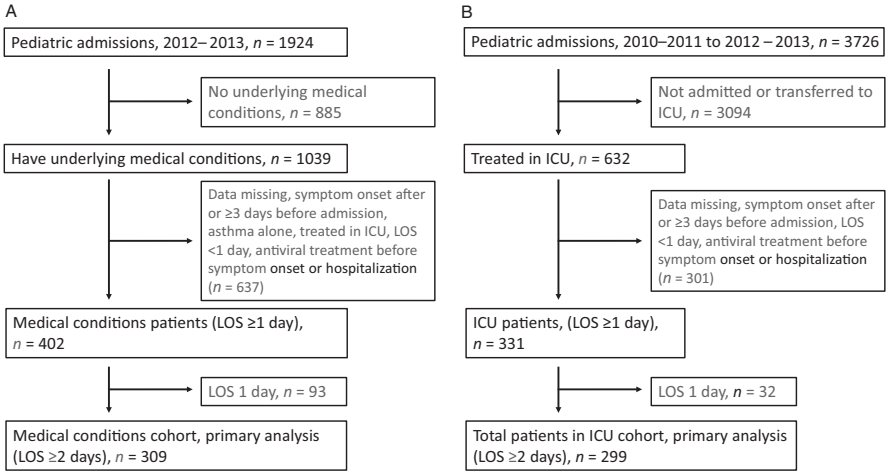

FIGURE 1
Flowchart revealing children with laboratory-confirmed influenza-associated hospitalization in FluSurv-NET comprising final analytic data sets for A, the underlying medical conditions cohort (2012–2013); and B, ICU cohort (2010–2011, 2011–2012, and 2012–2013).

receiving supplemental oxygen (HR: 0.63–0.71) or respiratory therapy treatments (HR: 0.75), and diagnosed with pneumonia (HR: 0.66, Table 2). Antivirals were never started in 73 (24%), started ≤2 days after symptom onset in 199 (64%), and started ≥3 days after symptom onset in 37 (12%); no

TABLE 1 Patient Characteristics and Their Effect on Hospital Discharge Among Children in the Medical Conditions and ICU Cohorts, FluSurv-NET

	Medical Conditions Cohort (n = 309)				ICU Cohort (n = 299)			
Variable	Total	No. (%) with characteristic	HR	P	Total	No. (%) with characteristic	HR	P
Age category, y								
<1	309	57 (18)	1.13	.39	299	74 (25)	0.94	.45
1–4	309	94 (30)	1.19	n/a	299	115 (38)	1.11	n/a
5–17	309	158 (51)	ref	n/a	299	110 (37)	ref	n/a
Male sex	309	164 (53)	1.03	.78	299	162 (54)	1.00	.99
Race and ethnicity								
Hispanic	309	57 (18)	1.10	.65	299	62 (21)	0.99	>.99
White, non-Hispanic	309	96 (31)	0.96	n/a	299	104 (35)	1.01	n/a
Black, non-Hispanic	309	110 (36)	1.14	n/a	299	87 (29)	1.00	n/a
Other, non-Hispanic (including race unknown)	309	46 (15)	ref	n/a	299	46 (15)	ref	n/a
Underlying medical condition								
Any	309	309 (100)	n/a	n/a	286	206 (72)	0.85	.21
Asthma or reactive airways disease	309	77 (25)	0.81	.11	299	87 (29)	0.92	.52
Chronic lung disease	309	45 (15)	0.59[a]	<.01[a]	299	37 (12)	0.90	.38
Cardiovascular disease	309	47 (15)	0.84	.27	299	25 (8)	0.78	.26
Neurologic or neuromuscular	309	104 (34)	0.93	.53	299	90 (30)	0.77[a]	.01[a]
Immunocompromised condition	309	62 (20)	0.95	.69	299	16 (5)	0.72[a]	.05[a]
Prematurity[b]	113	37 (33)	0.89	.58	47	21 (45)	0.77	.37
Other[c]	309	176 (57)	1.10	.43	299	53 (18)	0.67[a]	<.01[a]
Received current season influenza vaccination	296	143 (48)	0.88	.29	186	68 (37)	0.98	.87
Reason for current hospital admission (per medical record)								
Acute respiratory illness[d]	309	230 (74)	1.05	.71	299	210 (70)	0.92	.51
Asthma and/or COPD exacerbation	309	14 (5)	0.85	.55	299	38 (13)	1.19	.29
Pneumonia	309	5 (2)	0.69	.40	299	18 (6)	1.17	.26
Other respiratory or cardiac condition	309	37 (12)	1.07	.71	299	69 (23)	0.96	.76
Fever alone	309	38 (12)	1.18	.35	299	22 (7)	1.30	.13
Initial admission to ICU	0	n/a	n/a	n/a	289	247 (85)	1.39[a]	<.01[a]

Total denotes number of nonmissing values; HRs were determined by using a single-variable Cox model; HRs <1 indicate a lower risk of discharge and longer length of hospital stay and vice versa. COPD, chronic obstructive pulmonary disease; n/a, not applicable; ref, reference category.
[a] Denotes a statistically significant result.
[b] Recorded only for children <2 y old.
[c] Includes chronic metabolic disease, blood disorder, and renal and liver disease.
[d] Per the case report form instructions, acute respiratory illness was defined as bronchitis, cough, influenza, influenza-like disease, upper respiratory infection, respiratory infection, rhinorrhea or runny nose, viral syndrome, viral upper respiratory illness, or fever and any of the previously listed symptoms.

TABLE 2 Clinical Findings and Their Effects on Hospital Discharge Among Children in the Medical Conditions or ICU Cohorts, FluSurv-NET

	Medical Conditions Cohort (n = 309)				ICU Cohort (n = 299)			
Variable	Total	No. (%) With Characteristic	HR	P	Total	No. (%) With Characteristic	HR	P
Clinical findings within first 24 h of admission								
Respiratory findings								
Dyspnea	304	72 (24)	0.80	.11	288	165 (57)	0.84	.12
Apnea	304	6 (2)	1.43	.39	287	25 (9)	0.70[a]	.05[a]
Wheezing	303	67 (22)	0.97	.85	290	99 (34)	1.16	.18
Chest wall retractions (sub- or intercostal)	302	41 (14)	0.86	.39	289	106 (37)	1.11	.31
Nasal flaring	304	7 (2)	0.70	.36	284	37 (13)	1.04	.73
Cyanosis	304	12 (4)	1.38	.27	285	30 (11)	0.72	.07
Grunting	300	9 (3)	1.04	.91	284	24 (8)	1.07	.67
Mental status change								
Lethargy or decreased activity	305	102 (33)	0.90	.41	283	99 (35)	0.98	.85
Confusion or delirium	305	17 (6)	1.03	.90	285	29 (10)	0.65[a]	.02[a]
Unconscious	306	5 (2)	2.11	.10	286	15 (5)	0.63	.15
Maximum respiratory rate higher than median	300	147 (49)	0.95	.69	288	142 (49)	1.03	.80
Minimum oxygen saturation <92% on room air	286	63 (22)	0.84	.21	254	125 (49)	0.79[a]	.05[a]
Supplemental oxygen	307	104 (34)	0.71[a]	.01[a]	296	230 (78)	0.60[a]	<.01[a]
Invasive mechanical ventilation	102	0 (0)	n/a	n/a	222	80 (36)	0.42[a]	<.01[a]
Respiratory/breathing treatment	303	111 (37)	0.84	.13	292	175 (60)	0.85	.17
Clinical findings at 24 h after admission								
Supplemental oxygen	306	71 (23)	0.63[a]	<.01[a]	293	196 (67)	0.49[a]	<.01[a]
Invasive mechanical ventilation	66	1 (2)	0.35	.30	192	70 (36)	0.40[a]	<.01[a]
Respiratory/breathing treatment	302	99 (33)	0.75[a]	.02[a]	277	148 (53)	0.83	.12
Chest radiograph within 3 d of admission								
Abnormal	309	168 (54)	0.97	.19	299	146 (49)	0.79[a]	.01[a]
Normal	309	58 (19)	0.75	n/a	299	125 (42)	0.60[a]	n/a
Not performed	309	83 (27)	ref	n/a	299	28 (9)	ref[a]	n/a
Pneumonia	309	27 (9)	0.66[a]	.04[a]	293	72 (25)	0.71[a]	<.01[a]
Extracorporeal membranous oxygenation	309	0 (0)	n/a	n/a	296	5 (2)	0.13[a]	<.01[a]

Total denotes number of total nonmissing values; HRs were determined by using a single-variable Cox model; HRs <1 indicate a lower risk of discharge and longer length of hospital stay and vice versa. n/a, not applicable. ref, reference category.

[a] Denotes a statistically significant result.

patient characteristics or clinical findings were associated with promptness of antiviral start (Supplemental Table 4).

Modeling of receipt on individual days revealed significant effects for antiviral agents started 1 to 2 days (HR: 1.41–1.43) but not ≥3 days (HR: 0.89–1.20) after symptom onset (Table 3, Model 1a). In Model 2a we collapsed categories to show that antiviral agents were associated with a shorter LOS when started ≤2 days (HR: 1.43) but not ≥3 days (HR: 1.09) after symptom onset. Controlling for potentially confounding variables in Model 3a confirmed a shorter LOS when antiviral agents were started ≤2 days after symptom onset (adjusted hazard ratio [aHR]: 1.37, P = .02, corresponding to a 37% increase in discharge probability per day) and revealed a longer LOS for children with chronic lung disease (aHR: 0.65) and those receiving supplemental oxygen 24 hours after admission (aHR: 0.67). The effect of antiviral receipt ≤2 days after symptom onset did not violate the proportional hazards assumption (P = .39) and was similar when including children with LOS ≥1 day (aHR: 1.47, P = .001) and controlling for site as a random effect (aHR: 1.36, P = .03). LOS was significantly shorter for the treatment group (mean 3.5 vs 4.6 days, median 2 vs 3 days, logrank P = .005; Fig 2). One additional patient would be discharged by hospital day 3 for each 5.8 (95% confidence limits, 3.3–26.7) patients promptly started on antiviral agents.

ICU Cohort

Over the expanded 3-season study period, of 3726 total influenza-associated hospitalizations among children, 632 (17%) patients were admitted to the ICU (Fig 1B). After exclusions, the final ICU cohort included 299 children reported from 43 centers (range 1–26 per center). Among 221 (74%) receiving antiviral agents, 150 (68%) received oseltamivir only, 2 (1%) received oseltamivir and zanamivir, and the remainder had missing data. Median (range) LOS was 5 (2–73) days; among the 221 started on antiviral agents, time from symptom onset to

TABLE 3 Cox Models of Antiviral Effect on Hospital Discharge Among Children in the Medical Conditions or ICU Cohorts, FluSurv-NET

		Medical Conditions Cohort (n = 309)				ICU Cohort (n = 299)			
Model	Antiviral Use	No. Patients	HR	95% Confidence Interval	P	No. Patients	HR	95% Confidence Interval	P
1a, 1b	None[a]	73	ref	n/a	n/a	86	ref	n/a	n/a
	Started on day of illness onset	34	1.48	0.98–2.23	.06	36	1.11	0.72–1.70	.64
	Started 1 d after illness onset	89	1.43	1.05–1.94	.02	72	0.99	0.74–1.33	.95
	Started 2 d after illness onset	76	1.41	1.02–1.95	.03	60	1.11	0.83–1.49	.48
	Started 3 d after illness onset	24	1.20	0.76–1.91	.44	28	1.05	0.75–1.47	.79
	Started ≥4 d after illness onset	13	0.89	0.46–1.71	.73	17	1.08	0.65–1.79	.77
2a, 2b	None[a]	73	ref	n/a	n/a	86	ref	n/a	n/a
	Started day 0–2 after illness onset	199	1.43	1.09–1.87	.01	168	1.05	0.82–1.35	.67
	Started day ≥3 d after illness onset	37	1.09	0.72–1.65	.68	45	1.06	0.77–1.46	.72
3a, 3b	None[a]	72	ref	n/a[b]	n/a	86	ref	n/a[c]	n/a
	Started day 0–2 after illness onset	198	1.37	1.05–1.80	.02	168	1.46	1.11–1.92	.007
	Started day ≥3 d after illness onset	36	1.02	0.67–1.54	.94	45	1.20	0.85–1.69	.29

Models 1a, 1b, 2a, 2b are unadjusted, whereas models 3a and 3b are adjusted for confounding effects (see footnote below); HRs were determined by using the Cox model with time-dependent values for antiviral treatment; HRs <1 indicate a lower risk of discharge and longer length of hospital stay and vice versa. n/a, not applicable; ref, reference category.

[a] "None" includes 57 never started on antiviral agents and 16 started on the day of discharge (73 total, medical conditions cohort); and 78 never started and 8 started on discharge (86 total, ICU cohort).

[b] Model 3a is based on 306 children; adjusted for chronic lung disease (aHR: 0.65) and supplemental oxygen 24 h after admission (aHR: 0.67).

[c] Model 3b is based on 100 data sets with missing data imputed (Supplemental Information); adjusted for other underlying condition (chronic metabolic disease, blood disorder, renal and liver disease; aHR: 0.69), cyanosis (aHR: 0.66), initial admission to ICU (aHR: 1.94), invasive mechanical ventilation at ICU admission (aHR: 0.61) and 24 h after ICU admission (aHR: 0.65), supplemental oxygen 24 h after admission (aHR: 0.57), pneumonia diagnosis (aHR: 0.76), and treatment with extracorporeal membrane oxygenation (aHR: 0.14).

antiviral start was 2 (0–15) days and from admission to antiviral start was 1 (−1 to 15) days. Eight (2.7%) patients died.

Among the 299 children, most had ≥1 chronic condition (72%), were admitted for acute respiratory illness (70%, Table 1), had dyspnea (57%), and received supplemental oxygen (67% to 78%) and respiratory therapy (53% to 60%, Table 2). Univariable Cox models revealed that several variables, particularly those relating to mechanical ventilation and oxygen receipt, were associated with longer LOS (Tables 1, 2). Antivirals were never started in 86 (29%), started ≤2 days after symptom onset in 168 (56%), and started ≥3 days after

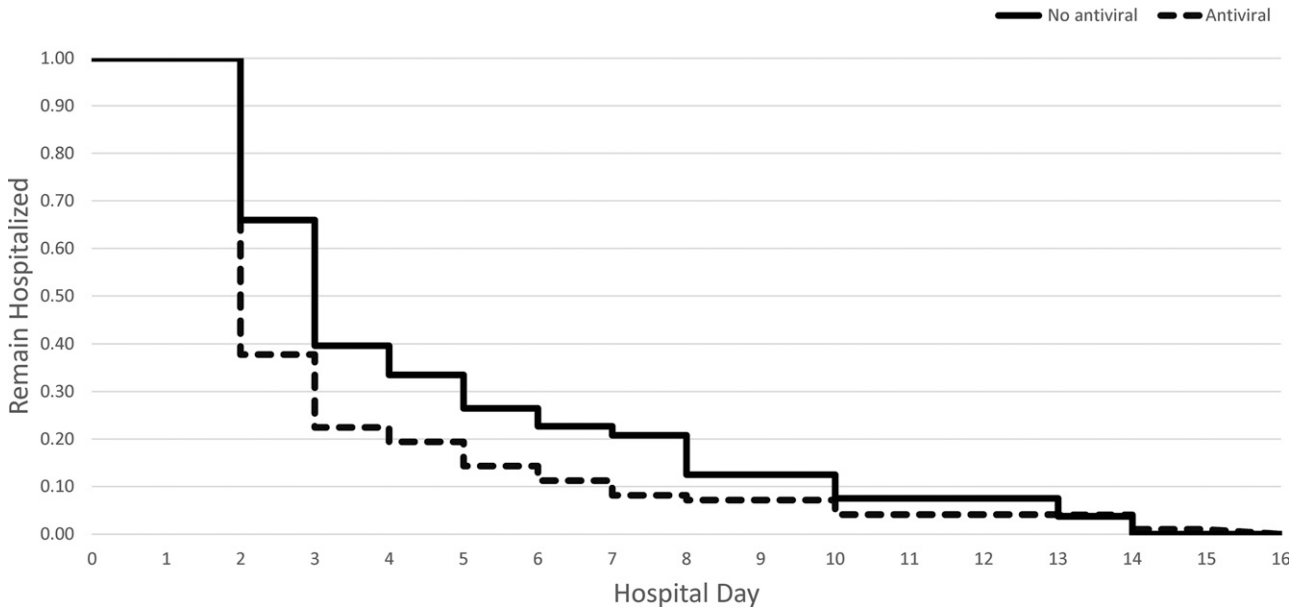

FIGURE 2
Kaplan–Meier analysis of hospital LOS by antiviral treatment among children with laboratory-confirmed influenza-associated hospitalization in the medical conditions cohort, FluSurv-NET (n = 98 treated, 211 not treated; 2012–2013). The treatment group included 98 children started on antiviral agents on the day of admission and ≤2 days after illness onset. The no treatment group included 57 never started on antiviral agents, 16 started on day of discharge and 138 started during admission and censored on the day of antiviral start (211 total).

symptom onset in 45 (15%); several patient and clinical characteristics were associated with promptness of antiviral start (Supplemental Table 5).

Initial unadjusted models revealed no effect of antiviral agents (Table 3, Models 1b, 2b). Sixteen variables tested in multivariable analyses had ≥1 missing value (range 1% to 36%, Supplemental Information). After imputing missing data, other underlying conditions, cyanosis, mechanical ventilation, oxygen therapy, pneumonia diagnosis, and extracorporeal membrane oxygenation therapy were associated with longer LOS; initial admission to the ICU (versus transfer after admission) was associated with shorter LOS (Table 3, Model 3b). After adjusting for these variables, receipt of antiviral agents ≤2 days after symptom onset was associated with a shorter LOS (aHR: 1.46, $P = .007$, a 46% increase in discharge probability per day). This estimate did not violate the proportional hazards assumption ($P = .17$) and was similar when including children with LOS ≥1 day (aHR: 1.60, $P < .001$) and controlling for site as a random effect (aHR: 1.41, $P = .02$).

DISCUSSION

Using data from a large surveillance network documenting hospitalized children with laboratory-confirmed influenza, we found among children with underlying medical conditions and children treated in the ICU that early antiviral treatment, almost exclusively with oseltamivir, within 2 days of symptom onset was associated with a shortened hospital LOS compared with no or later treatment. Among children with medical conditions, mean and median LOS was ∼1 day shorter in those treated within 2 days. Later treatment at ≥3 days after illness onset had no significant effect.

To study antiviral effects, we used Cox models with time-dependent covariates. This allowed us to analyze a child as "not on antivirals" up to the day antiviral agents were started and "on antivirals" beginning the day after antiviral start, enabling a careful assessment of antiviral effect. Analyses that compare LOS by time that antiviral agents are started after symptom onset can be biased, because only patients with a longer LOS can have antiviral agents started a longer time after symptom onset.

In the medical conditions cohort, controlling for confounding variables had little effect, and antiviral agents started ≤2 days after illness onset were associated with a shorter LOS in both unadjusted (HR: 1.43) and adjusted (aHR: 1.37) analyses. In contrast, in the ICU cohort, there were several potential confounding variables, some with missing data, and antiviral agents had no effect in unadjusted analyses. However, after imputation of missing data, in a multivariable model controlling for measured confounding variables, we found that antiviral agents started ≤2 days after illness onset were significantly associated with a shorter hospital LOS (summary aHR: 1.36). The aHRs were strikingly similar in the 2 cohorts.

We excluded children admitted ≥3 days after illness onset because they might be more likely to have complications such as secondary bacterial infections that are unresponsive to antiviral agents and clinical trials showed that optimal timing for NAI use is within 2 days of illness onset. Among those we studied, 24% to 29% were never started on antiviral agents, 56% to 64% were started 0 to 2 days, and 12% to 15% were started ≥3 days after illness onset. Among those otherwise eligible for the study, only 27% (medical conditions cohort) and 31% (ICU cohort) were admitted ≥3 days after symptom onset. Thus, if treated on hospital admission, most of the children would have received antiviral treatment early in the course of illness and might have received clinical benefit that contributed to a shorter LOS. Our data support CDC recommendations for early empiric therapy of those hospitalized with confirmed or suspected influenza without awaiting results of laboratory testing.[7,8] However, the use of sensitive molecular diagnostic testing with rapid turnaround has been reported to improve the proportion who receive recommended early antiviral therapy,[21,22] and molecular testing is recommended for all hospitalized patients with suspected influenza.[7,23]

NAIs were the recommended influenza antiviral drugs during the study period.[24] Our findings are consistent with the few observational studies in which researchers have reported improved outcomes in children receiving early compared with later NAI treatment of influenza.[14,15] Researchers in 1 study used administrative data and propensity score matching to compare outcomes of children directly admitted to an ICU with influenza and treated with oseltamivir within 24 hours of admission with untreated children and showed that total hospital stay was shorter in the treated group.[14] In another study, researchers analyzed California surveillance data and found that receipt of NAI treatment was associated with decreased mortality among children hospitalized in the ICU with influenza, although these results are potentially subject to immortal time bias because many of the children who died in the untreated group may not have had the opportunity to receive treatment before death.[15]

Our results did not reveal beneficial effect in the small number of children treated ≥3 days after symptom onset. However, there are data suggestive of some benefit from antiviral treatment after 2 days in adults.[1,25–29] Also, a randomized clinical trial in children with uncomplicated influenza revealed a modest reduction in symptom duration and influenza virus shedding in patients treated after 48 hours; post hoc analysis suggested that oseltamivir treatment initiated 72 hours after illness onset reduced symptoms by 1 day compared with placebo.[30] CDC recommends starting antiviral agents as soon as possible in all hospitalized patients without consideration of time from symptom onset.

Our study has some limitations. We limited our analysis to 2 cohorts of hospitalized children likely to have the most severe illness. This focused on children with the most potential benefit from antiviral agents but did not allow us to assess all hospitalized children. The medical conditions cohort analysis was limited by having data for only 1 season. Our study is observational, and we may not have been able to identify and control for all potential confounders among treatment groups. Missing data were a problem for the ICU cohort, and our result is based on adjustment for multiple variables after imputation of missing values; these analyses assume that data were missing at random and may not be valid if this assumption was incorrect. Although data on specific antiviral received were frequently missing, these children most likely received oseltamivir. Regarding timing of treatment, we stratified by days instead of hours, because more detailed timing data were unavailable. Information regarding timing of antiviral initiation was limited by retrospective manual chart abstraction by trained surveillance officers. Future studies of hospitalized children may benefit from more detailed timing data, potentially combined with symptom diaries in hospitalized children to provide additional evidence for medication effects. Finally, we were not powered to assess interactions among timing variables (eg, onset to treatment and onset to admission).

CONCLUSIONS

These data suggest benefit of early antiviral treatment of hospitalized children with laboratory-confirmed influenza. Efforts should be directed to encourage families of children at higher risk for complications for influenza to seek care early in the course of influenza-like illness.[8] Additional studies in non–high-risk and non-ICU patients will be important, and further study is warranted to understand clinical factors that influence providers to treat for influenza in hospitalized children.

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ABBREVIATIONS

aHR: adjusted hazard ratio
FluSurv-NET: Influenza Hospitalization Surveillance Network
HR: hazard ratio
LOS: length of stay
NAI: neuraminidase inhibitor

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REFERENCES

1. Rolfes MA, Foppa IM, Garg S, et al. Annual estimates of the burden of seasonal influenza in the United States: A tool for strengthening influenza surveillance and preparedness. *Influenza Other Respir Viruses*. 2018;12(1):132–137
2. Centers for Disease Control and Prevention. Estimated influenza illnesses, medical visits, hospitalizations, and deaths in the United States — 2017–2018 influenza season. Available at: https://www.cdc.gov/flu/about/burden/2017-2018.htm. 2018. Accessed December 28, 2020
3. Centers for Disease Control and Prevention. Burden estimates for the 2016-2017 influenza season. Available at: https://www.cdc.gov/flu/about/burden/2016-2017.html. 2017. Accessed December 28, 2020
4. Centers for Disease Control and Prevention. Estimated influenza illnesses, medical visits, hospitalizations, and deaths in the United States — 2018–2019 influenza season. Available at: https://www.cdc.gov/flu/about/burden/2018-2019.html. 2020. Accessed December 28, 2020
5. Harper SA, Bradley JS, Englund JA, et al; Expert Panel of the Infectious Diseases Society of America. Seasonal influenza in adults and children–diagnosis, treatment, chemoprophylaxis, and institutional outbreak management: clinical practice guidelines of the Infectious Diseases Society of America. *Clin Infect Dis*. 2009;48(8):1003–1032
6. Garg S, Fry AM, Patton M, Fiore AE, Finelli L. Antiviral treatment of influenza in children. *Pediatr Infect Dis J*. 2012;31(2):e43–e51
7. Uyeki TM, Bernstein HH, Bradley JS, et al. Clinical practice guidelines by the Infectious Diseases Society of America: 2018 update on diagnosis, treatment, chemoprophylaxis, and institutional outbreak management of seasonal influenza. *Clin Infect Dis*. 2019;68(6):895–902
8. Centers for Disease Control and Prevention. Influenza antiviral medications: summary for clinicians. Available at: https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm. Accessed December 28, 2020
9. Dobson J, Whitley RJ, Pocock S, Monto AS. Oseltamivir treatment for influenza in adults: a meta-analysis of randomised controlled trials. *Lancet*. 2015;385(9979):1729–1737
10. Malosh RE, Martin ET, Ortiz JR, Monto AS. The risk of lower respiratory tract infection following influenza virus infection: a systematic and narrative review. *Vaccine*. 2018;36(1):141–147
11. Venkatesan S, Myles PR, Leonardi-Bee J, et al. Impact of outpatient neuraminidase inhibitor treatment in patients infected with influenza A(H1N1)pdm09 at high risk of hospitalization: an individual participant data metaanalysis. *Clin Infect Dis*. 2017;64(10):1328–1334
12. Muthuri SG, Venkatesan S, Myles PR, et al; PRIDE Consortium Investigators. Effectiveness of neuraminidase inhibitors in reducing mortality in patients admitted to hospital with influenza A H1N1pdm09 virus infection: a meta-analysis of individual participant data. *Lancet Respir Med*. 2014;2(5):395–404
13. Katzen J, Kohn R, Houk JL, Ison MG. Early oseltamivir after hospital admission is associated with shortened hospitalization: a 5-year analysis of oseltamivir timing and clinical outcomes. *Clin Infect Dis*. 2019;69(1):52–58
14. Coffin SE, Leckerman K, Keren R, Hall M, Localio R, Zaoutis TE. Oseltamivir shortens hospital stays of critically ill children hospitalized with seasonal influenza: a retrospective cohort study. *Pediatr Infect Dis J*. 2011;30(11):962–966
15. Louie JK, Yang S, Samuel MC, Uyeki TM, Schechter R. Neuraminidase inhibitors for critically ill children with influenza. *Pediatrics*. 2013;132(6):e1539–e1545
16. Eşki A, Öztürk GK, Gülen F, Çiçek C, Demir E. Risk factors for influenza virus related severe lower respiratory tract infection in children. *Pediatr Infect Dis J*. 2019;38(11):1090–1095
17. Appiah GD, Chaves SS, Kirley PD, et al. Increased antiviral treatment among hospitalized children and adults with laboratory-confirmed influenza, 2010-2015. *Clin Infect Dis*. 2017;64(3):364–367
18. Chaves SS, Lynfield R, Lindegren ML, Bresee J, Finelli L. The US Influenza Hospitalization Surveillance Network. *Emerg Infect Dis*. 2015;21(9):1543–1550
19. Centers for Disease Control and Prevention. Influenza Hospitalization Surveillance Network (FluSurv-NET). Available at: https://www.cdc.gov/flu/weekly/influenza-hospitalization-surveillance.htm. Accessed December 28, 2020
20. Centers for Disease Control and Prevention. FluView past weekly surveillance reports. Available at: https://www.cdc.gov/flu/weekly/pastreports.htm. Accessed December 28, 2020
21. Lee BR, Hassan F, Jackson MA, Selvarangan R. Impact of multiplex molecular assay turn-around-time on antibiotic

utilization and clinical management of hospitalized children with acute respiratory tract infections. *J Clin Virol*. 2019;110:11–16

22. Vos LM, Bruning AHL, Reitsma JB, et al. Rapid molecular tests for influenza, respiratory syncytial virus, and other respiratory viruses: a systematic review of diagnostic accuracy and clinical impact studies. *Clin Infect Dis*. 2019;69(7):1243–1253
23. Centers for Disease Control and Prevention. Overview of influenza testing methods. Available at: https://www.cdc.gov/flu/professionals/diagnosis/overview-testing-methods.htm. Accessed December 28, 2020
24. Fiore AE, Fry A, Shay D, Gubareva L, Bresee JS, Uyeki TM; Centers for Disease Control and Prevention (CDC). Antiviral agents for the treatment and chemoprophylaxis of influenza — recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2011;60(1):1–24
25. Aoki FY, Macleod MD, Paggiaro P, et al; IMPACT Study Group. Early administration of oral oseltamivir increases the benefits of influenza treatment. *J Antimicrob Chemother*. 2003;51(1):123–129
26. Louie JK, Yang S, Acosta M, et al. Treatment with neuraminidase inhibitors for critically ill patients with influenza A (H1N1)pdm09. *Clin Infect Dis*. 2012;55(9):1198–1204
27. Yu H, Feng Z, Uyeki TM, et al. Risk factors for severe illness with 2009 pandemic influenza A (H1N1) virus infection in China. *Clin Infect Dis*. 2011;52(4):457–465
28. McGeer A, Green KA, Plevneshi A, et al; Toronto Invasive Bacterial Diseases Network. Antiviral therapy and outcomes of influenza requiring hospitalization in Ontario, Canada. *Clin Infect Dis*. 2007;45(12):1568–1575
29. Siston AM, Rasmussen SA, Honein MA, et al; Pandemic H1N1 Influenza in Pregnancy Working Group. Pandemic 2009 influenza A(H1N1) virus illness among pregnant women in the United States. *JAMA*. 2010;303(15):1517–1525
30. Fry AM, Goswami D, Nahar K, et al. Efficacy of oseltamivir treatment started within 5 days of symptom onset to reduce influenza illness duration and virus shedding in an urban setting in Bangladesh: a randomised placebo-controlled trial. *Lancet Infect Dis*. 2014;14(2):109–118

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