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Pediatrics 2011;128:e27; originally published online June 6, 2011;
DOI: 10.1542/peds.2010-3343

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://pediatrics.aappublications.org/content/128/1/e27.full.html>

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American Academy of Pediatrics

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Children With Asthma Hospitalized With Seasonal or Pandemic Influenza, 2003–2009

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KEY WORDS

influenza, asthma, pandemic

ABBREVIATIONS

EIP—Emerging Infections Program

ICD-9—International Classification of Diseases, Ninth Revision

The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.

www.pediatrics.org/cgi/doi/10.1542/peds.2010-3343

doi:10.1542/peds.2010-3343

Accepted for publication Feb 28, 2011

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

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FINANCIAL DISCLOSURE: *The authors have indicated that they have no personal financial relationships relevant to this article to disclose.*



WHAT’S KNOWN ON THIS SUBJECT: Asthma is recognized as a condition conferring higher risk for influenza complications. Seasonal influenza hospitalization rates are higher among asthmatic children than healthy children, and asthmatic people accounted for a large proportion of all patients hospitalized with 2009 pandemic H1N1 influenza.



WHAT THIS STUDY ADDS: This analysis provides the first description of the characteristics and clinical courses of asthmatic children hospitalized with seasonal or 2009 pandemic H1N1 influenza in the United States and documents the substantial burden of influenza complications among these children.

abstract

OBJECTIVE: To describe the characteristics and clinical courses of asthmatic children hospitalized with seasonal or 2009 pandemic H1N1 influenza and compare complications by influenza type.

METHODS: During the 2003–2009 influenza seasons and the 2009 pandemic, we conducted surveillance of 5.3 million children aged 17 years or younger for hospitalization with laboratory-confirmed influenza and identified those with asthma (defined as those aged 2–17 years with a history of asthma in their medical record or a discharge code for acute asthma exacerbation or status asthmaticus). We collected data from medical records on medical history and clinical course; data on asthma severity and control were not routinely collected.

RESULTS: During the 2003–2009 influenza seasons, 701 (32%) of 2165 children hospitalized with influenza had asthma; during the 2009 pandemic, 733 (44%) of 1660 children had asthma. The median age of the asthmatic children was 7 years, and 73% had no additional medical conditions. Compared with asthmatic children with seasonal influenza, a higher proportion with 2009 pandemic H1N1 influenza required intensive care (16% vs 22%; $P = .01$) and were diagnosed with pneumonia (40% vs 46%; $P = .04$), whereas equal proportions had respiratory failure (5% vs 5%; $P = .8$) and died (1% vs 1%; $P = .4$). More asthmatic children with influenza A (seasonal or pandemic) had diagnoses of asthma exacerbations compared with those with influenza B (51% vs 29%; $P < .01$).

CONCLUSIONS: The majority of asthmatic children hospitalized with influenza have no additional medical conditions. Complications such as pneumonia and need for intensive care occur in a substantial proportion, highlighting the importance of influenza prevention through vaccination among asthmatic children. *Pediatrics* 2011;128:e27–e32

An estimated 7 million children in the United States had asthma in 2008,¹ making it the most common chronic underlying medical condition among US children. Since the 1960s, asthma has been recognized as a medical condition conferring higher risk for influenza-associated complications during typical influenza seasons,² and seasonal influenza-attributable hospitalization rates are substantially higher among children with asthma than among healthy children.^{3,4} More recently, during the 2009 influenza pandemic, 2 large case series of patients hospitalized with 2009 pandemic H1N1 (2009 H1N1) influenza reported that patients with asthma accounted for 22% to 29% of all hospitalized cases.^{5,6} Differences in the virulence of seasonal influenza A and B viruses also have been observed in a previous analysis in which hospitalized patients with influenza A virus infections were more likely to have severe influenza.⁷ However, no study to date has described the characteristics and clinical outcomes of a large and geographically diverse cohort of children with asthma hospitalized with either seasonal or 2009 H1N1 influenza in the United States or evaluated whether differences in characteristics and clinical presentations exist between children with asthma hospitalized with seasonal influenza A or B or 2009 H1N1 virus infections. Using data from the Emerging Infections Program (EIP) surveillance for pediatric hospitalizations with laboratory-confirmed influenza from the 2003–2009 influenza seasons and the 2009 influenza pandemic, we describe the characteristics and clinical courses of children with asthma hospitalized with seasonal or 2009 H1N1 influenza, and we explore the relationship between influenza-associated complications and influenza virus type in these children.

METHODS

Case Definitions and Case Ascertainment

Since 2003, the EIP Network has conducted population-based surveillance for pediatric hospitalizations with laboratory-confirmed influenza in 10 states, including a catchment-area population of 5.3 million children aged 17 years and younger, as previously described.⁸ A case of pediatric influenza requiring hospitalization was defined as a child residing in the surveillance area who was hospitalized in a surveillance-area hospital with laboratory confirmation of influenza virus infection within 14 days of admission from the 2003–2009 influenza seasons (October 1 through April 30 during 2003–2008 and October 1, 2008, through April 14, 2009) and during the 2009 influenza pandemic (April 15, 2009, through December 31, 2009). Laboratory testing for influenza was ordered at the discretion of clinicians providing clinical care. Data were collected from patient medical records regarding patient demographic characteristics, medical history, clinical course, and discharge *International Classification of Diseases, Ninth Revision* (ICD-9) codes.

EIP case subjects with asthma were identified by (1) the presence of an ICD-9 code for acute asthma exacerbation (code 493.91) or status asthmaticus (code 493.92), or (2) the presence of the diagnosis of asthma noted anywhere in the medical record. Because the diagnosis of asthma can be difficult to make in infants and young children, EIP case subjects aged younger than 2 years were excluded from this analysis. EIP case subjects with a diagnosis of pneumonia were identified by the presence of any ICD-9 code for infectious pneumonia (viral, bacterial, fungal, or organism unspecified) among children who had at least 1 chest radiograph during their hospitalizations.

Data Analysis and Statistical Methods

The following groups were compared in bivariate analysis: (1) EIP case subjects with asthma from the 2003–2009 influenza seasons versus case subjects with asthma from the 2009 pandemic and (2) EIP case subjects with asthma with confirmed influenza B virus infections versus seasonal influenza A virus infections versus 2009 H1N1 virus infections. During all seasons, case subjects with confirmed influenza B virus infections were used as the reference group for comparison with case subjects with either seasonal influenza A or 2009 H1N1 virus infections. In the analysis comparing case subjects by influenza type, case subjects with untyped influenza virus infections were excluded during the 2003–2008 seasons and were assumed to have 2009 H1N1 virus infections during the 2009 pandemic on the basis of national influenza virologic surveillance data, which indicated that the 2009 H1N1 virus accounted for 99% of all circulating influenza viruses in the United States during the 2009 pandemic.⁹

χ^2 tests were used to calculate *P* values in bivariate analyses. Statistical analyses were conducted by using SAS 9.1 (SAS Institute, Cary, NC).

Human Subjects Review

The nature of this data collection was determined by the Centers for Disease Control and Prevention to be for routine public health surveillance purposes and was not subject to institutional review board approval for human research protections.

RESULTS

During the 2003–2009 influenza seasons, 2165 children aged 2 years or older were hospitalized with laboratory-confirmed influenza, of whom 701 (32%) had asthma. During the 2009

TABLE 1 Characteristics of Children With Asthma Hospitalized With Laboratory-Confirmed Influenza, EIP Surveillance for Influenza-Associated Hospitalizations, 2003–2009 (*N* = 1434)

	2003–2004		2004–2005		2005–2006		2006–2007		2007–2008		2008–2009		2009 Pandemic	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
Total EIP cases aged ≥ 2 y	536		313		306		232		386		392		1660	
EIP cases aged ≥ 2 y with asthma	184	34	95	30	105	34	63	27	125	32	129	33	733	44
Median age, y	7		7		6		5		6		5		7	
2–5	64	35	32	34	38	36	24	38	47	38	50	39	174	24
6–9	49	27	27	28	30	29	23	37	44	35	42	32	300	41
10–13	39	21	12	13	20	19	6	9	15	12	14	11	156	21
14–17	32	17	24	25	17	16	10	16	19	15	23	18	103	14
Male	114	62	50	53	57	54	49	78	70	56	80	62	459	63
White	66	36	31	33	31	30	23	37	48	38	53	41	262	36
Black	88	48	37	39	36	34	21	33	52	42	43	33	267	37
No other underlying condition ^a	153	83	67	71	72	69	40	63	90	72	85	66	540	74
Received seasonal influenza vaccine ^b	66/162	41	44/85	52	31/86	36	24/53	45	40/112	36	56/121	46	131/507 ^c	26
Median length of stay, d	3		4		3		3		3		3		3	
Received antiviral treatment ^d	48/100	48	24/52	46	35/65	54	17/41	41	36/80	45	20/68	29	408/463	88
Had a chest radiograph	156	85	76	80	89	85	60	95	107	86	109	84	628	86
ICD-9 diagnosis of pneumonia ^e	57/149	38	30/73	41	33/86	38	27/58	47	44/103	43	38/106	36	276/603	46
ICU admission	32	17	13	14	16	15	15	24	16	13	21	16	158	22
Respiratory failure ^f	4	2	4	4	5	5	7	11	5	4	11	9	35	5
Extracorporeal membrane oxygenation	0		1	<1	1	<1	0		0		0		5	1
Death	1	<1	1	<1	1	<1	0		1	<1	0		7	1

^a Of the following underlying conditions: cardiovascular disease; chronic lung disease; chronic metabolic disease; febrile seizures; hemoglobinopathies; immunosuppression; neurologic disorders, including cerebral palsy and seizure disorders; and pregnancy.

^b At least 1 dose.

^c Of patients admitted after August 31, 2009, when seasonal influenza vaccine became available.

^d Of patients admitted within 2 days of symptom onset.

^e Of children who had chest radiographs during their hospitalizations and had available ICD-9 code data.

^f Defined as requiring mechanical ventilation.

pandemic, 1660 children aged 2 years or older were hospitalized with presumed or confirmed 2009 H1N1 influenza, of whom 733 (44%) had asthma. Children with asthma made up a significantly larger proportion of all children hospitalized with influenza during the 2009 pandemic compared with previous influenza seasons (44% vs 32%; $P < .01$). Of 1434 case subjects meeting the definition for a case with asthma hospitalized with influenza, 607 children (43%) had an acute asthma ICD-9 code (for either acute asthma exacerbation or status asthmaticus) and a diagnosis of asthma in the medical record, 761 children (53%) had a diagnosis of asthma but did not have an acute asthma ICD-9 code, and 66 children (5%) had an acute asthma ICD-9 code but no diagnosis of asthma in the medical record.

During all seasons, the median age of children with asthma hospitalized with

influenza ranged from 5 to 7 years, although a larger proportion of children with asthma were aged older than 5 years during the 2009 pandemic than during previous seasons (76% vs 64%; $P < .01$). Fifty-three percent to 78% of children with asthma hospitalized with influenza were male, and 63% to 83% had no additional medical conditions (Table 1). Among children with a medical condition in addition to asthma, seizure disorders (21%); neuromuscular disorders, including cerebral palsy (20%); and hemoglobinopathies (17%) were the most common conditions.

During the 2003–2009 influenza seasons, only 36% to 52% of hospitalized children with asthma with known vaccination status had received at least 1 dose of the current seasonal influenza vaccine. For children with asthma aged 2 through 8 years who required 2 doses of influenza vaccine to be fully vaccinated in their first season of influ-

enza vaccination, full vaccination status could not be determined because of incomplete data on the number of vaccine doses received during the current season.

During 2003–2009, 406 (58%) of 701 children with asthma and influenza were admitted to the hospital within 2 days of symptom onset. During the 2009 pandemic, 463 (63%) of 733 children with asthma and influenza were admitted within 2 days of symptom onset. Among children with asthma admitted within 2 days of symptom onset, a larger proportion of children admitted during the 2009 pandemic were treated with antiviral medications than those admitted during 2003–2009 (88% vs 44%; $P < .01$). The effect of antiviral treatment on hospital course could not be evaluated because data on the timing of hospital events (eg, diagnosis of pneumonia, ICU admis-

sion, respiratory failure) in relation to antiviral treatment were not collected.

Compared with children with asthma hospitalized with influenza during 2003–2009, a larger proportion of children with asthma hospitalized during the 2009 pandemic were diagnosed with pneumonia (of children with chest radiographs during hospitalization: 40% vs 46%; $P < .01$), and a larger proportion of those whose only underlying medical condition was asthma required admission to an ICU (no additional medical conditions: 14% vs 21%, $P = .01$; ≥ 1 additional medical conditions: 22% vs 24%, $P = .6$). However, the proportion of children with asthma with respiratory failure was not significantly different during the 2003–2009 influenza seasons and the 2009 pandemic, irrespective of the presence of additional medical conditions (no additional medical conditions: 3% vs 3%, $P = .5$; ≥ 1 additional medical conditions: 10% vs 11%, $P = .7$). During the 2003–2009 influenza seasons, 2 (<1%) children with asthma hospitalized with influenza required extracorporeal membrane oxygenation, and 4 (1%) children died. During the 2009 pandemic, 5 (1%) children with asthma required extracorporeal membrane oxygenation, and 7 (1%) children died. Of 11 children with asthma who died during the 2003–2009 influenza seasons and 2009 pandemic, asthma was the only known underlying medical condition in 6 (55%).

Comparison of Complications and Outcomes by Influenza Type

During the 2003–2009 influenza seasons and the 2009 pandemic, among children with asthma hospitalized with influenza, 116 had confirmed influenza B virus infections, 494 had seasonal influenza A virus infections, and 733 had presumed 2009 H1N1 virus infection. Children hospitalized with influenza A virus infections were more likely to

TABLE 2 Health Status and Complications Among Children With Asthma Hospitalized With Laboratory-Confirmed Influenza, EIP Surveillance for Influenza-Associated Hospitalizations, 2003–2009 ($N = 1343$)

	B, Reference, <i>n</i> (%)	Seasonal A, <i>n</i> (%)	Odds Ratio (95% Confidence Interval)	2009 H1N1, <i>n</i> (%)	Odds Ratio (95% Confidence Interval)
Total	116	494		733	
No additional underlying medical conditions ^a	67 (58)	365 (74)	2.1 (1.4–3.1)	540 (74)	2.0 (1.4–3.1)
ICD-9 diagnosis of pneumonia ^{b,c}	37/92 (40)	157/404 (39)	0.9 (0.6–1.5)	276/603 (46)	1.3 (0.8–2.0)
ICD-9 diagnosis of asthma exacerbation ^b	33/112 (29)	233/469 (50)	2.4 (1.5–3.7)	359/700 (51)	2.5 (1.6–3.9)
ICU admission	17 (15)	85 (17)	1.2 (0.7–2.1)	158 (22)	1.6 (0.9–2.8)
Respiratory failure ^d	7 (6)	24 (5)	0.8 (0.3–1.9)	35 (5)	0.8 (0.3–1.8)

^a Of the following underlying conditions: cardiovascular disease; chronic lung disease; chronic metabolic disease; febrile seizures; hemoglobinopathies; immunosuppression; neurologic disorders, including cerebral palsy and seizure disorders; and pregnancy.

^b Excluding cases with missing ICD-9 code data.

^c Of children who had chest radiographs during their hospitalizations.

^d Defined as requiring mechanical ventilation.

have no additional underlying medical conditions than children hospitalized with influenza B virus infections (seasonal influenza A: odds ratio: 2.1 [95% confidence interval: 1.4–3.1]; 2009 H1N1: odds ratio: 2.0 [95% confidence interval: 1.4–3.1]). Children with asthma hospitalized with influenza A virus infections also were more likely to be hospitalized with acute asthma exacerbations or status asthmaticus (seasonal influenza A: odds ratio: 2.4 [95% confidence interval: 1.5–3.7]; 2009 H1N1: odds ratio: 2.5 [95% confidence interval: 1.6–3.9]) compared with children with asthma with influenza B virus infections who were more likely to be hospitalized with a nonasthma acute diagnosis (Table 2).

DISCUSSION

In this analysis, children with asthma accounted for 32% of children aged 2 to 17 years hospitalized with seasonal influenza and 44% of children aged 2 to 17 years hospitalized with 2009 H1N1 influenza. Among children with asthma who were hospitalized with influenza, the majority did not have additional underlying medical conditions, and a substantial proportion had pneumonia or required ICU admission. In addition, compared with children with asthma

hospitalized with seasonal influenza, a greater proportion of those with 2009 H1N1 influenza had evidence of a severe hospital course, as indicated by an increased incidence of pneumonia and need for intensive care, although the proportion of children with asthma who developed respiratory failure was the same among children with seasonal or 2009 H1N1 influenza.

Despite long-standing recommendations for influenza vaccination of people with asthma,^{10,11} and that influenza vaccination remains the most effective influenza prevention strategy,¹¹ influenza vaccination coverage among US children with asthma remains poor.¹² Among hospitalized children with asthma in our cohort, less than one-half had received at least 1 dose of seasonal influenza vaccine for the current season, consistent with national estimates of influenza vaccination coverage among people with asthma. The effect of influenza vaccination on hospital course and outcomes among children in our cohort could not be evaluated because data on the number of doses of influenza vaccine received were incomplete for children aged 2 through 8 years who require 2 doses of influenza vaccine in their first year

of influenza vaccination to be considered fully vaccinated. Although it is unclear whether influenza vaccination is effective against preventing influenza-associated asthma exacerbations,^{13,14} influenza vaccination has been shown to be effective in preventing laboratory-confirmed influenza among children with asthma and should be encouraged in this high-risk group.¹⁵ Children with asthma with additional underlying medical conditions are likely to have contact with multiple providers within the health care system, which should be recognized as additional opportunities to provide influenza vaccination to this vulnerable population.

Both influenza strain-specific and, to a lesser degree, type-specific differences in clinical manifestations and influenza severity have been observed in previous epidemiologic studies⁷ but still are not well defined. In this analysis, we found that children with asthma hospitalized with influenza A virus infections were more than twice as likely to be hospitalized with acute asthma exacerbations or status asthmaticus as children hospitalized with influenza B virus infections. Hospitalized children with influenza A virus infections also were more likely to have no additional underlying medical conditions. This observation might suggest that influenza A viruses are capable of inducing more severe airway inflammation and bronchial hyperresponsiveness in children with asthma, although this propensity also may vary by influenza A virus strain.

Our analysis was limited by lack of data on underlying asthma disease severity and asthma control among children in the analysis cohort. Although underlying asthma disease severity may not necessarily correlate with asthma exacerbation severity,¹⁰ asthma severity and asthma control may be important predictors of severe influenza-associated complications (eg, ICU admission, respiratory failure) in children with asthma admitted for reasons other than asthma exacerbations. In addition, because only data on ICD-9 codes were collected consistently during all analysis seasons, whereas data on radiologists' or clinicians' interpretations of chest radiographs were not, our analysis used ICD-9 codes to identify children with influenza-associated pneumonia among children who had chest radiographs during hospitalization. Before the 2008–2009 influenza season, when the EIP system collected both ICD-9 code data and data from clinicians' or radiologists' notes about patients' chest radiographs, 68% of children with ICD-9 codes for infectious pneumonia had medical records containing clinicians' or radiologists' notes indicating the presence of radiologically-confirmed pneumonia suggesting that use of ICD-9 codes to identify radiologically confirmed pneumonia is less specific. However, use of ICD-9 code data allowed for comparison of children across all seasons in this analysis, using a consistent definition of influenza-associated pneumonia. Finally, EIP surveillance for influenza-associated hospitalizations identified patients through clinician-initiated influenza diagnostic testing,

and influenza testing practices likely changed during the 2009 pandemic with increased attention given to influenza and availability of highly sensitive RT-PCR testing for influenza viruses. These changes in influenza testing practices may have led to differences in case ascertainment with a larger proportion of all influenza-associated hospitalizations detected during the 2009 pandemic than during previous seasons.

CONCLUSIONS

Based on data from 1400 children hospitalized with asthma and influenza during 6 influenza seasons and the 2009 pandemic, we provide the first description of the characteristics and clinical courses of children with asthma hospitalized with influenza in the United States. Our analysis documents the substantial burden of influenza-associated complications among children with asthma hospitalized with influenza during both typical influenza seasons and the 2009 pandemic and suggests that influenza A virus infections may be more likely than influenza B virus infections to result in acute asthma exacerbations and severe illness requiring hospitalization among children with asthma without additional underlying medical conditions. Given the consistently low influenza vaccine coverage levels among children with asthma in the United States, our findings highlight the importance of actively working to increase annual influenza vaccination of children with asthma.

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