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Child, Household, and Caregiver Characteristics Associated with Hospitalization for Influenza Among Children 6–59 Months of Age

An Emerging Infections Program Study

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Background: Young children are at increased risk of severe outcomes from influenza illness, including hospitalization. We conducted a case-control study to identify risk factors for influenza-associated hospitalizations among children in US Emerging Infections Program sites.

Methods: Cases were children 6–59 months of age hospitalized for laboratory-confirmed influenza infections during 2005–2008. Age- and zip-code-matched controls were enrolled. Data on child, caregiver and household characteristics were collected from parents and medical records. Conditional logistic regression was used to identify independent risk factors

for hospitalization.

Results: We enrolled 290 (64%) of 454 eligible cases and 1089 (49%) of 2204 eligible controls. Risk for influenza hospitalization increased with maternal age <26 years [odds ratio (OR): 1.8, 95% confidence interval (CI): 1.1–2.9]; household income below the poverty threshold (OR: 2.2, 95% CI: 1.4–3.6); smoking by >50% of household members (OR: 2.9, 95% CI: 1.4–6.6); lack of household influenza vaccination (OR: 1.8, 95% CI: 1.2–2.5) and presence of chronic illnesses, including hematologic/oncologic (OR: 11.8, 95% CI: 4.5–31.0), pulmonary (OR: 2.9, 95% CI: 1.9–4.4) and neurologic (OR: 3.8, 95% CI: 1.6–9.2) conditions. Full influenza immunization decreased the risk among children 6–23 months of age (OR: 0.5, 95% CI: 0.3–0.9) but not among those 24–59 months of age (OR: 1.5, 95% CI: 0.8–3.0; *P* value for difference = 0.01).

Conclusions: Chronic illnesses, young maternal age, poverty, household smoking and lack of household influenza vaccination increased the risk of influenza hospitalization. These characteristics may help providers to identify young children who are at greatest risk for severe outcomes from influenza illness.

Key Words: influenza, risk factors, hospitalization, children, household

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Compared with older children and adults, young children, especially those <2 years of age, are at increased risk for influenza-associated complications, including hospitalization.^{1–6} Characteristics previously identified to increase the risk of severe outcomes from seasonal influenza illness include male gender,⁴ age <12 months,⁴ gestational age <37 weeks⁷ and underlying medical conditions including pulmonary,^{7,8} neurologic/neuromuscular disease^{8,9} or cardiac conditions.^{7–9}

Few studies have had sufficient power to assess whether social and economic factors such as daycare attendance, caregiver education level, crowding and poverty increase the risk of severe outcomes. The Emerging Infections Program (EIP)¹⁰ of the US Centers for Disease Control and Prevention (CDC) is a collaboration of federal, state and local academic and public health partners that conducts population-based surveillance in 10 states, including surveillance for laboratory-confirmed pediatric influenza hospitalizations. During 2005–2008, the EIP network conducted a case-control study to assess the vaccine effectiveness of trivalent-inactivated vaccine in preventing influenza-associated hospitalizations among young children. In this analysis, we sought to identify child, household and caregiver factors associated with hospitalizations because of laboratory-confirmed influenza among children who are recommended to receive the influenza vaccine (children 6–59 months of age).

MATERIALS AND METHODS

Study Population

The study population was drawn from children residing in selected counties in 9 states that participated in EIP surveillance for influenza hospitalizations: California, Colorado, Connecticut, Georgia, Minnesota, New Mexico, New York, Oregon and Tennessee (see Appendix). The catchment area represented approximately 9% of all US children <5 years of age, and the counties from which study subjects were enrolled are highlighted in Figure 1. The age criteria for inclusion were based on the current Advisory Committee on Immunization Practices recommendations for influenza vaccination: during 2005–2006, children 6–23 months of age were included,¹¹ and during 2006–2008, children 6–59 months of age were included because of revised Advisory Committee on Immunization Practices recommendations.¹² Children were considered eligible for enrollment if they were in the appropriate age range on October 1st of each season.

Case and Control Identification

A case was defined as a child who was hospitalized with a respiratory illness within 14 days of testing positive with a clinician-ordered laboratory test for an influenza infection. Acceptable laboratory tests for influenza included commercially available rapid diagnostic tests, immunofluorescence antibody staining, reverse transcription polymerase chain reaction or viral culture. For each case enrolled, up to 4 control children from the community who had not been hospitalized with laboratory-confirmed influenza or a respiratory illness during that influenza season were enrolled. Controls were identified through birth certificate registry files and were matched to the case's date of birth (± 2 weeks). Controls were also matched by area of residence, by using the case's zip code of residence at admission and identifying controls whose mother resided in that zip code or an adjacent zip code, as recorded on the child's birth certificate. Data on whether control children were hospitalized with laboratory-confirmed influenza or a respiratory illness during that influenza season were collected by self-report from the control child's caregiver.

Data Collection

After obtaining caregiver consent, study personnel conducted a standardized telephone interview in English or Spanish within 120 days of the hospitalized case child's admission date. Caregivers were interviewed about child characteristics, household characteristics and caregiver characteristics. For variables that may have changed with time, questions focused on a reference period defined for cases as 30 days before admission and for controls as the calendar month that most closely overlapped with the corresponding case's reference period. The child's primary care providers were contacted to collect data on vaccination status (including dates of administration for all routine vaccines, including influenza vaccine) and the diagnosis of medical conditions.

Definitions

The start of each influenza season was determined at each local site, generally as the first week after October 1st of each year in which influenza-like illness had increased for at least 2 weeks and culture- or RT-PCR-confirmed influenza infections were reported by local hospitals or the state public health laboratory. The end of the season was set as April 30th of each year.

Parents were asked to identify their child's race and ethnicity by categories that were defined by the investigators; data on race and ethnicity were collected because they have been associated with the risk of hospital admission among children and may be proxies for other possible risk factors for hospitalization, including socioeconomic status. Children were considered immunized if they received influenza vaccine after September 1st and at least 14 days before the date of case admission. Children were defined as fully immunized for influenza if they received either 2 doses since September 1st of the current season or 1 dose in the current season but at least 2 doses in any prior season and not fully immunized if they received only a single dose since September 1st of the current season and 0–1 doses in a prior season or if they received no doses since September 1st of the current season.¹²

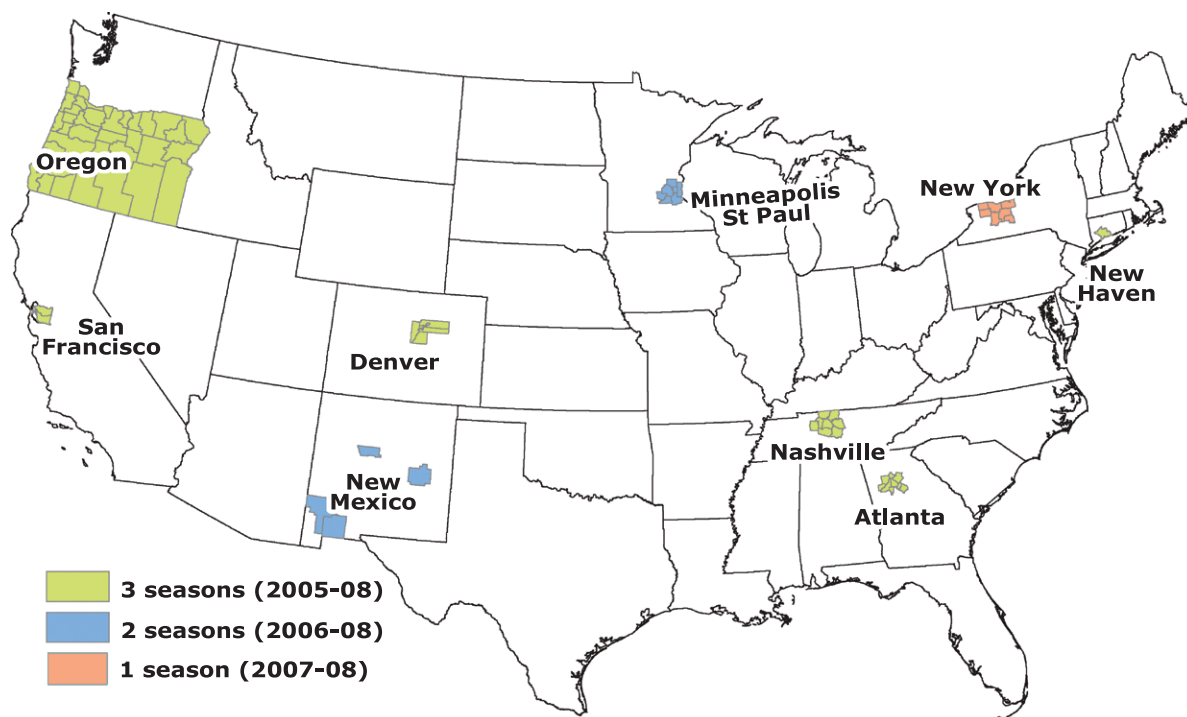


FIGURE 1. Participating Emerging Infections Program sites, color coded by season(s) of participation, 2005-2008.

TABLE 1. Number of Case Children in Each Age Group by Enrollment Site

State	6–23 months (2005–2008)	24–59 months (2006–2008)	Total
CA	18	12	30
CO	29	16	45
CT	24	16	40
GA	20	20	40
MN	32	24	56
NM	6	4	10
NY	6	6	12
OR	28	16	44
TN	12	1	13
Total	175	115	290

Household poverty status was defined using US Census Bureau poverty thresholds for 2007 by size of family and number of related children <18 years of age.¹³ A household crowding index was determined for each child using the Equivalent Crowding Index.¹⁴ This index is calculated using household composition and the number of separate bedrooms as follows: [(1/2 number of children <10 years of age) + (number of couples) + (all other people ≥10 years of age)]/number of bedrooms. We defined crowded for this study as greater than the median value for all households surveyed.

Data Analysis

Analyses were conducted using conditional logistic regression to identify factors associated with influenza hospitalizations, stratifying by the matching variables of age and zip code. A conditional logistic regression model was built using all identified risk factors with *P* < 0.1, including influenza immunization status and possible effect modifiers. The main effects model was reduced by removing the least significant variables one at a time from a full model, provided that removing the variable did not change an odds ratio (OR) for any retained variables by ≥10%.¹⁵ Subsequently, three 2-way interaction terms (child age and household member

influenza vaccination status, child influenza vaccination status and household member influenza vaccination status and child age and child influenza vaccination status) and one 3-way interaction term (child influenza vaccination status, household member influenza vaccination status and child age) were added to the model, and the model was reduced further by removing the least significant product terms beginning with the 3-way interaction, provided that removing the product term did not change an OR for any retained main effects variable by ≥15% (see Appendix for model code). ORs with *P* < 0.05 were considered statistically significant in the final model. All statistical analyses were conducted using SAS Version 9.1 (SAS Institute, Cary, NC).

Human Subjects

The CDC determined that this assessment did not constitute research but rather represented the evaluation of a vaccine program for public health purposes. This project therefore did not need Institutional Review Board approval at CDC. If required by the state, participating EIP sites submitted the study to their state IRBs for review and approval.

RESULTS

Over 3 influenza seasons, 290 (64%) of 454 eligible cases and 1089 (49%) of 2204 eligible controls were enrolled from 9 states after parental consent was obtained (Table 1). Among all children enrolled, 191 (14%) were enrolled in 2005–2006, 439 (32%) in 2006–2007 and 749 (54%) in 2007–2008. The median age was 20 months (range 6.01–59.6); 60% were 6–23 months of age and 40% were 24–59 months of age. The number of cases enrolled in each season by week of hospital admission is shown in Figure 2. The most common influenza diagnostic tests used to confirm influenza infection included rapid diagnostic test (57%), immunofluorescence antibody staining (29%), viral culture (7%) and reverse transcription polymerase chain reaction (4%). The mean time between each case’s hospital admission date and the positive influenza test result was 1.4 hours (standard deviation ± 26.2). The median number of days from case admission to case and control interviews was 53.5 (range 7–148) and 113.5 (range

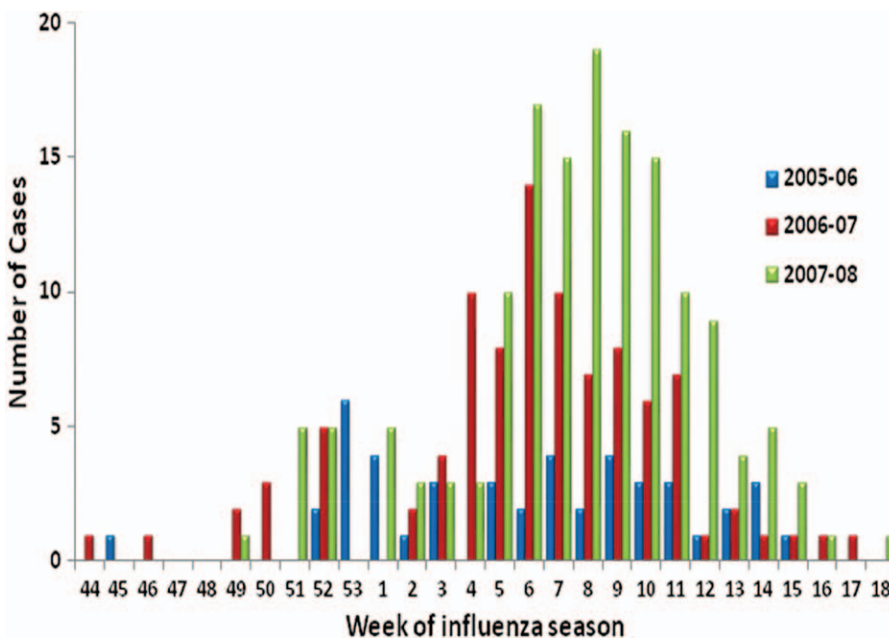


FIGURE 2. Number of cases of hospitalized laboratory-confirmed influenza identified by week of influenza season by the Emerging Infections Program, 2005–2008.

15–278), respectively. Enrolled cases were slightly older than eligible cases who were not enrolled (mean age: 24 vs. 20 months; $P = 0.003$) and more likely to be white than non-white (56% vs. 28%; $P < 0.001$), but no significant differences by sex, black race or Hispanic ethnicity, length of hospitalization or number of medical conditions were found.

Children who were male, of Hispanic ethnicity, black race or low birth weight were at increased risk of hospitalization with laboratory-confirmed influenza (Table 2). Children who were never

breast-fed were also at increased risk, but whether the child was breast-fed during the reference period or not was not significant (data not shown). Breast-feeding for ≥ 6 months was protective among infants, reducing risk of hospitalization by $\geq 50\%$, compared with never being breast-fed. Not having private insurance and not being fully vaccinated for influenza were also identified as risk factors for hospital admission with influenza.

Daycare attendance was not a risk factor for hospital admission with influenza. The number of hours per week in daycare,

TABLE 2. Matched Univariate Analysis of Child Risk Factors for Hospitalization With Laboratory-confirmed Influenza Virus Infection Compared With Community Controls

Risk Factor	Cases (N = 290)		Controls (N = 1089)	
	n (%)	n (%)	OR (95% CI)	P Value*
Gender				
Female	123 (42)	543 (50)	Ref	
Male	167 (58)	546 (50)	1.3 (1.0–1.8)	0.04
Missing	0	0		
Hispanic				
No	194 (67)	794 (73)	Ref	
Yes	96 (33)	293 (27)	1.4 (1.0–2.0)	0.04
Unknown	0	2 (0.2)		
Missing	0	0		
Race				
White only	190 (66)	798 (73)	Ref	
Black only	45 (16)	91 (8)	2.6 (1.6–4.2)	0.0001
Asian only	9 (3)	45 (4)	0.9 (0.4–1.9)	0.73
Hawaiian/Pacific Islander only	0	5 (0.5)	N/A	0.98
American Indian/Alaska Native only	1 (0.3)	4 (0.4)	0.7 (0.1–6.6)	0.75
Other race only†	19 (7)	53 (5)	1.6 (0.9–3.0)	0.12
Multiracial‡	24 (8)	88 (8)	1.2 (0.7–2.0)	0.48
Unknown	0	3 (0.3)		
Refused	1 (0.3)	1 (0.1)		
Did not indicate any race	1 (0.3)	1 (0.1)		
Missing	0	0		
Birth weight§				
Normal and overweight (>2500 g)	250 (86)	1026 (94)	Ref	
Low birth weight (1501–2500 g)	25 (9)	44 (4)	2.3 (1.3–4.0)	0.003
Very low (≤ 1500 g)	10 (3)	16 (1)	2.2 (0.9–5.2)	0.10
Unknown	5 (2)	3 (0.3)		
Missing	0	0		
Ever breast-fed				
Yes	214 (74)	902 (83)	Ref	
No	74 (26)	186 (17)	1.8 (1.3–2.4)	0.001
Unknown	2 (0.7)	0		
Missing	0	1		
If breast-fed, age in months all breast-feeding was stopped, median (range)	6 (0–36)	6 (0–36)		
Duration of breast-feeding				
Patients 6–23 months of age	n = 175	n = 651		
Never breast-fed	44 (25)	115 (18)	Ref	
0–5 months	62 (35)	199 (31)	0.7 (0.5–1.2)	0.22
6–11 months	32 (18)	158 (24)	0.5 (0.3–0.8)	0.008
≥ 12 months	16 (9)	106 (16)	0.3 (0.2–0.6)	0.001
Still breast-feeding	7 (4)	23 (4)		
Unknown	12 (7)	32 (5)		
Missing	2 (1)	18 (3)		
Patients 24–59 months of age	n = 115	n = 438		
Never breast-fed	30 (26)	71 (16)	Ref	
0–5 months	33 (29)	118 (27)	0.7 (0.4–1.2)	0.15
6–11 months	25 (22)	115 (26)	0.5 (0.3–0.9)	0.03
≥ 12 months	26 (23)	132 (30)	0.5 (0.3–0.8)	0.01
Still breast-feeding	0	0		
Unknown	1 (0.9)	2 (0.5)		
Missing	0	0		

(Continued)

TABLE 2. Continued

Risk Factor	Cases (N = 290)	Controls (N = 1089)	OR (95% CI)	P Value*
	n (%)	n (%)		
Health insurance				
Private	150 (52)	748 (69)	Ref	
Not private (government, none, other)	140 (48)	340 (31)	2.5 (1.8–3.4)	<0.0001
Unknown	0	1 (0.1)		
Missing	0	0		
Vaccination status (other than influenza)				
Completely up to date¶	81 (28)	345 (32)	Ref	
Up to date, except for Hepatitis B	66 (23)	221 (20)	1.4 (0.9–2.1)	0.17
Up to date only for DTP, MMR and pneumococcal vaccinations	45 (16)	199 (18)	0.99 (0.6–1.7)	0.99
Other	98 (34)	324 (30)	1.4 (0.9–2.1)	0.11
Vaccinated for influenza				
Fully vaccinated	52 (18)	294 (27)	Ref	
Not fully vaccinated	238 (82)	795 (73)	1.7 (1.2–2.4)	0.004
Missing	0	0		
Attended daycare during reference period				
No	174 (60)	666 (61)	Ref	
Yes	115 (40)	423 (39)	1.1 (0.8–1.4)	0.71
Unknown	1 (0.3)	0		
Missing	0	0		
Daycare type				
No daycare	174 (60)	666 (61)	Ref	
Daycare center	39 (13)	117 (11)	1.2 (0.8–1.9)	0.29
Preschool	41 (14)	162 (15)	1.0 (0.6–1.6)	0.95
Home daycare	32 (11)	139 (13)	0.9 (0.6–1.4)	0.63
Other	3 (1)	5 (0.5)	2.6 (0.6–12.0)	0.22
Unknown	1 (0.3)	0		
Missing	0	0		
Presence of underlying medical condition				
No	154 (53)	914 (84)	Ref	
Yes	136 (47)	175 (16)	5.1 (3.7–7.0)	<0.0001
Missing	0	0		
Number of medical conditions				
0	154 (53)	914 (84)	Ref	
1	85 (29)	157 (14)	3.6 (2.6–5.1)	<0.0001
>1	51 (18)	18 (2)	17.7 (9.7–32.5)	<0.0001
Missing	0	0		
Type of underlying medical condition				
No underlying medical condition	154 (53)	914 (84)	Ref	
Multiple underlying medical conditions	51 (18)	18 (2)	17.6 (9.6–32.3)	<0.0001
Pulmonary‡ condition(s) only	66 (23)	127 (12)	3.5 (2.4–5.0)	<0.0001
Hematologic/oncologic** condition(s) only	10 (3)	8 (0.7)	7.6 (2.7–21.3)	0.0001
Neurologic‡‡ condition(s) only	5 (2)	7 (0.7)	4.4 (1.3–15.1)	0.02
Cardiac condition(s) only	1 (0.3)	7 (0.6)	1.6 (0.2–14.1)	0.67
Diabetes only	1 (0.3)	0	N/A	0.99
Chronic kidney condition(s) only	0	4 (0.4)	N/A	0.98
Other chronic medical condition(s) only	2 (0.7)	4 (0.4)	3.5 (0.6–21.3)	0.17

N/A, not applicable; DTP, diphtheria-tetanus toxoids-pertussis; MMR, measles-mumps-rubella.

*All P values are computed exact except for the following variables: race, duration of breast-feeding, type of underlying medical condition, age of mother/stepmother, percent of persons in the household that received the influenza vaccine.

†Sixty-nine (96%) of patients who reported “other race” also described themselves as Hispanic. Of the 3 (4%) who did not describe themselves as Hispanic, 1 described themselves as “Indian”, 1 as “African” and 1 as “unknown”.

‡Self-described as >1 race.

§Birth weight taken from birth certificates unless unavailable; then as reported by the caregiver.

¶Definition of up to date vaccinations: receipt of all recommended childhood vaccinations except influenza vaccine, based on child’s age on enrollment.

‡Chronic asthma condition, chronic lung condition, birth defect or chronic condition making breathing or swallowing difficult, condition requiring equipment for breathing or handling secretions, condition that an operation was done to make breathing/secretions easier and condition requiring surgery or equipment for breathing/secretions.

**Sickle cell disease, malignancy, history of bone marrow or organ transplant, chronic immunologic condition.

‡‡Spinal cord injury, history of seizure, severe developmental delay or mental retardation.

daycare attendance during the reference period, duration of time spent in daycare before the reference period and the number of children in the same room with the child in daycare were not associated with admission (data not shown). Data on sibling daycare attendance were not collected.

Detailed information on the prevalence of chronic underlying medical conditions among study participants is presented in Table 3. Having 1 or more chronic illnesses was a risk factor for hospitalization (Table 2) and pulmonary, hematologic/oncologic and neurologic conditions were identified as statistically

significant risk factors. Although most children with any chronic illness had only 1 condition, the risk of hospitalization increased 17-fold if the child had >1 underlying medical conditions compared with none.

Caregiver and household characteristics associated with an increased risk of hospitalization are listed in Table 4. Having a mother or caregiver <26 years of age was a risk factor compared with a reference group 26–35 years of age, and having a caregiver ≥36 years of age old was protective. Having a caregiver with less than some college attendance and living in a non-single family home were identified as risk factors. A household crowding index greater than the median (0.75), having >1 person/bedroom in the household or ≥2 children sleeping in the same bedroom with the study child were risk factors. Although the absolute number of smokers in the household was not an identified risk factor, having a high proportion of persons living in the household who reported smoking (>50%) was. Very few household members reported smoking inside the home (data not shown). Influenza vaccination of any household member

decreased the risk of hospitalization. Household income <2 times the poverty threshold increased the risk of hospitalization, and this risk increased substantially as household income decreased to below the poverty threshold.

In multivariable analyses, factors associated with influenza hospitalization were identified in a main effects model (Table 5). A final multivariable model including an interaction term between child age and child influenza immunization status was constructed (Table 6). Independent factors associated with influenza hospitalization included: maternal age <26 years, household income below the poverty threshold, the presence of specific chronic illnesses (including hematologic or oncologic, pulmonary and neurologic conditions), lack of a household member being vaccinated for influenza and >50% household members who reported smoking (Table 6). A significant interaction ($P = 0.01$) was identified between child age and child influenza immunization status (Table 6). Full immunization of the child for influenza decreased the risk of hospitalization among children 6–23 months of age [OR: 0.5, 95% confidence interval (CI): 0.3–0.9; $P = 0.01$], but not among children 24–59 months of age (OR: 1.5, 95% CI: 0.8–3.0; $P = 0.24$).

TABLE 3. Underlying Medical Conditions of Study Participants

Underlying Medical Conditions	Cases (N = 290)	Controls (N = 1089)
	n (%)	n (%)
Any underlying medical condition		
No	154 (53)	914 (84)
Yes	136 (47)	175 (16)
Missing	0	0
Number of medical conditions		
0	154 (53)	914 (84)
1	72 (25)	148 (14)
2	28 (10)	18 (2)
3	18 (6)	4 (0.4)
4	12 (4)	5 (0.5)
>4	6 (2)	0
Missing	0	0
Type of underlying condition		
Asthma (including reactive airway disease or >1 episode of wheezing)	95 (33)	137 (13)
Takes medication for wheezing, reactive airway disease or asthma	76 (26)	91 (8)
Takes oral or intravenous steroid medications	68 (23)	58 (5)
Condition affecting breathing or swallowing*	36 (12)	20 (2)
Severe developmental delay or mental retardation	31 (11)	16 (1)
Chronic immune condition, including congenital	21 (7)	8 (0.7)
Cardiac	14 (5)	13 (1)
Seizure disorder	13 (4)	1 (0.1)
Chronic pulmonary condition	12 (4)	3 (0.3)
Malignancy	10 (3)	1 (0.1)
Sickle cell disease	8 (3)	3 (0.3)
Kidney disease	5 (2)	5 (0.5)
Bone marrow or organ transplant	5 (2)	0
Diabetes	1 (0.3)	1 (0.1)
Spinal cord injury	1 (0.3)	1 (0.1)
Other chronic medical condition	14 (5)	7 (0.6)

*Birth defect or chronic condition making breathing or swallowing difficult, condition requiring equipment for breathing or handling secretions, condition that an operation was done to make breathing/secretions easier and condition requiring surgery or equipment for breathing/secretions.

DISCUSSION

We identified a number of factors that increased the risk of hospitalization for influenza among children 6–59 months of age in the EIP population during 3 consecutive US influenza seasons. Maternal age <26 years, household income below the poverty threshold, lack of household member influenza vaccination and smoking by >50% of household members were identified as independent risk factors for hospitalization with laboratory-confirmed influenza. Consistent with prior studies,^{7–9} specific chronic illnesses logically increased the risk for hospitalization with influenza. Among younger children, full immunization for influenza decreased the risk of hospitalization.

Our findings that several caregiver- and household-level factors increased the risk of an influenza-associated hospitalization were not unexpected. For example, an inverse relationship was demonstrated between maternal age and the risk of acute lower respiratory tract infection among children <59 months of age in a study conducted in Western Australia,¹⁶ and a US study found that maternal age <25 years was associated with increased risk of lower respiratory tract infection deaths among children <1 year of age.¹⁷ Young maternal age may increase the risk of hospitalization with influenza because younger mothers and their peers may have less experiential knowledge and/or less social support. Younger women also may be more susceptible to respiratory infections than older women¹⁸ and thus may be more likely to transmit influenza infections to their young children.

We collected data for several factors related to socioeconomic status, including household income, household crowding and receipt of Medicaid insurance. In other studies, a number of such indicators of low socioeconomic status have been identified as risk factors for hospitalization with common acute infectious diseases among young children. For example, receiving Medicaid insurance has been identified as risk factors among young children for hospitalization with rotavirus gastroenteritis.^{19,20} In our analysis, only household income was identified as an independent risk factor for an influenza hospitalization, suggesting it may be a more encompassing predictor of risk than type of insurance. Low family income has been shown to increase the risk of lower respiratory tract infections, asthma attacks and respiratory-related hospitalizations among children²¹ and has been associated with worse outcomes in infants with respiratory syncytial virus infection.²² A

TABLE 4. Matched Univariate Analysis of Caregiver and Household Risk Factors for Hospitalization With Laboratory-confirmed Influenza Virus Infection Compared With Community Controls

Risk Factor	Cases (N = 290)	Controls (N = 1089)	OR (95% CI)	P Value*
	n (%)	n (%)		
Caregiver characteristics				
Mother/stepmother described as primary caregiver				
Yes	250 (86)	960 (88)	Ref	
No	40 (14)	129 (12)	1.2 (0.8–1.7)	0.51
Missing	0	0		
Age of mother/stepmother, years				
16 to <22	20 (7)	38 (3)	2.2 (1.2–4.0)	0.01
22 to <26	49 (17)	97 (9)	2.1 (1.4–3.1)	0.0004
26 to <36	149 (51)	599 (55)	Ref	
≥36	64 (22)	347 (32)	0.7 (0.5–1.0)	0.045
Missing	8 (3)	8 (0.7)		
Primary caregiver education				
At least some college	159 (55)	750 (69)	Ref	
None-Grade 12 or Certificate of High School Equivalency	127 (44)	332 (30)	2.0 (1.4–2.7)	<0.0001
Refused	4 (1)	7 (0.6)		
Missing	0	0		
Household characteristics				
Type of residence				
Single family home	176 (61)	828 (76)	Ref	
Other	114 (39)	261 (24)	2.5 (1.8–3.4)	<0.0001
Missing	0	0		
Crowding index†				
≤0.75 (median)	120 (41)	618 (57)	Ref	
>0.75	162 (56)	463 (43)	1.9 (1.4–2.5)	<0.0001
Missing	8 (3)	8 (0.7)		
Number of persons/bedroom				
≤1	71 (24)	367 (34)	Ref	
>1	216 (74)	719 (66)	1.6 (1.1–2.2)	0.005
Missing	3 (1)	3 (0.3)		
Number of children sleeping in the bedroom with the child				
<2	260 (90)	1021 (94)	Ref	
≥2	29 (10)	66 (6)	1.9 (1.1–3.1)	0.02
Missing	1 (0.3)	2 (0.2)		
Number of smokers in the household				
0	214 (74)	834 (77)	Ref	
1	31 (11)	116 (11)	1.1 (0.7–1.7)	0.77
≥ 2	26 (9)	67 (6)	1.5 (0.9–2.5)	0.13
Missing	19 (7)	72 (7)		
Percent of household members who are smokers				
None	214 (74)	834 (77)	Ref	
≤50%	38 (13)	152 (14)	1.0 (0.7–1.5)	1.0
>50%	19 (7)	31 (3)	2.3 (1.2–4.3)	0.01
Missing	19 (7)	72 (7)		
Number smokers per bedroom				
0	212 (73)	832 (76)	Ref	
>0–1	51 (18)	179 (16)	1.2 (0.8–1.7)	0.48
>1	6 (2)	4 (0.4)	6.0 (1.4–29.4)	0.01
Missing	21 (7)	74 (7)		
Any household member received influenza vaccine				
Yes	146 (50)	655 (60)	Ref	
No	135 (47)	414 (38)	1.5 (1.1–2.0)	0.007
Unknown	9 (3)	20 (2)		
Missing	0	0		
Percent of persons in household that received influenza vaccine				
0	135 (47)	414 (38)	Ref	
1–25%	26 (9)	71 (7)	1.2 (0.7–1.9)	0.58
26–50%	54 (19)	246 (23)	0.6 (0.4–0.9)	0.02
51–75%	31 (11)	148 (14)	0.6 (0.4–1.0)	0.04
76–100%	35 (12)	190 (17)	0.5 (0.4–0.8)	0.005
Unknown	9 (3)	20 (2)		
Missing	0	0		
Household income				
≥200% poverty threshold	149 (51)	738 (68)	Ref	
100% to <200% poverty threshold	39 (13)	123 (11)	1.8 (1.2–2.9)	0.009
50% to <100% poverty threshold	54 (19)	102 (9)	3.6 (2.3–5.5)	<0.0001
<50% poverty threshold	14 (5)	39 (4)	3.0 (1.5–6.3)	0.003
Refused	13 (4)	29 (3)		
Missing	21 (7)	58 (5)		

*All P values are computed exact except for the following variables: race, duration of breast-feeding, type of underlying medical condition, age of mother/stepmother, percent of persons in the household that received the influenza vaccine.

†Crowding Index = [(1/2 number of persons <10 years old) + (number of couples) + (number of persons >10 years old)]/number of bedrooms.

TABLE 5. Matched Multivariate Regression Analysis of Factors Associated With Hospitalization With Laboratory-confirmed Influenza Virus Infection: Matched Multivariate Regression Main Effects Model Without Interaction Term

Risk Factor	aOR (95% CI)	P
Maternal age <26 years	1.8 (1.2–2.9)	0.01
Household income below the poverty threshold	2.2 (1.4–3.5)	0.001
Underlying medical conditions		
Hematologic or oncologic condition*	11.2 (4.3–29.2)	<0.0001
Pulmonary condition†	2.8 (1.9–4.2)	<0.0001
Neurologic condition‡	3.8 (1.6–9.1)	0.003
Other condition	5.7 (1.0–31.7)	0.046
>50% of household members smoked	2.9 (1.3–6.3)	0.009
No household member vaccinated for influenza	1.7 (1.2–2.4)	0.006
Child vaccinated for influenza (vs. unvaccinated reference group)	1.4 (0.9–2.1)	0.15

*Sickle cell disease, malignancy, history of bone marrow or organ transplant, chronic immunologic condition.

†Chronic asthma condition, chronic lung condition, birth defect or chronic condition making breathing or swallowing difficult, condition requiring equipment for breathing or handling secretions, condition that an operation was done to make breathing/secretions easier, and condition requiring surgery or equipment for breathing/secretions.

‡Spinal cord injury, history of seizure, severe developmental delay or mental retardation.

aOR, adjusted OR.

TABLE 6. Matched Multivariate Regression Analysis of Factors Associated With Hospitalization With Laboratory-confirmed Influenza Virus Infection: Matched Multivariate Regression With Interaction Term

Risk Factor	aOR (95% CI)	P
Maternal age <26 years	1.8 (1.1–2.9)	0.01
Household income below the poverty threshold	2.2 (1.4–3.6)	0.001
Underlying medical conditions		
Hematologic or oncologic condition*	11.8 (4.5–31.0)	<0.0001
Pulmonary condition†	2.9 (1.9–4.4)	<0.0001
Neurologic condition‡	3.8 (1.6–9.2)	0.003
Other condition	6.7 (1.1–39.6)	0.03
>50% of household members smoked	2.9 (1.4–6.6)	0.006
No household member vaccinated for influenza	1.8 (1.2–2.5)	0.003
Child vaccinated for influenza (vs. unvaccinated reference group) by child age category		0.01§
6–23 months of age	0.5 (0.3–0.9)	0.01
24–59 months of age	1.5 (0.8–3.0)	0.24

*Sickle cell disease, malignancy, history of bone marrow or organ transplant, chronic immunologic condition.

†Chronic asthma condition, chronic lung condition, birth defect or chronic condition making breathing or swallowing difficult, condition requiring equipment for breathing or handling secretions, condition that an operation was done to make breathing/secretions easier, and condition requiring surgery or equipment for breathing/secretions.

‡Spinal cord injury, history of seizure, severe developmental delay or mental retardation.

§P value for the interaction term = 0.01

aOR, adjusted OR.

recent study examining risks of hospitalization with 2009 H1N1 influenza found an inverse association between odds of hospitalization and neighborhood poverty among adults and children.²³ Of course, lower socioeconomic status is associated with other factors,

including poor access to medical care because of lack of transportation and fewer general available resources, which might mediate this increased risk.²⁴

Smoking by the mother and other household members is known to increase the risk of infectious and noninfectious respiratory illness in children. In a recent meta-analysis,²⁵ exposure to smoking by any household member was associated with an OR of 1.5 for lower respiratory infections among children <2 years of age. Our findings are consistent with those of other studies and provide evidence that exposure to passive smoking specifically increases the risk of serious outcomes related to influenza infection.

Our finding that full immunization for influenza decreased the risk of hospitalization among younger children (6–23 months of age) but not among older children (24–59 months of age) was unexpected, but may be because of an unmeasured case ascertainment bias related to differences in health-seeking behavior. Advisory Committee on Immunization Practices recommendations for influenza vaccination were expanded during our study enrollment to include children in the older age group. It is possible that older children who received the vaccination in line with the new recommendations were more likely to have seen a physician in general and therefore more likely to seek medical attention for a respiratory illness and be identified as a case.

Neither child race nor ethnicity was associated with an increased risk for influenza hospitalization in our case-control study. Although racial disparities for hospitalization associated with acute respiratory illness including influenza have been reported,^{26,27} it is likely that other data we collected in our study, including household income and the presence of specific chronic medical conditions, accounted for any greater risk of influenza hospitalization among select racial/ethnic groups. For example, other studies have found that black children have higher asthma prevalence,²⁸ black and Hispanic women have lower maternal age at first parity²⁹ and blacks and Hispanics have highest US poverty rates.³⁰ It also should be noted that our sample size of non-Caucasian children was small, and therefore it is unlikely that this study was powered to detect small differences in risk, especially after controlling for the factors mentioned above.

This study has several limitations. First, cases were identified by influenza laboratory tests ordered by clinicians and not through use of a standardized protocol. Therefore, our results may not be representative of all children hospitalized (but not necessarily diagnosed) with influenza. Second, the diagnostic tests used to diagnose influenza infection were of variable sensitivity and specificity. In particular, there is concern with the use of commercially available influenza antigen detection assays, as the sensitivity and specificity of these tests can be quite variable.^{31,32} In the context of a case-control study, the specificity of the test used to provide laboratory confirmation of influenza infection in the cases is of great importance, as false positives can lead to substantial bias in the results.³² Third, because household member vaccination status was collected by self-report and not verified by physician records and because the date of household member vaccination was not collected, some household members may have reported incorrect information about their vaccination status and/or may have been vaccinated after the case was hospitalized. Fourth, recall bias may have affected parental responses to some questions; differential recall bias by case or control status is possible, as the controls as a group were interviewed later than cases were compared with the reference period. Fifth, selection bias is always a possibility in observational studies and may be of particular concern in case-control studies. Children eligible to be controls of higher socioeconomic status may have been easier to

reach and enroll than other eligible controls, which would likely bias the strength of associations, especially for sociodemographic indicators, away from the null. However, it is also possible that case children of lower socioeconomic status were less likely to be enrolled if their caregivers were more difficult to reach because of lack of contact information or difficulty traveling to the hospital. As a lower proportion of controls were enrolled compared with cases, the potential for selection bias may be a greater concern among controls.

However, a strength of our study is that the eligible controls represented the true population from which the cases arose and included all children exposed to influenza viruses. Recently, a variation of traditional case-control study design known as the test negative design has become widely used in studies of influenza vaccine effectiveness. In such studies, all subjects are tested for influenza infection; cases are those testing positive and “controls” are those testing negative.^{33,34} These studies are popular because they permit investigators to enroll cases and non-cases from only those persons tested for influenza. For example, in a study of risk factors for influenza-related hospitalizations, one would only enroll children tested in the hospital for influenza infection. Such studies do have limitations, however, and by not limiting control selection to children tested for influenza, we were able to evaluate factors that might lead children to have more intense exposure to influenza viruses (such as daycare attendance or household crowding) as well as factors potentially associated with more severe influenza infections (including chronic illnesses and having household members who smoke).

We found child, caregiver and household factors associated with hospitalization with influenza infection among young children eligible for influenza vaccination (ie, 6 months of age and older). Our findings that chronic illnesses, young maternal age, poverty, household smoking and lack of household member influenza vaccination increase the risk of an influenza hospitalization may help providers to identify young children at greatest risk for poor outcomes from influenza illness, including those for whom early interventions such as treatment with influenza antivirals is of paramount importance.

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APPENDIX

METHODS: COUNTIES PARTICIPATING IN THE EIP PEDIATRIC INFLUENZA HOSPITALIZED SURVEILLANCE PROJECT

Selected counties in 9 states that participated in the EIP Pediatric Influenza Hospitalized Surveillance Project: California (Alameda, Contra Costa, San Francisco); Colorado (Adams, Arapahoe, Denver, Douglas, Jefferson); Connecticut (New Haven); Georgia (Clayton, Cobb, DeKalb, Douglas, Fulton, Gwinnett, Newton, Rockdale); Minnesota (Anoka, Carver, Dakota, Hennepin, Ramsey, Scott, Washington); New Mexico (2006–08: Bernalillo, Doña Ana, Grant, Luna; 2007–2008: Chaves and Santa Fe added), New York (Genesee, Livingston, Monroe, Ontario, Orleans, Wayne, Yates), Oregon (2005–2006: Clackamas, Multnomah, Washington; 2006–2008: all 36 Oregon counties) and Tennessee (Cheatham, Davidson, Dickson, Robertson, Rutherford, Sumner, Williamson, Wilson).

CODE FOR MULTIVARIABLE ANALYSES PRESENTED IN TABLES 5 AND 6

Table 5: Matched multivariable regression analysis of factors associated with hospitalization with laboratory-confirmed influenza virus infection, main effects model without interaction term

```
proc logistic data=a;
  model enrolltype = perccat hemeonccat lungcat neurocat
othchron totalpersonsvax matagecat poverty_status immunstatus /
  clodds=wald;
  strata CaseID;
  run;
```

Table 6: Matched multivariable regression analysis of factors associated with hospitalization with laboratory-confirmed influenza virus infection, with interaction term

```
proc logistic data=a;
  model enrolltype = perccat hemeonccat lungcat neurocat
othchron totalpersonsvax matagecat
  poverty_status immunstatus agegrouprecat
agegrouprecat*immunstatus / clodds=wald;
  strata CaseID;
  CONTRAST agegrouprecat 0 immunstatus -1
agegrouprecat*immunstatus -1 / estimate=exp;
  CONTRAST agegrouprecat 0 immunstatus -1
agegrouprecat*immunstatus 0 / estimate=exp;
  run;
```

Variables key

perccat: >50% of household members smoked
hemeonccat: hematologic or oncologic condition

lungcat: pulmonary condition

neurocat: neurologic condition

othchron: other condition

totalpersonsvax: no household member vaccinated for influenza

matagecat: maternal age < 26 years

poverty_status: household income below the poverty threshold

immunstatus: child vaccinated for influenza (vs. unvaccinated reference group)

agegrouprecat: age category of child (6–23 months vs. 24–59 months)