

ORIGINAL ARTICLE

The Underrecognized Burden of Influenza in Young Children

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ABSTRACT

BACKGROUND

The disease burden of influenza infection among children is not well established. We conducted a population-based surveillance of medical visits associated with laboratory-confirmed influenza.

METHODS

Eligible children were younger than five years of age, resided in three U.S. counties, and had a medical visit for an acute respiratory tract infection or fever. Nasal and throat swabs were tested for the influenza virus by viral culture and polymerase-chain-reaction assay. Epidemiologic data were collected from parental surveys and chart reviews. Children who were hospitalized were enrolled prospectively from 2000 through 2004. Population-based rates of hospitalizations associated with influenza were calculated. Children who were seen in selected pediatric clinics and emergency departments during two influenza seasons (2002–2003 and 2003–2004) were systematically enrolled. The rates of visits to clinics and emergency departments associated with influenza were estimated.

RESULTS

The average annual rate of hospitalization associated with influenza was 0.9 per 1000 children. The estimated burden of outpatient visits associated with influenza was 50 clinic visits and 6 emergency department visits per 1000 children during the 2002–2003 season and 95 clinic visits and 27 emergency department visits per 1000 children during the 2003–2004 season. Few children who had laboratory-confirmed influenza were given a diagnosis of influenza by the treating physician in the inpatient (28 percent) or outpatient (17 percent) settings.

CONCLUSIONS

Among young children, outpatient visits associated with influenza were 10 to 250 times as common as hospitalizations. Few influenza infections were recognized clinically.

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INFLUENZA VIRUS IS AN IMPORTANT CAUSE of respiratory illness among children. Modeling studies suggest that children younger than two years of age have high rates of hospitalization attributable to influenza; these rates are similar to rates of hospitalization attributable to influenza among older adults.^{1,2} However, rates of hospitalization and outpatient visits attributable to laboratory-confirmed influenza infections are not well described.

In 1999, the New Vaccine Surveillance Network (NVSN), sponsored by the Centers for Disease Control and Prevention (CDC), began prospective surveillance to determine population-based rates of laboratory-confirmed influenza and to assess the effects of recommendations regarding vaccination.³ Before 2002, annual vaccination against influenza was recommended only for children older than six months of age with certain coexisting conditions and for household contacts of those children. During the 2002–2003 and 2003–2004 influenza seasons, vaccination was encouraged for all children 6 to 23 months of age. Routine vaccination of all children 6 to 23 months of age was recommended beginning in 2004.

To determine rates of visits attributable to influenza, we performed active, prospective surveillance among children younger than five years of age who resided in three counties and presented to the inpatient and outpatient settings with acute respiratory tract infections or fever. This study differed from two previous NVSN reports. One report included only data from the first year of surveillance from inpatient settings, and the other was a brief summary of hospitalization rates for four years.^{3,4} In the current study, we determined hospitalization rates, estimated rates of outpatient visits, and compared the relative burdens attributable to influenza in the inpatient and outpatient settings of visits before the recommendation for routine vaccination against influenza of all children 6 to 23 months of age. We also determined the proportion of these influenza illnesses that was recognized clinically.

METHODS

STUDY DESIGN

Inpatient Population

A prospective, population-based study of hospitalizations attributable to laboratory-confirmed influenza was performed year-round in counties

that encompass Nashville and Rochester, New York, beginning in October 2000 and in Cincinnati beginning in October 2003. Each site conducted surveillance through September 2004 at hospitals in which at least 95 percent of hospitalizations for acute respiratory tract infections or fever occurred among children residing in the county. More detailed information on site selection, comparison with the U.S. population, and specific laboratory methods, as well as calculations of the rates of inpatient and outpatient visits, are in the Supplementary Appendix (available with the full text of this article at www.nejm.org).

Study nurses enrolled children from Sunday to Thursday within 48 hours after admission to surveillance hospitals. Eligible children were county residents, were younger than five years of age, and were admitted with a diagnosis of acute respiratory tract infection or fever. Excluded were children with respiratory symptoms for more than 14 days; children with fever, and neutropenia associated with chemotherapy; children hospitalized in the prior 4 days or transferred from another surveillance hospital; and newborns never discharged from the hospital.

Outpatient Population

A prospective study of laboratory-confirmed influenza among county children presenting to selected clinics and emergency departments with symptoms of acute respiratory tract infection or fever was performed during the 2002–2003 and 2003–2004 influenza seasons in Nashville and Rochester, and during 2003–2004 in Cincinnati. Study nurses enrolled approximately six to eight children per setting per surveillance day in clinics and emergency departments using similar inclusion and exclusion criteria. Because several eligible children might have been available concurrently, to avoid selection bias nurses approached eligible children in the order in which they checked in. Children were enrolled one or two days per week in one to four pediatric clinics per county and were enrolled three or four days per week in the only emergency department associated with the children's hospital in each county. The percentage of all visits attributable to acute respiratory tract infection or fever for county children seen at these emergency departments was 30 percent in Nashville, 70 percent in Rochester, and 95 percent in Cincinnati.

Written informed consent was obtained from

each child's parent or guardian before enrollment. The institutional review boards at each study site, the participating surveillance hospitals, and the CDC approved the study.

DEMOGRAPHIC AND CLINICAL INFORMATION

Demographic information, medical and social history, and influenza-vaccination status were obtained from a standardized survey administered to the parent or guardian. Race and ethnicity were determined by parental report and, for children with missing data, by chart review. We obtained the history of the underlying medical conditions for which vaccination against influenza is routinely recommended, laboratory and radiographic results, hospital course, and discharge diagnoses from a chart review.³

LABORATORY TESTS

At each site, one nasal swab and one throat swab were collected from each enrolled child. A specimen was defined as being influenza-positive if viral culture or duplicate reverse-transcriptase-polymerase-chain-reaction (RT-PCR) assays were positive for influenza A or B.^{3,5}

DEFINITION OF INFLUENZA SEASON FOR OUTPATIENT SURVEILLANCE

Outpatient surveillance began the first week after two positive tests for respiratory syncytial virus or influenza virus were identified in two consecutive weeks in local research or hospital laboratories. Surveillance ended after fewer than two positive tests were detected in two consecutive weeks. The influenza season comprised the 13 consecutive weeks that contained the maximum number of influenza cases.

STATISTICAL ANALYSIS

Characteristics of children were evaluated with the use of chi-square analysis for covariates and Student's *t*-test for continuous variables. The test for trend described by Armitage⁶ and Cochran⁷ was used to compare the proportions of children vaccinated according to year. A two-sided *P* value of less than 0.05 was considered to indicate statistical significance. All statistical analyses were performed with SAS software (version 9.1) and Stata software (versions 8.1 and 8.2).

We calculated the number of hospitalizations per 1000 children using the seasonal weighted number of hospitalizations attributable to influ-

enza-related acute respiratory tract infections or fever, adjusting for the number of days of surveillance and proportion enrolled, divided by the county population according to the 2000 U.S. Census and multiplied by 1000. The 95 percent confidence intervals were calculated with the use of 1000 bootstrap samples for each rate.³

For each 13-week influenza season, we calculated the proportion of children with confirmed influenza infection enrolled in the selected clinics and emergency departments at each site. The 95 percent confidence intervals were computed with the use of the binomial distribution.⁸

Outpatient surveillance was not population-based, so to estimate population-based rates of visits for acute respiratory tract infection or fever we used the National Ambulatory Medical Care Survey (NAMCS) and the National Hospital Ambulatory Medical Care Survey (NHAMCS) data from January to March of 1998 through 2002; these data encompassed five influenza seasons.^{9,10}

We estimated rates of acute respiratory tract infection or fever attributable to influenza by multiplying the influenza burden for each age group, setting, and study year (from outpatient surveillance) by the estimated age-specific rate of acute respiratory tract infection or fever (from NAMCS/NHAMCS). The 95 percent confidence intervals accounted for the estimation in both the burden (according to setting) and the rate of acute respiratory tract infection or fever with the use of the delta method.¹¹ We also calculated the population-based rates for the Cincinnati and Rochester pediatric emergency departments and compared them with the 95 percent confidence intervals for the estimated rates of emergency department visits.

RESULTS

INPATIENT SURVEILLANCE

Study Population

Of 3359 eligible children with acute respiratory tract infection or fever from October 2000 through September 2004, 2797 (83 percent) were enrolled. Of this group of enrolled children, 160 (6 percent) had laboratory-confirmed influenza. Characteristics of children hospitalized with influenza infections were similar at each site and in each study year, so we present cumulative results (Table 1). Younger children accounted for most of the hospitalizations — nearly half were younger than

Table 1. Characteristics of Children with Symptoms of Acute Respiratory Tract Infection or Fever, According to Enrollment Setting and Status on Influenza Testing.*

Characteristic	Inpatient Population†			Outpatient Population‡		
	Influenza-Positive (N=160) no. (%)	Influenza-Negative (N=2637) no. (%)	P Value	Influenza-Positive (N=267) no. (%)	Influenza-Negative (N=1401) no. (%)	P Value
Sex			0.01			0.49
Female	86 (54)	1150 (44)		130 (49)	650 (46)	
Male	74 (46)	1487 (56)		137 (51)	751 (54)	
Age			0.87			<0.001
0–5 mo	79 (49)	1250 (47)		20 (7)	250 (18)	
6–23 mo	49 (31)	856 (32)		107 (40)	659 (47)	
24–59 mo	32 (20)	531 (20)		140 (52)	492 (35)	
Race§			0.31			0.05
White	68 (42)	1266 (48)		86 (32)	561 (40)	
Black	57 (36)	898 (34)		116 (43)	526 (38)	
Other	35 (22)	473 (18)		64 (24)	314 (22)	
High-risk illness			0.004			0.96
Asthma	20 (12)	621 (24)		44 (16)	241 (17)	
Other	14 (9)	235 (9)		11 (4)	58 (4)	
None	126 (79)	1781 (67)		212 (79)	1102 (79)	
Insurance			0.16			0.09
Public	98 (61)	1378 (52)		180 (67)	845 (60)	
Private	50 (31)	973 (37)		76 (28)	486 (35)	
None	10 (6)	232 (9)		0	0	
Unknown	2 (1)	54 (2)		11 (4)	70 (5)	

* Diagnoses of acute respiratory tract infection on admission included acute respiratory illness, apnea, asthma, bronchiolitis, croup, exacerbation of cystic fibrosis, hypothermia, fever without a localizing source, febrile seizure, influenza infection, otitis media, other respiratory infections, paroxysmal cough, pharyngitis, pneumonia, respiratory distress, respiratory syncytial virus infection, suspected sepsis, sinusitis, tonsillitis, upper respiratory illness, and wheezing. Percentages may not total 100 because of rounding.

† Patients were evaluated year-round from October 2000 through September 2004. Seven patients whose test results were positive for influenza and 67 patients whose test results were negative for influenza were enrolled as outpatients and were subsequently hospitalized. In this table, they are reported as inpatients only.

‡ Patients were evaluated during 13-week seasons in 2002–2003 and 2003–2004.

§ Race was determined by parental report and, for those children for whom data were not available, by chart review. For one child with laboratory-confirmed influenza, race was not known.

6 months of age and 80 percent were younger than 24 months of age. Both children with and those without influenza averaged 4 days of symptoms before enrollment (3.7 with influenza vs. 4.0 without influenza, $P=0.43$).

Clinical Manifestations

Hospitalized children with influenza who were 0 to 5 months of age and 6 to 59 months of age had a median of 3 and 4 symptom days (range, 1 to 14) before admission, respectively; however, a mean (\pm SE) of 35 ± 4 percent had symptoms for 2 days or less. Most children had fever (93 ± 2 per-

cent), cough (87 ± 3 percent), and rhinorrhea (83 ± 3 percent). Fewer children 0 to 5 months of age than those 6 to 59 months of age had cough (80 percent vs. 94 percent, $P=0.01$) or both fever and cough (70 percent vs. 91 percent, $P=0.001$). Children with influenza were hospitalized for a median of two days, and 4 ± 2 percent were admitted to the intensive care unit (Table 2). Children 0 to 5 months of age as compared with those 6 to 59 months of age required oxygen less often but had more blood, urine, or cerebrospinal fluid cultures obtained and had proportionally fewer chest radiographs ($P<0.05$ for each). Bacterial

Table 2. Characteristics of Hospitalizations Attributable to Influenza, According to Age Group (2000–2004).

Characteristic	Age of Patient			P Value
	0–5 Mo (N=79)	6–23 Mo (N=49)	24–59 Mo (N=32)	
Length of stay — days				0.40
Median	2	2	2	
Range	1–7	0–15	1–17	
Admission to ICU — no. (%) [*]	2 (3)	2 (4)	3 (9)	0.22
Oxygen requirement — no. (%)	10 (13)	15 (31)	11 (34)	0.01
Bacterial coinfection — no. (%)	1 (1)	0	0	1.00
Viral coinfection — no. (%)	12 (15)	7 (14)	3 (9)	0.72
Diagnostic evaluation — no. (%)				
Chest radiograph	36 (46)	37 (76)	23 (72)	0.001†
Blood culture	59 (75)	30 (61)	16 (50)	0.03†
Urine culture	56 (71)	11 (22)	7 (22)	<0.001†
Cerebrospinal fluid culture	48 (61)	6 (12)	0	<0.001†
Discharge diagnosis — no. (%)				
Influenza	22 (28)	12 (24)	11 (34)	0.62
Bronchiolitis	20 (25)	10 (20)	1 (3)	0.02†
Pneumonia	4 (5)	9 (18)	5 (16)	0.04†
Asthma	1 (1)	6 (12)	2 (6)	0.02†
Seizure	0	4 (8)	3 (9)	0.01†
Viral illness	17 (22)	3 (6)	9 (28)	0.02†
Fever/suspected sepsis	15 (19)	5 (10)	1 (3)	0.06

* ICU denotes intensive care unit.

† P<0.05 for the comparison among age groups.

coinfection was identified in only one child, a one-month-old infant with group B streptococcal bacteremia. Twenty-two children with influenza had other viral coinfections (17 had respiratory syncytial virus, 4 adenovirus, and 1 parainfluenza virus), but their hospital course was similar to that of children without coinfections. Bronchiolitis, viral illness, and fever or suspected sepsis were diagnosed in half of all children with influenza. Of all children with laboratory-confirmed influenza, influenza was diagnosed in only 28±3 percent.

Vaccinations against Influenza

Among all children 6 to 59 months of age with acute respiratory tract infection or fever who were hospitalized from November through March, parents reported that 16 percent, 11 percent, 23 percent, and 23 percent had received one or more doses of influenza vaccine during year 1, year 2, year 3, and year 4 of the study, respectively (P<0.01

for trend). For children with and those without coexisting conditions for which influenza vaccine is specifically recommended, 26 percent and 9 percent were vaccinated, respectively (P<0.001). For healthy children 6 to 23 months of age, influenza vaccination rates were 11 percent, 4 percent, 10 percent, and 16 percent during year 1, year 2, year 3, and year 4, respectively (P<0.01 for trend).

Diagnosis of Influenza Infection

Of laboratory-confirmed influenza infections in 160 hospitalized children, 46±4 percent were identified by culture and PCR, 48±4 percent were identified by PCR only, and 7±2 percent were identified by viral culture alone. Influenza A accounted for 89±2 percent of infections. Surveillance laboratory results were not available to the clinicians before the patients were discharged, so only 28±4 percent of all children and 43±19 percent of children admitted to the intensive care unit with influenza infections had a discharge diagnosis of

influenza. Other common discharge diagnoses varied according to age group (Table 2). Only 52 of 160 children (33±4 percent) had an influenza test as part of their clinical care. Overall, only 38 of the 160 children (24±3 percent) identified as having influenza by the NVSN were also identified as having influenza by one or more clinical tests for influenza (26 by rapid antigen detection, 19 by viral culture, and 3 by PCR) during hospitalization. Some children had both a viral culture and rapid test that was positive for influenza.

Hospitalization Rates

From 2000 to 2004, an average of 0.9 per 1000 children 0 to 59 months of age were hospitalized with laboratory-confirmed influenza (95 percent confidence interval, 0.8 to 1.1 per 1000) with annual variations according to age group, year, and site (Table 3 and Fig. 1). Average annual rates of hospitalization attributable to influenza were 4.5 per 1000 children 0 to 5 months of age (95 percent confidence interval, 3.4 to 5.5 per 1000), 0.9 per 1000 children 6 to 23 months of age (95 percent confidence interval, 0.7 to 1.2 per 1000), and 0.3 per 1000 children 24 to 59 months of age (95 percent confidence interval, 0.2 to 0.5 per 1000).

OUTPATIENT SURVEILLANCE

Study Population

Among all 1742 children enrolled in outpatient clinics and emergency departments during the

13-week influenza seasons, 274 children (16 percent) had confirmed influenza infections. Children with influenza and children without influenza had similar characteristics (Table 1) except that influenza was detected more often in older children. Both children with influenza and children without influenza had 3.9 days of symptoms before enrollment ($P=0.93$), and 42±4 percent of children in the emergency department and 25±4 percent of children in the clinic had symptoms for 2 days or less. Among children presenting to clinics, 8±2 percent of children 0 to 5 months of age had influenza, and 28±9 percent of them were subsequently hospitalized; 14±1 percent of children 6 to 23 months of age had influenza, and 4±2 percent of them were hospitalized; and 22±2 percent of children 24 to 59 months of age had influenza, and less than 1 percent of them were hospitalized.

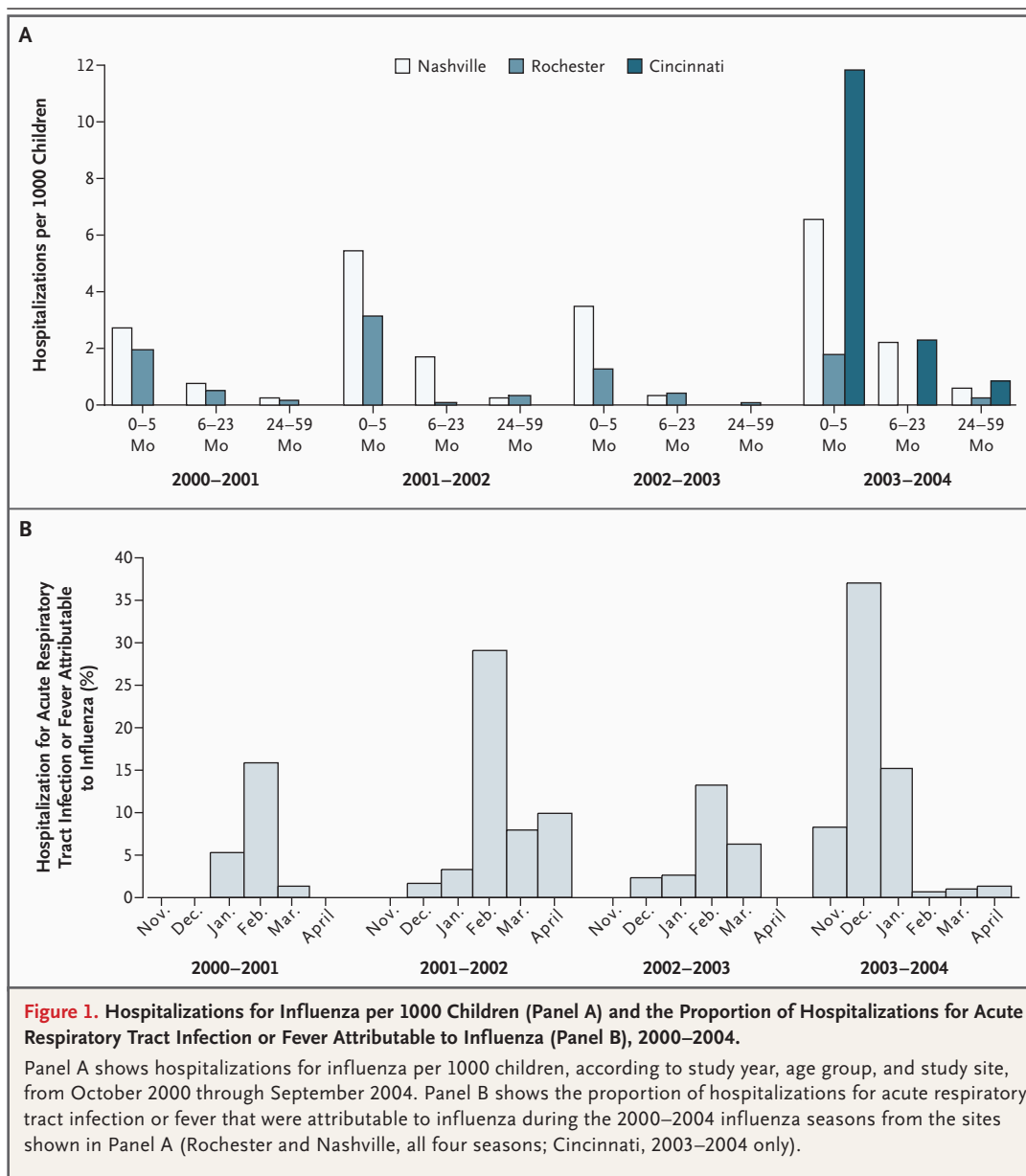
Clinical Manifestations

Clinical manifestations of influenza in the outpatient settings were similar among all age groups. Common symptoms included fever (95±1 percent of the children), cough (96±1 percent), and rhinorrhea (96±1 percent). Most children (91±2 percent) had fever and cough. Otitis media was diagnosed in approximately 28±1 percent of the children, pneumonia in 6±0.6 percent, and seizures in 1±0.2 percent; the frequency of these diagnoses did not differ significantly between children with

Table 3. Rate of Hospitalizations Attributable to Influenza per 1000 Children, According to Age Group and Study Year.*

Age Group	2000–2001	2001–2002	2002–2003	2003–2004	2000–2004
0–5 mo of age					
Weighted count	20	37	20	103	180
Rate (95% CI)	2.4 (1.0–3.9)	4.3 (2.2–6.6)	2.3 (0.9–3.8)	7.2 (5.3–9.2)	4.5 (3.4–5.5)
6–23 mo of age					
Weighted count	16	22	10	66	114
Rate (95% CI)	0.6 (0.2–1.2)	0.9 (0.4–1.3)	0.4 (0.1–0.7)	1.5 (1.0–2.1)	0.9 (0.7–1.2)
24–59 mo of age					
Weighted count	11	17	2	50	80
Rate (95% CI)	0.2 (0.1–0.4)	0.3 (0.1–0.6)	0.04 (0.00–0.13)	0.6 (0.3–0.9)	0.3 (0.2–0.5)
0–59 mo of age					
Weighted count	47	76	32	219	374
Rate (95% CI)	0.6 (0.3–0.8)	0.9 (0.6–1.2)	0.4 (0.2–0.6)	1.5 (1.2–1.9)	0.9 (0.8–1.1)

* Numbers are combined rates for three sites in the NVSN. CI denotes confidence interval. Counts were weighted for days of surveillance and proportion of eligible children enrolled.



influenza and children without influenza. Asthma occurred less frequently among children with influenza than among children without influenza (6 percent vs. 12 percent, $P=0.003$). Overall, only 17 ± 2 percent of children in outpatient settings with laboratory-confirmed influenza infections were given a diagnosis of influenza by their providers. Of these children with a diagnosis of influenza, some children received a diagnosis of asthma, pneumonia, or seizures, and the rest were given a nonspecific diagnosis of a viral infection.

Vaccinations against Influenza

More parents reported that enrolled children 6 to 59 months of age who presented to the clinic had received a vaccination against influenza during the 2003–2004 season than during the 2002–2003 season (30 percent vs. 12 percent, $P<0.001$), but only 7 percent of parents of enrolled children who presented to the emergency department during both seasons reported that their children were vaccinated. Parental report of vaccinations against influenza increased for healthy children 6 to 23 months of age enrolled from the clinic during

the two study years (from 11 percent to 39 percent, $P < 0.001$).

Practice-Based Burden

Laboratory-confirmed influenza infections accounted for a mean of 10.2 percent of weekly clinic visits for acute respiratory tract infection or fever during the influenza season of 2002–2003 and 19.4 percent of weekly clinic visits for acute respiratory tract infection or fever during the influenza season of 2003–2004. In the emergency department, laboratory-confirmed influenza infections accounted for a mean of 5.9 percent of weekly visits for acute respiratory tract infection or fever in 2002–2003 and 28.8 percent of weekly visits for acute respiratory tract infection or fever in 2003–2004 (Table 4). National rates of visits for acute respiratory tract infection or fever were 489 clinic visits and 94 emergency department visits per 1000 children younger than five years of age. The estimated rates of visits attributable to influenza, obtained by multiplying NVSN data on the percentage of visits for influenza by the national rates of visits, yielded 50 and 95 outpatient visits and 6 and 27 emergency department visits per 1000 children younger than five years of age in the two successive surveillance years.

Surveillance of the Rochester and Cincinnati

emergency departments included close to 70 percent and 95 percent of county children, respectively, so we also calculated the rates of population-based emergency department visits directly in those locales. In Rochester in 2002–2003, the weighted outpatient population-based rate was 5 per 1000 children, as compared with the estimated rate of 4 to 9 per 1000 children (Table 4). In 2003–2004, the population-based rates were 26 and 30 per 1000 children in Rochester and Cincinnati, respectively, as compared with an estimated rate of 22 to 33 per 1000 children.

Overall, rates of visits to clinics and emergency departments attributable to influenza were highest among children 6 to 23 months of age and lowest among children 0 to 5 months of age. Altogether, visits attributable to influenza were common, with 56 visits to clinics and emergency departments per 1000 children 0 to 59 months of age during the 2002–2003 influenza season and 122 visits to clinics and emergency departments per 1000 children 0 to 59 months of age during the 2003–2004 season.

DISCUSSION

We used active, prospective surveillance with laboratory confirmation over a period of four years

Table 4. Outpatient Visits for Acute Respiratory Tract Infection or Fever Associated with Confirmed Influenza.*

Age Group	Visits for Acute Respiratory Tract Infection or Fever Associated with Confirmed Influenza		Mean Rate of Visits for Acute Respiratory Tract Infection or Fever, 1998–2002†	Estimated Rate of Visits Attributable to Influenza‡	
	2002–2003	2003–2004		2002–2003	2003–2004
	% (95% CI)			no./1000 children (95% CI)	
Outpatient clinics					
0–5 mo	4.6 (0.1–15.5)	9.7 (4.0–19.0)	611 (428–794)	28 (7–111)	59 (28–128)
6–23 mo	7.3 (4.0–11.9)	17.5 (12.8–23.1)	711 (555–869)	52 (30–90)	125 (87–179)
24–59 mo	14.9 (10.0–21.1)	24.8 (19.0–31.2)	357 (277–437)	53 (35–81)	88 (64–123)
0–59 mo	10.2 (7.5–13.6)	19.4 (16.0–23.1)	489 (387–591)	50 (35–71)	95 (72–125)
Emergency departments					
0–5 mo	0.0 (0–4.1)	18.2 (11.8–26.2)	127 (95–159)	0	23 (15–36)
6–23 mo	5.5 (2.6–10.2)	26.2 (20.9–32.1)	150 (127–173)	8 (4–16)	39 (30–51)
24–59 mo	11.4 (6.0–19.1)	39.0 (32.0–46.4)	60 (49–71)	7 (4–12)	23 (18–30)
0–59 mo	5.9 (3.7–8.9)	28.8 (25.0–32.7)	94 (78–110)	6 (4–9)	27 (22–33)

* CI denotes confidence interval.

† The mean rate of visits for acute respiratory tract infection or fever per 1000 children was calculated from the National Ambulatory Medical Care Survey/National Hospital Ambulatory Medical Care Survey.¹⁰

‡ Rates were calculated by multiplying the proportions of visits for acute respiratory tract infection or fever associated with confirmed influenza (columns 2 and 3) by the mean rate of visits for acute respiratory tract infection or fever, 1998–2002 (column 4).

to estimate rates of influenza infection among children in inpatient and outpatient settings. We found a much higher burden of influenza infection in the outpatient setting than in the inpatient setting, a large variation in burden according to the year and site, and a lack of clinical recognition of influenza during most visits. Much of this influenza disease burden may be prevented through vaccination.

In our study, most influenza infections in children were not diagnosed clinically. Only 28 percent of hospitalizations and 17 percent of outpatient visits by children with laboratory-confirmed influenza infections had a discharge diagnosis of influenza, despite the usefulness of rapid influenza tests.¹²⁻¹⁴ As previously noted, surveillance that relies on data from physician-directed testing alone substantially underestimates the influenza burden.^{15,16} In addition, approximately 35 percent of children presented within two days after the onset of illness, when antiviral medications may have shortened the duration and severity of illness. Increased use of rapid influenza testing may raise awareness of the influenza burden among children, increase the use of antiviral medications, improve infection-control activities, and increase the perceived need for and use of influenza vaccine.

Although hospitalization rates attributable to influenza are important, the average annual rates of outpatient visits attributable to influenza were approximately 10, 100, and 250 times as high as hospitalization rates for children 0 to 5 months, 6 to 23 months, and 24 to 59 months of age, respectively.

The annual rates of hospitalization attributable to influenza, as determined prospectively by the NVSN, correspond to previously reported rates from retrospective studies. Previous estimates of rates of hospitalization attributable to influenza that used different study years, populations, and methods have ranged from 0.6 to 2.7 per 1000 children younger than five years of age.^{1,2,15,17-21} Similarly, our estimate of the outpatient influenza burden compares favorably with those of previous reports using different study years, populations, and methods.^{1,19,20} Taken together, these studies document a substantial overall influenza burden among young children. Although the rationale for enhanced vaccination against influenza in children has been based primarily on hospitalization rates, reducing the number of out-

patient visits attributable to the prevention of influenza by vaccination would have an even greater effect on costs.²²

Despite the strength of the NVSN data, several limitations should be noted. Surveillance was performed in two geographically diverse counties (in the Northeast and South) during the first three years and in a third county (in the Midwest) during the last year. Additional geographically diverse sites would enhance the generalizability of the findings. Geographic variation in influenza rates may have occurred, although the outpatient burden of influenza in 2002-2003 and 2003-2004 was similar across sites.²³ The lower rates of hospitalization attributable to influenza in Rochester may in part reflect differences in health care use; these differences are similar to those shown in previous studies.^{24,25} Although enrolled patients appeared to be representative of the eligible population, failure to enroll all eligible children and partial-week surveillance may have introduced bias. Because some eligible children were missed or did not meet our enrollment criteria, the observed rates modestly underestimate the true total influenza burden.¹⁶ However, the detection of influenza infections was maximized by means of both viral culture and PCR testing. Influenza A was the predominant virus isolated, and additional years of surveillance are necessary to determine the effect of influenza B.

Outpatient surveillance was performed in selected clinics and pediatric emergency departments. Hence, we used national estimates of visits to clinics and emergency departments from January to March of 1998 to 2002 to estimate the 13-week rate of visits attributable to influenza-related acute respiratory tract infection or fever. This seasonal definition included the majority of visits associated with influenza for each influenza season.²⁶ Estimates of rates of visits attributable to influenza that were based on national rates of visits attributable to acute respiratory tract infection or fever were similar to the direct calculation of rates of population-based visits to emergency departments in Cincinnati and Rochester that were attributable to influenza; this similarity lends further credence to this method.

Children's vaccination status was determined by parental report. Although the report of vaccination against influenza by adults is highly sensitive and specific,²⁷ the accuracy of parental report is not yet known. However, these rates are simi-

lar to those in previous reports and the National Immunization Survey.^{28,29}

Influenza illnesses cause a substantial health burden, yet most influenza infections are unrecognized clinically. Enhanced recognition of influenza can provide the opportunity for improved infection control, education about vaccination, and antiviral therapy. Although the universal recommendation that all children 6 to 23 months of age be vaccinated was driven primarily by high hospitalization rates, our findings demonstrate that the outpatient burden of influenza is substantial.

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REFERENCES

- Neuzil KM, Mellen BG, Wright PF, Mitchel EF Jr, Griffin MR. The effect of influenza on hospitalizations, outpatient visits, and courses of antibiotics in children. *N Engl J Med* 2000;342:225-31.
- Izurieta HS, Thompson WW, Kramarz P, et al. Influenza and the rates of hospitalization for respiratory disease among infants and young children. *N Engl J Med* 2000;342:232-9.
- Iwane MK, Edwards KM, Szilagyi PG, et al. Population-based surveillance for hospitalizations associated with respiratory syncytial virus, influenza virus, and parainfluenza viruses among young children. *Pediatrics* 2004;113:1758-64.
- Griffin MR, Walker FJ, Iwane MK, Weinberg GA, Staat MA, Erdman DD. Epidemiology of respiratory infections in young children: insights from the New Vaccine Surveillance Network. *Pediatr Infect Dis J* 2004;23:Suppl:S188-S192.
- Weinberg GA, Erdman DD, Edwards KM, et al. Superiority of reverse-transcription polymerase chain reaction to conventional viral culture in the diagnosis of acute respiratory tract infections in children. *J Infect Dis* 2004;189:706-10.
- Armitage P. Test for linear trend in proportions and frequencies. *Biometrics* 1955;11:375-86.
- Cochran W. Some methods for strengthening the common chi-square test. *Biometrics* 1954;10:417-51.
- Brown LD, Cai TT, DasGupta A. Interval estimation for a binomial proportion. *Stat Sci* 2001;16:101-33.
- Estimate means, totals, ratios, and proportions for survey data. In: *Survey data reference manual*, release 8. College Station, Tex.: Stata Press, 2003.
- National Center for Health Statistics. National Ambulatory Medical Care Survey (NAMCS) and National Hospital Ambulatory Medical Care Survey (NHAMCS). Accessed June 16, 2006, at <http://www.cdc.gov/nchs/about/major/ahcd/ahcd1.htm>.
- Properties of a random sample. In: Casella G, Berger RL, eds. *Statistical inference*. Pacific Grove, Calif.: Duxbury/Thomson Learning, 2002.
- Poehling KA, Griffin MR, Dittus RS, et al. Bedside diagnosis of influenza virus infections in hospitalized children. *Pediatrics* 2002;110:83-8.
- Bonner AB, Monroe KW, Talley LI, Klasner AE, Kimberlin DW. Impact of the rapid diagnosis of influenza on physician decision-making and patient management in the pediatric emergency department: results of a randomized, prospective, controlled trial. *Pediatrics* 2003;112:363-7.
- Sharma V, Dowd MD, Slaughter AJ, Simon SD. Effect of rapid diagnosis of influenza virus type A on the emergency department management of febrile infants and toddlers. *Arch Pediatr Adolesc Med* 2002;156:41-3.
- Surveillance for laboratory-confirmed, influenza-associated hospitalizations — Colorado, 2004–05 influenza season. *MMWR Morb Mortal Wkly Rep* 2005;54:535-7.
- Grijalva CG, Craig AS, Dupont WD, et al. Estimating influenza hospitalizations among children. *Emerg Infect Dis* 2006;12:103-9.
- Mullooly JP, Barker WH. Impact of type A influenza on children: a retrospective study. *Am J Public Health* 1982;72:1008-16.
- Thompson WW, Shay DK, Weintraub E, et al. Influenza-associated hospitalizations in the United States. *JAMA* 2004;292:1333-40.
- O'Brien MA, Uyeki TM, Shay DK, et al. Incidence of outpatient visits and hospitalizations related to influenza in infants and young children. *Pediatrics* 2004;113:585-93.
- Neuzil KM, Zhu Y, Griffin MR, et al. Burden of inter-pandemic influenza in children younger than 5 years: a 25-year prospective study. *J Infect Dis* 2002;185:147-52.
- Glezen WP, Greenberg SB, Atmar RL, Piedra PA, Couch RB. Impact of respiratory virus infections on persons with chronic underlying conditions. *JAMA* 2000;283:499-505.
- Meltzer MI, Neuzil KM, Griffin MR, Fukuda K. An economic analysis of annual influenza vaccination of children. *Vaccine* 2005;23:1004-14.
- Update: influenza activity — United States and worldwide, 2003–04 season, and composition of the 2004–05 influenza vaccine. *MMWR Morb Mortal Wkly Rep* 2004;53:547-52.
- Homer CJ, Szilagyi P, Rodewald L, et al. Does quality of care affect rates of hospitalization for childhood asthma? *Pediatrics* 1996;98:18-23.
- Perrin JM, Greenspan P, Bloom SR, et al. Primary care involvement among hospitalized children. *Arch Pediatr Adolesc Med* 1996;150:479-86.
- Centers for Disease Control and Prevention. Flu activity: reports and surveillance methods in the United States. (Accessed June 9, 2006, at <http://www.cdc.gov/flu/weekly/fluactivity.htm>.)
- Mac Donald R, Baken L, Nelson A, Nichol KL. Validation of self-report of influenza and pneumococcal vaccination status in elderly outpatients. *Am J Prev Med* 1999;16:173-7.
- Hemingway CO, Poehling KA. Change in recommendation impacts influenza vaccinations among children 6 to 59 months of age. *Pediatrics* 2004;114:948-52.
- Centers for Disease Control and Prevention. National Immunization Survey (NIS). (Accessed June 9, 2006, at <http://www.cdc.gov/nip/coverage/#NIS>.)

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