The Burden of Influenza in Young Children, 2004–2009

AUTHORS: Katherine A. Poehling, MD, MPH,^{a,b} Kathryn M. Edwards, MD,^c Marie R. Griffin, MD, MPH,^{d,e} Peter G. Szilagyi, MD, MPH,^f Mary A. Staat, MD, MPH,^g Marika K. Iwane, PhD, MPH,^h Beverly M. Snively, PhD,ⁱ Cynthia K. Suerken, MS,ⁱ Caroline B. Hall, MD,^{f,j} Geoffrey A. Weinberg, MD,^f Sandra S. Chaves, MD, MSc,^h Yuwei Zhu, MD, MS,^k Monica M. McNeal, MS,^g and Carolyn B. Bridges, MD^h

Departments of ^aPediatrics, ^bEpidemiology and Prevention, and ^cBiostatistical Sciences, Wake Forest School of Medicine, Winston-Salem, North Carolina; Departments of ^dPediatrics, ^eMedicine, ^fPreventive Medicine, and ^gBiostatistics, Vanderbilt University Medical Center, Nashville, Tennessee; Departments of ^hPediatrics and ⁱMedicine, University of Rochester Schools of Medicine and Dentistry, Rochester, New York; ^jDepartment of Pediatrics, University of Cincinnati College of Medicine, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio; and ^kNational Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia

KEY WORDS

influenza, epidemiology, influenza vaccine, hospitalization, ambulatory care

ABBREVIATIONS

CDC—Centers for Disease Control and Prevention

ED—emergency department

NVSN—New Vaccine Surveillance Network

RT-PCR—reverse transcriptase-polymerase chain reaction

(Continued on last page)

WHAT'S KNOWN ON THIS SUBJECT: Influenza is an important cause of medically attended illness in young children before expanding influenza vaccine recommendations for children.

WHAT THIS STUDY ADDS: This study characterizes the health care burden of influenza in young children over 5 years (2004–2009) when influenza vaccine recommendations were expanded to all children aged ≥ 6 months.

abstract

OBJECTIVE: To characterize the health care burden of influenza from 2004 through 2009, years when influenza vaccine recommendations were expanded to all children aged ≥ 6 months.

METHODS: Population-based surveillance for laboratory-confirmed influenza was performed among children aged < 5 years presenting with fever and/or acute respiratory illness to inpatient and outpatient settings during 5 influenza seasons in 3 US counties. Enrolled children had nasal/throat swabs tested for influenza by reverse transcriptase-polymerase chain reaction and their medical records reviewed. Rates of influenza hospitalizations per 1000 population and proportions of outpatients (emergency department and clinic) with influenza were computed.

RESULTS: The study population comprised 2970, 2698, and 2920 children from inpatient, emergency department, and clinic settings, respectively. The single-season influenza hospitalization rates were 0.4 to 1.0 per 1000 children aged < 5 years and highest for infants < 6 months. The proportion of outpatient children with influenza ranged from 10% to 25% annually. Among children hospitalized with influenza, 58% had physician-ordered influenza testing, 35% had discharge diagnoses of influenza, and 2% received antiviral medication. Among outpatients with influenza, 7% were tested for influenza, 7% were diagnosed with influenza, and $< 1\%$ had antiviral treatment. Throughout the 5 study seasons, $< 45\%$ of influenza-negative children ≥ 6 months were fully vaccinated against influenza.

CONCLUSIONS: Despite expanded vaccination recommendations, many children are insufficiently vaccinated, and substantial influenza burden remains. Antiviral use was low. Future studies need to evaluate trends in use of vaccine and antiviral agents and their impact on disease burden and identify strategies to prevent influenza in young infants. *Pediatrics* 2013;131:207–216

Influenza remains a major cause of medically attended respiratory illness in young children. This has led to the Advisory Committee on Immunization Practices of the Centers for Disease Control and Prevention (CDC) expanding influenza vaccination recommendations from children ≥ 6 months old with underlying medical conditions, to all children 6 to 23 months old in 2004,¹ to all children 6 to 59 months old in 2006,² and to all children ≥ 6 months in 2008.³

It is hoped that expanding vaccine recommendations would result in rising immunization coverage and declining disease burden, yet it is challenging to evaluate trends in disease burden of influenza. The circulating influenza virus strains and their match to vaccine strains and the timing and severity of the influenza season vary annually. Therefore, assessment of the disease burden over multiple years is needed to estimate the impact of new strategies on the burden of influenza. Previously, we evaluated the overall burden of influenza in children enrolled in the New Vaccine Surveillance Network (NVSN) from 2000 through 2004 and found an average of 0.9 (range 0.4–1.5) influenza hospitalizations per 1000 children aged < 5 years annually. Among outpatients, influenza caused 8% and 22% of acute respiratory illness and/or fever visits during the 2002–2003 and 2003–2004 influenza seasons, respectively.⁴

Since 2004, vaccination recommendations have expanded, and improved diagnostic tests and antiviral therapies have become available.^{1–3} Thus, an evaluation of the population-based burden of influenza is essential for assessing these control strategies. This report uses NVSN data from 2004 through 2009 to determine the burden of laboratory-confirmed influenza, vaccination coverage, and the frequency of physician-ordered influenza-specific

tests, influenza-specific discharge diagnoses, and antiviral prescriptions.

METHODS

We prospectively enrolled children aged < 5 years who resided in Hamilton County, Ohio (Cincinnati); Monroe County, New York (Rochester); and Davidson County, Tennessee (Nashville) from 2004–2005 through 2008–2009, all before the 2009 influenza A (H1N1) pandemic in this network. County children who were hospitalized during influenza season (generally November–April) with fever and/or acute respiratory symptoms or who presented to the emergency department (ED) or outpatient clinic with these symptoms were eligible for enrollment. Surveillance was population-based in the inpatient and ED settings.^{4,5} After obtaining informed consent, a standardized parental questionnaire was administered, combined nasal turbinate and throat swabs were collected and stored for each child to identify laboratory-confirmed influenza illness,⁶ and the child's medical record was reviewed.

Inpatient Surveillance

Population-based inpatient surveillance included all 3 sites during the 2004–2005 and 2008–2009 seasons, and 2 sites (Rochester and Nashville) during the 3 intervening seasons. A protocol deviation affected 70% of all hospitalized children enrolled at the Cincinnati site from 2005–2008; thus all hospitalized children enrolled in Cincinnati during these 3 years, including those not affected by this protocol deviation, were excluded (Fig 1). Surveillance was performed annually from November 1 through April 30 but was extended if influenza was detected earlier (beginning with ≥ 2 influenza-positive samples per site per week detected in local research or hospital laboratories) or ended later (continuing until < 2 positive samples were detected in 2 consecutive weeks). In 2004–2005 inpatient surveillance increased from 4 to 7 days/week when influenza was detected. From 2005–2006 through 2008–2009, inpatient surveillance increased from 2 to 5 days per week when influenza was detected.

*Reasons for children not being enrolled included parent/guardian declination (61%), lack of parent/guardian availability (16%), interpreter not available (13%), missed or discharged prior to enrollment (9%), and physician refusal (1%).

† Indeterminate RT-PCR had no detectable human RNA, indicating an inadequate sample.

FIGURE 1

Study population over 5 consecutive influenza seasons (November–April) from 2004 through 2009.

Outpatient Surveillance

In 2004–2005, samples were collected in the pediatric ED in Cincinnati; in 3 pediatric clinics (1 hospital-based and 2 private practices) in Nashville; and in the pediatric ED, 5 pediatric clinics (2 hospital-based and 3 private practices), and 1 family medicine clinic in Rochester. In all other years, all sites collected samples in the pediatric ED and 1 hospital-based, pediatric clinic. Surveillance in the EDs occurred every fourth day in 2004–2005 and 2005–2006. Surveillance was increased from 1 to 2 days/week when influenza was detected locally from 2006–2007 through 2008–2009 in the ED and for all years in the clinic.

Parental Report and Chart Review

Race/ethnicity and high-risk medical conditions for which influenza vaccine are specifically recommended were determined by parental report and/or chart review.^{1–3,7,8} The presence of asthma included any history of physician diagnosed asthma or reactive airway disease. Discharge diagnoses were determined by medical chart review not billing codes.

The child's influenza vaccination status was obtained at enrollment by parental report and confirmed by vaccination records from health care providers in all sites and also through the Ohio State Immunization Registry, which served as the vaccination record for some practices in Cincinnati.⁹ Fully vaccinated children had received either 2 doses of influenza vaccine ≥ 24 days apart and ≥ 14 days before illness onset in that season or 1 dose of influenza vaccine that season and had been previously vaccinated. Partially vaccinated children had received only 1 of 2 recommended doses ≥ 14 days before illness onset and had not been previously vaccinated. Unvaccinated children had not received any influenza

vaccine that season or had received 1 dose < 14 days before illness onset.

Laboratory-Confirmed Influenza

All study children had nasal/throat swabs tested for influenza A and B by reverse transcriptase-polymerase chain reaction (RT-PCR), and many had viral cultures.^{4,10,11} Study-protocol-confirmed influenza A or B virus infections were defined as either 2 consecutive positive RT-PCRs or positive culture.⁶ Indeterminate RT-PCR had no detectable human RNA, indicating an inadequate sample. Because viral subtyping was performed on only a few samples, subtyping data were not analyzed. Study results were not shared with families or physicians providing patient care.

Analysis

The proportions of enrolled children by laboratory-confirmed influenza status and demographic or clinical characteristics were assessed by using χ^2 analyses, Fisher exact tests, or Cochran-Armitage test for trend. The 95% confidence intervals for proportions were generated by using the Wilson confidence intervals for binomial distribution.¹²

To compute rates of influenza hospitalizations, the numerator was weighted for both the days of surveillance and the proportion of eligible children enrolled. The denominators were derived from the US post-2000 census estimates by age for each county and year.¹³ The estimated rate per 1000 children equaled the weighted number of influenza hospitalizations divided by the estimated population in surveillance counties for each year multiplied by 1000. The 95% confidence intervals for rates were generated by using 2000 bootstrap samples.¹⁴ Stata 8.1 (Stata Corp, College Station, TX) and SAS 9.2 (SAS Institute Inc, Cary, NC) were used to analyze data.

This study was approved by the institutional review boards of each study site and the CDC.

RESULTS

Inpatient Burden

Among 3589 eligible hospitalized children, 2970 (83%) children were enrolled with adequate nasal/throat samples (Fig 1). During the 5 surveillance seasons, study protocol-confirmed influenza was detected for a median of 18 weeks (range 15–22 weeks) with the influenza-positive proportion during each peak season being similar for all sampled days of the week. Almost half (48%) of hospitalized children were < 6 months of age. No significant differences existed among influenza-positive and influenza-negative children by age group, race/ethnicity, or high-risk conditions (Table 1). Significantly more influenza-positive than influenza-negative children had public insurance, were unvaccinated, and had symptoms for ≤ 2 days.

Among 2970 enrolled children, 7% had study protocol-confirmed influenza, ranging from 4% to 11% over 5 seasons. This proportion increased to 10% (range 4%–15%) during the peak 13 weeks of influenza activity. Among hospitalized children, 159 (80%) had influenza A and 40 (20%) had influenza B. Overall, the proportion of influenza A-positive children was 80% (range 64%–88%).

Average annual influenza hospitalization rates for children aged < 5 years were 0.58 per 1000 (range 0.36–0.97, Table 2 and Fig 2). Rates of influenza hospitalizations were highest among children < 6 months of age and lowest among children aged 2 to < 5 years (Table 2 and Supplemental Table 4). Influenza A caused $\sim 85\%$ and 50% of all influenza hospitalizations among children < 2 years and 2 to < 5 years, respectively.

Outpatient Burden

Among 3496 eligible children seen in the ED from November through April

TABLE 1 Demographic Characteristics of the Enrolled Study Population Over 5 Influenza Seasons (November–April) Overall and Among Those Who Had Study-Confirmed Influenza Infection

Characteristics	Inpatient				Outpatient			
	Total <i>N</i>	<i>n</i> Influenza + (row %)	RR ^a	<i>P</i> Value	Total <i>N</i>	<i>n</i> Influenza + (row %)	RR ^a	<i>P</i> Value
Age				.74				<.001
0–<6 mo	1423	96 (6.7)	1.00		1059	52 (4.9)	1.00	
6mo–<2y	970	69 (7.1)	1.05		2556	253 (9.9)	2.02	
2y–<5y	577	34 (5.9)	0.87		2003	311 (15.5)	3.16	
Race/ethnicity ^b				.11				<.001
Non-Hispanic white	1216	69 (5.7)	1.00		1560	133 (8.5)	1.00	
Non-Hispanic black	951	69 (7.3)	1.28		2615	330 (12.6)	1.48	
Hispanic	526	35 (6.7)	1.17		977	107 (11.0)	1.28	
Other	273	24 (8.8)	1.55		456	46 (10.1)	1.18	
Site				<.001				.04
Nashville	1271	103 (8.1)	2.61		1878	218 (11.6)	1.24	
Rochester	1023	75 (7.3)	2.36		2038	239 (11.7)	1.26	
Cincinnati ^c	676	21 (3.1)	1.00		1702	159 (9.3)	1.00	
Insurance ^d				.008				.09
Public	1848	135 (7.3)	1.35		4239	486 (11.5)	1.25	
Private	979	53 (5.4)	1.00		1112	102 (9.2)	1.00	
None	133	10 (7.5)	1.39		244	25 (10.2)	1.12	
Vaccination status ^e				.003				<.001
Full	332	14 (4.2)	1.00		864	82 (9.5)	1.00	
Partial	293	19 (6.5)	1.54		996	97 (9.7)	1.03	
None	815	72 (8.8)	2.10		2619	377 (14.4)	1.52	
High risk ^f				.08				.23
Yes	913	50 (5.5)	0.76		1278	152 (11.9)	1.11	
Yes, asthma	627	25 (4.0)	0.55		1126	125 (11.1)	1.04	
No	2057	149 (7.2)	1.00		4340	464 (10.7)	1.00	
Symptom days ^g				<.001				<.001
≤2	773	85 (11.0)	2.11		573	201 (35.1)	4.36	
>2	2190	114 (5.2)	1.00		5033	405 (8.0)	1.00	

^a Relative risk (RR) is calculated by dividing the percentage who are influenza-positive in each category by the percentage who are influenza-positive in the reference category, denoted by RR = 1.00.

^b Race/ethnicity was missing for 14 children.

^c Inpatient data for Cincinnati includes 2 seasons (2004–2005 and 2008–2009).

^d Insurance status was missing for 33 children.

^e Vaccination status determined by provider confirmation for children 6 to 59 months of age.

^f The *P* values for high-risk compare yes/no responses, excluding yes asthma, by influenza status.

^g Symptom days were missing for 7 influenza-negative inpatients and for 2 influenza-negative outpatients.

each year, 2698 (77%) children comprised the ED study population. Among 4009 eligible children seen in the outpatient clinics, 2920 (73%) comprised the clinic study population (Fig 1). All but 2 influenza-positive outpatient samples were detected from November through April each year with the median duration of influenza detection being 18 weeks (range 15–23 weeks).

Overall, 11% (range 8%–17%) of the enrolled outpatient children had study protocol-confirmed influenza with the proportion being slightly higher in the ED than the clinic (12% vs 10%, *P* = .05). A higher proportion of influenza-positive than influenza-negative children were

≥6 months of age, were black, resided in Rochester, were unvaccinated, and had symptoms for ≤2 days (Table 1). During the peak 13-week influenza seasons, the proportion of outpatient children <5 years who were influenza-positive was 16% (range 10%–25%, Fig 3 and Supplemental Table 4).

Among 616 influenza-positive children seen in outpatient settings, 70% had influenza A infection, 30% had influenza B infection, and <1% (*n* = 2) had both influenza A and B infections concurrently. The proportion of influenza A-positive children varied annually, ranging from 60% to 92% in the ED and from 53% to 91% in the clinic.

Influenza Vaccination Status

The influenza vaccination status among influenza-negative children ≥6 months of age varied by year (Fig 4 A and B), but overall, <45% of children were fully vaccinated in any setting. Partially vaccinated children were common in all settings. Among clinic children, a significant increase in fully and partially vaccinated children occurred over time.

Clinical Diagnostic Laboratory Testing for Influenza

Among inpatients with and without study protocol-confirmed influenza, treating physicians ordered influenza

TABLE 2 Rates of Laboratory-Confirmed Influenza Hospitalization per 1000 Children and 95% Confidence Intervals by Age Group, Influenza Season (November–April), and Influenza Virus Type

Season	Rate per 1000 Children (95% Confidence Interval)			
	<6 mo	6 mo–<2 y	2 y–<5 y	<5 y
All influenza				
2004–5	3.4 (2.5–4.5)	0.7 (0.4–1.0)	0.19 (0.09–0.30)	0.67 (0.53–0.83)
2005–6	2.4 (1.0–4.0)	0.6 (0.3–1.0)	0.15 (0.03–0.29)	0.50 (0.31–0.71)
2006–7	2.0 (0.9–3.3)	0.4 (0.1–0.7)	0.07 (0.00–0.18)	0.36 (0.20–0.55)
2007–8	4.3 (2.5–6.3)	1.3 (0.7–1.8)	0.22 (0.07–0.40)	0.97 (0.71–1.25)
2008–9	1.6 (0.7–2.6)	0.4 (0.1–0.7)	0.27 (0.11–0.46)	0.44 (0.28–0.61)
2004–9	2.7 (2.1–3.3)	0.6 (0.5–0.8)	0.19 (0.13–0.25)	0.58 (0.50–0.67)
Influenza A				
2004–5	2.8 (2.0–3.8)	0.6 (0.4–0.9)	0.10 (0.03–0.17)	0.53 (0.40–0.66)
2005–6	1.8 (0.7–3.1)	0.6 (0.3–1.0)	0.15 (0.03–0.29)	0.44 (0.28–0.63)
2006–7	1.3 (0.4–2.5)	0.4 (0.1–0.7)	0.04 (0.00–0.11)	0.27 (0.14–0.43)
2007–8	4.2 (2.5–6.3)	1.0 (0.6–1.6)	0.11 (0.00–0.25)	0.84 (0.59–1.11)
2008–9	1.3 (0.5–2.2)	0.3 (0.1–0.5)	0.08 (0.00–0.19)	0.27 (0.15–0.41)
2004–9	2.3 (1.7–2.8)	0.5 (0.4–0.7)	0.09 (0.05–0.14)	0.46 (0.38–0.53)
Influenza B^a				
2004–9	0.4 (0.2–0.7)	0.08 (0.03–0.15)	0.10 (0.05–0.15)	0.13 (0.09–0.17)

^a Overall rates of influenza B are shown because the number of influenza B cases identified in each age group by individual year was much smaller than the number of influenza A cases.

FIGURE 2

Influenza hospitalization rates per 1000 children <5 years of age with any influenza, influenza A, or influenza B, by influenza season (November–April). Line bars show the 95% confidence intervals for each rate.

diagnostic testing for 35% of enrolled children, ranging from 22% in 2004–2005 to 53% in 2007–2008. Among all hospitalized children who had physician-ordered influenza tests, the annual proportion of physician-ordered influenza tests that were positive varied (range 5%–17%).

Among children with study protocol-confirmed influenza, 93% of inpatients and 98% of outpatients with physician-ordered influenza testing had rapid

influenza testing performed and were positive for 66 (62%) of 107 hospitalized children and for 23 (56%) of 41 outpatient children with study protocol-confirmed influenza.

Among hospitalized children with study protocol-confirmed influenza, physician-ordered influenza testing was highest among infants <6 months (Table 3) and was more common among children with study protocol-confirmed influenza in

the inpatient setting (58%) than in the ED (9%) or clinic (1%, $P < .001$).

Influenza Diagnosis

Discharge diagnoses specified influenza in 35% of children hospitalized with study protocol-confirmed influenza, ranging annually from 30% to 44% ($P = .65$). A specific influenza diagnosis was significantly more common among infants <6 months of age than older children (Table 3) and among study protocol-confirmed influenza-positive children who also had positive rather than negative rapid influenza tests (91% vs 2%, $P < .001$).

Overall, discharge diagnoses specified influenza in 7% of outpatient visits with study protocol-confirmed influenza and were similar in the ED and clinic settings and across age groups. Eighteen (42%) of 43 children with a specific discharge diagnosis of influenza had a positive rapid influenza test. Children with study protocol-confirmed influenza but with negative rapid influenza tests infrequently (<1%) had a discharge diagnosis of influenza.

Influenza Treatment

Antiviral medications were prescribed for 3 hospitalized influenza-positive children aged 1 to 23 months and for 3 influenza-positive children aged 16 to 29 months in the outpatient setting. One child in each setting had high-risk medical conditions. Antivirals were infrequently prescribed among all sites and years, even though 43% of influenza-positive children were hospitalized within 2 days of symptom onset.

DISCUSSION

Over 5 influenza seasons from 2004 through 2009, the overall influenza vaccination coverage changed little, whereas the rates of influenza hospitalization and prevalence of influenza among outpatients varied annually. Influenza testing among children with

FIGURE 3

Proportion of outpatient (ED and clinic) children <5 years of age with fever or acute respiratory illness who had any influenza, influenza A, or influenza B during the peak 13 weeks, by season. Line bars show the 95% confidence intervals for each proportion.

FIGURE 4

Proportion of influenza-negative children ≥6 months and <5 years of age who were (A) fully vaccinated or (B) received any vaccine against influenza, by influenza season (November–April) and setting. * Significant increase ($P < .001$) over time by Cochran-Armitage test for trend.

study protocol-confirmed influenza was highest among hospitalized infants aged <6 months. Although influenza-specific diagnoses were more common in inpatient than outpatient settings,

a minority of hospitalized children with study protocol-confirmed influenza had physician-ordered testing, and <2% were prescribed antiviral therapy.

In our earlier study conducted in 2000–2004, influenza-specific discharge diagnoses among all hospitalized infants <6 months with study protocol-confirmed influenza were 28%.⁴ In this study, the proportion of infants <6 months with study protocol-confirmed influenza who were discharged from the hospital with an influenza-specific diagnosis increased to 48%. However, for children 6 months to <5 years of age, the proportion diagnosed with influenza remained similar in the 2 time periods (28% in 2000–2004 and 23% in 2004–2009). These data suggest that physician awareness of influenza has increased among infants <6 months of age but not among older children. Thus, it should be possible to increase the diagnosis of influenza among hospitalized children ≥6 months of age who represent half of all study children <5 years of age admitted with influenza.

During 5 study seasons (2004–2009), rates of hospitalization for influenza ranged from 0.4 to 1.0 per 1000 children aged <5 years with an annual average of 0.58 (95% confidence interval 0.50–0.67) per 1000 children. We had previously reported rates ranging from 0.4 to 1.5 with an annual average of 0.9 (95% confidence interval 0.8–1.1) per 1000 children in 2000–2004. Although the average hospitalization rate was 36% lower in 2004–2009 than in 2000–2004, there was much variability with overlapping annual rates during some years.

Although influenza vaccination coverage among hospitalized children 6 months to <5 years was higher in 2004–2009 than in earlier years,¹⁵ complete vaccination still remained <50% and did not increase appreciably among hospitalized children over the later study years. Only in the clinic population did full vaccination coverage increase significantly. National estimates using different methodologies demonstrated an increase in partial and

TABLE 3 Influenza-Specific Testing, Discharge Diagnosis, and Treatment Among Children With Laboratory-Confirmed Influenza by Age Group and Setting Over 5 Influenza Seasons (November–April)

	Total	<6 months	6 months–<2 y	2–<5 y	P Value
Inpatient					
No. of observations	199	96	69	34	
Influenza testing	58%	67%	46%	56%	.03 ^a
Discharge diagnosis	35%	48%	23%	24%	.001 ^a
Antiviral treatment	1.5%	1.2%	3.2%	0.0%	.46
Outpatient (ED or clinic)					
No. of observations	616	52	253	311	
Influenza testing	7%	12%	6%	7%	.29
Discharge diagnosis	7%	8%	5%	8%	.33
Antiviral treatment	0.5%	0.0%	0.8%	0.3%	.63

^a P value of <.05 represents heterogeneity of that outcome by age group for that setting.

full influenza vaccination coverage in children from 2004–2005 through 2008–2009 with wide variability. Our results fall within these reported ranges.^{15–27}

Thus, it is difficult to determine the impact of expanded influenza vaccination recommendations on influenza disease burden beyond estimates based on vaccine effectiveness.^{5,28,29} Other secular trends could account for the differences in disease rates between 2000–2004 and 2004–2009. For example, the large burden of influenza in 2003–2004, predominantly influenza A H3N2 with a suboptimal vaccine match, was associated with higher disease rates and could at least partially explain this difference. Also, heptavalent pneumococcal conjugate vaccine was introduced in 2000 and has been associated with a decrease in all-cause and influenza-associated pneumonia hospitalizations among children <5 years of age during these time periods and likely affected rates of influenza disease over time.^{30,31} Additional study is needed to assess the impact of influenza vaccine on disease burden.

Similar to the inpatient setting, the proportions of outpatient children with influenza-positive samples varied annually for all age groups. During five 13-week peak influenza seasons in this study, the proportion of children with study protocol-confirmed influenza in either the ED or clinic ranged from 10% to 25% and was similar to the previously

reported proportions of 8% in 2002–2003 and 22% in 2003–2004.⁴

Our results of the sensitivity of physician-ordered rapid influenza tests (66% among inpatients and 56% among outpatients) fall within the previously reported range.^{32–35} Rapid influenza tests can provide clinically useful results in a timely fashion. However, many factors can influence the accuracy of rapid influenza test results including the pretest probability of influenza based on presenting clinical signs and symptoms, the local prevalence of influenza, the duration of illness, the quality and type of specimen collected, and the criterion standard to which the rapid test is compared.³⁶ Clinical practice often differs from current guidelines, which encourage presumptive treatment of hospitalized or children at high risk with influenza-like illnesses without requiring influenza confirmation.³⁷ We found that many clinicians appeared to rely on results of rapid influenza testing to determine influenza diagnoses as most children with influenza-specific discharge diagnoses had a positive rapid test. This reliance on positive rapid influenza tests is consistent with the literature but not with the current guidelines for treatment.³⁷ In 2006–2007, ED physicians reported being more likely to treat children and adults who presented within 48 hours of illness and who had a positive rapid influenza test than those who presented

later and/or did not have a rapid test performed.³⁸ The increased availability of molecular methods to diagnose influenza has the potential to significantly enhance the ability to reliably diagnose and treat children with influenza and will need to be evaluated in the post-2009 pandemic era. Only 3 hospitalized children with study protocol-confirmed influenza were treated with antiviral medications, including children who were admitted to the hospital within 2 days of illness onset. Surveys of physicians have indicated that antiviral medications are often not prescribed for multiple reasons including late presentation, self-limited disease, uncertain diagnosis of influenza, and expense.³⁹ However, timely administration of oseltamivir has been associated with shorter hospitalizations among critically ill children,⁴⁰ faster resolution of illness (1.0–1.5 days in healthy children), and less parental work absenteeism.^{41–43} Also, 43% to 44% fewer outpatient children who received oseltamivir within 48 hours of influenza symptoms developed acute otitis media.^{43–45} When the 2009 pandemic influenza began in the United States in mid-April 2009, recommendations were made for expanded use of antiviral medications and were associated with increased antiviral usage⁴⁶; thus, usage patterns from before versus after the 2009 pandemic may differ. In 2011, the CDC recommended antiviral treatment as early as possible for any patient with confirmed or suspected influenza who (1) is hospitalized; (2) has severe, complicated, or progressive illness; or (3) is at higher risk for complications.⁴⁷ More efforts are needed to increase awareness of these antiviral treatment guidelines in children.

Several limitations exist for this multicenter, multiyear study. Enrolled children could have systematically differed from nonenrolled children and/or from children presenting at nonsurveillance

times, and 3 years of inpatient surveillance were excluded from 1 site. Because influenza virus has infrequently (0%–2%) been detected by RT-PCR among asymptomatic children, it is possible that a few children could have had influenza detected without clinically relevant influenza infection.^{48–51} Circulating influenza viruses, vaccination trends, viral testing, discharge diagnoses, and antiviral use could vary geographically, and the NVSN results may not be reflective of the entire United States.

CONCLUSIONS

Our study shows that seasonal influenza remains an important cause of hospitalizations, ED visits, and outpatient visits among children and that

the use of tools known to reduce the burden of influenza (namely, vaccination and antiviral medications) were substantially underused during the study period. Additional efforts are needed for greater dissemination and use of the existing recommendations for influenza vaccination of children ≥ 6 months and of pregnant women, which partially protects younger infants.^{52–55} Also needed are the development and dissemination of evidence-based guidelines for laboratory testing and therapeutic options, including antiviral medications.

ACKNOWLEDGMENTS

We thank all the children and their families who generously contributed to this

study. We thank the following members of the NVSN: Nashville: Carol Ann Clay, RN, Erin Keckley, RN, Diane Kent, RN, Nayleen Whitehead, Mariah Daly, RN, and John Williams, MD; Rochester: Christina Albertin, MPH, Linda Anderson, RN, Charlene Freundlich, Geraldine Lofthus, PhD, Andrea Marino, Kenneth Schnabel, MBA, and Lynne G. Shelley; Cincinnati: Vanessa Florian, Diana Henderson, MPH, MSW, Michol Holloway, MPH, Linda Jamison, RN, BSN, CIC, Monica Kishman, David Glazer, Jessica Scholemer, and Nancy Back, BSN, MPH; Centers for Disease Control and Prevention: Mila Prill, MSPH and Aaron Curns, MPH. We also thank the anonymous reviewers whose comments and suggestions enhanced this article.

REFERENCES

- Harper SA, Fukuda K, Uyeki TM, Cox NJ, Bridges CB; Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices (ACIP). Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2004;53(RR-6):1–40
- Smith NM, Bresee JS, Shay DK, Uyeki TM, Cox NJ, Strikas RA; Advisory Committee on Immunization Practices. Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2006;55(RR-10):1–42
- Fiore AE, Shay DK, Broder K, et al; Centers for Disease Control and Prevention (CDC); Advisory Committee on Immunization Practices (ACIP). Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2008. *MMWR Recomm Rep*. 2008;57(RR-7):1–60
- Poehling KA, Edwards KM, Weinberg GA, et al; New Vaccine Surveillance Network. The underrecognized burden of influenza in young children. *N Engl J Med*. 2006;355(1):31–40
- Staat MA, Griffin MR, Donauer S, et al. Vaccine effectiveness for laboratory-confirmed influenza in children 6–59 months of age, 2005–2007. *Vaccine*. 2011;29(48):9005–9011
- Iwane MK, Edwards KM, Szilagyi PG, et al; New Vaccine Surveillance Network. Population-based surveillance for hospitalizations associated with respiratory syncytial virus, influenza virus, and parainfluenza viruses among young children. *Pediatrics*. 2004;113(6):1758–1764
- Fiore AE, Shay DK, Haber P, et al; Advisory Committee on Immunization Practices (ACIP), Centers for Disease Control and Prevention (CDC). Prevention and control of influenza. Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2007. *MMWR Recomm Rep*. 2007;56(RR-6):1–54
- Harper SA, Fukuda K, Uyeki TM, Cox NJ, Bridges CB; Advisory Committee on Immunization Practices (ACIP), Centers for Disease Control and Prevention (CDC). Prevention and control of influenza. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2005;54(RR-8):1–40
- Consortium for Healthy and Immunized Communities (CHIC)—Immunization Registry. Available at: www.chicohio.com/immunereg.html. Accessed July 31, 2012
- Weinberg GA, Erdman DD, Edwards KM, et al; New Vaccine Surveillance Network Study Group. 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(4):706–710
- Weinberg GA, Hall CB, Iwane MK, et al; New Vaccine Surveillance Network. Parainfluenza virus infection of young children: estimates of the population-based burden of hospitalization. *J Pediatr*. 2009;154(5):694–699
- Brown LD, Cai TT, DasGupta A. Interval estimation for a binomial proportion. *Stat Sci*. 2001;16(2):101–133
- US Census Bureau. US Census. Available at: www.census.gov. Accessed April 23, 2012
- Rust KF, Rao JN. Variance estimation for complex surveys using replication techniques. *Stat Methods Med Res*. 1996;5(3):283–310
- Centers for Disease Control and Prevention. Influenza vaccination coverage among children aged 6–23 months—United States, 2008–2009. Available at: www.cdc.gov/flu/professionals/vaccination/coverage_6-23months.htm. Accessed April 23, 2012
- Smith PJ, Singleton JA; National Center for Immunization and Respiratory Diseases; Centers for Disease Control and Prevention (CDC). County-level trends in vaccination coverage among children aged 19–35 months—United States, 1995–2008. *MMWR Surveill Summ*. 2011;60(4):1–86
- Euler GL, Bridges CB, Brown CJ, et al; Centers for Disease Control and Prevention (CDC). Estimated influenza vaccination coverage among adults and children—United States, September 1, 2004–January 31, 2005. *MMWR Morb Mortal Wkly Rep*. 2005;54(12):304–307
- Euler GL, Lu PJ, Shefer A, et al; Centers for Disease Control and Prevention (CDC).

- Influenza vaccination coverage among children and adults—United States, 2008–09 influenza season. *MMWR Morb Mortal Wkly Rep.* 2009;58(39):1091–1095
19. Conklin M, Berry K, Enger KS, et al; Centers for Disease Control and Prevention (CDC). Influenza vaccination coverage among children aged 6–59 months—six immunization information system sentinel sites, United States, 2006–07 influenza season. *MMWR Morb Mortal Wkly Rep.* 2007;56(37):963–965
20. Fredrickson K, McLaren RP, Enger KS, et al; Centers for Disease Control and Prevention. Influenza vaccination coverage among children aged 6–23 months—six immunization information system sentinel sites, United States, 2005–06 influenza season. *MMWR Morb Mortal Wkly Rep.* 2006;55(49):1329–1330
21. Potter R, Pabst LJ, Fiore AE; Centers for Disease Control and Prevention (CDC). Influenza vaccination coverage among children aged 6 months–18 years—eight immunization information system sentinel sites, United States, 2008–09 influenza season. *MMWR Morb Mortal Wkly Rep.* 2009;58(38):1059–1062
22. William LJ, Fiore AE, White KE; Centers for Disease Control and Prevention (CDC). Influenza vaccination coverage among children aged 6–59 months—eight immunization information system sentinel sites, United States, 2007–08 influenza season. *MMWR Morb Mortal Wkly Rep.* 2008;57(38):1043–1046
23. Santibanez TA, Santoli JM, Bridges CB, Euler GL. Influenza vaccination coverage of children aged 6 to 23 months: the 2002–2003 and 2003–2004 influenza seasons. *Pediatrics.* 2006;118(3):1167–1175
24. Santibanez TA, Singleton MS, Shaw K, Santoli J, Euler GL, Bridges CB; Centers for Disease Control and Prevention (CDC). Childhood influenza vaccination coverage—United States, 2004–05 influenza season. *MMWR Morb Mortal Wkly Rep.* 2006;55(39):1062–1065
25. Santibanez TA, Fiore A, Mootrey G; Centers for Disease Control and Prevention (CDC). Influenza vaccination coverage among children aged 6–23 months—United States, 2006–07 influenza season. *MMWR Morb Mortal Wkly Rep.* 2008;57(38):1039–1043
26. Santibanez T, Santoli JM, Mootrey G, Euler GL, Fiore A; Centers for Disease Control and Prevention (CDC). Influenza vaccination coverage among children aged 6–23 months—United States, 2005–06 influenza season. *MMWR Morb Mortal Wkly Rep.* 2007;56(37):959–963
27. Santibanez TA, Fiore A, Singleton JA; Centers for Disease Control and Prevention (CDC). Influenza vaccination coverage among children aged 6–23 months—United States, 2007–08 influenza season. *MMWR Morb Mortal Wkly Rep.* 2009;58(38):1063–1066
28. Eisenberg KW, Szilagyi PG, Fairbrother G, et al; New Vaccine Surveillance Network. Vaccine effectiveness against laboratory-confirmed influenza in children 6 to 59 months of age during the 2003–2004 and 2004–2005 influenza seasons. *Pediatrics.* 2008;122(5):911–919
29. Szilagyi PG, Fairbrother G, Griffin MR, et al; New Vaccine Surveillance Network. Influenza vaccine effectiveness among children 6 to 59 months of age during 2 influenza seasons: a case-cohort study. *Arch Pediatr Adolesc Med.* 2008;162(10):943–951
30. Simonsen L, Taylor RJ, Young-Xu Y, Haber M, May L, Klugman KP. Impact of pneumococcal conjugate vaccination of infants on pneumonia and influenza hospitalization and mortality in all age groups in the United States. *MBio.* 2011;2(1):e00309–e00310
31. Grijalva CG, Nuorti JP, Arbogast PG, Martin SW, Edwards KM, Griffin MR. Decline in pneumonia admissions after routine childhood immunisation with pneumococcal conjugate vaccine in the USA: a time-series analysis. *Lancet.* 2007;369(9568):1179–1186
32. Uyeki TM. Influenza diagnosis and treatment in children: a review of studies on clinically useful tests and antiviral treatment for influenza. *Pediatr Infect Dis J.* 2003;22(2):164–177
33. Hurt AC, Alexander R, Hibbert J, Deed N, Barr IG. Performance of six influenza rapid tests in detecting human influenza in clinical specimens. *J Clin Virol.* 2007;39(2):132–135
34. Rouleau I, Charest H, Douville-Fradet M, Skowronski DM, De Serres G. Field performance of a rapid diagnostic test for influenza in an ambulatory setting. *J Clin Microbiol.* 2009;47(9):2699–2703
35. Uyeki TM, Prasad R, Vukotich C, et al. Low sensitivity of rapid diagnostic test for influenza. *Clin Infect Dis.* 2009;48(9):e89–e92
36. Centers for Disease Control and Prevention. Guidance for clinicians on the use of rapid influenza diagnostic tests. Available at: www.cdc.gov/flu/professionals/diagnosis/clinician_guidance_ridt.htm#interpretation. Accessed April 23, 2012
37. Harper SA, Bradley JS, Englund JA, et al; Expert Panel of the Infectious Diseases Society of America. Seasonal influenza in adults and children—diagnosis, treatment, chemoprophylaxis, and institutional outbreak management: clinical practice guidelines of the Infectious Diseases Society of America. *Clin Infect Dis.* 2009;48(8):1003–1032
38. Mueller MR, Smith PJ, Baumbach JP, et al. Influenza testing and antiviral prescribing practices among emergency department clinicians in 9 states during the 2006 to 2007 influenza season. *Ann Emerg Med.* 2010;55(1):32–39
39. Rothberg MB, Bonner AB, Rajab MH, Kim HS, Stechenberg BW, Rose DN. Effects of local variation, specialty, and beliefs on antiviral prescribing for influenza. *Clin Infect Dis.* 2006;42(1):95–99
40. Coffin SE, Leckerman K, Keren R, Hall M, Localio R, Zaoutis TE. Oseltamivir shortens hospital stays of critically ill children hospitalized with seasonal influenza: a retrospective cohort study. *Pediatr Infect Dis J.* 2011;30(11):962–966
41. Heinonen S, Silvennoinen H, Lehtinen P, et al. Early oseltamivir treatment of influenza in children 1–3 years of age: a randomized controlled trial. *Clin Infect Dis.* 2010;51(8):887–894
42. Wang K, Shun-Shin M, Gill P, Perera R, Harnden A. Neuraminidase inhibitors for preventing and treating influenza in children. *Cochrane Database Syst Rev.* 2012;1:CD002744
43. Whitley RJ, Hayden FG, Reisinger KS, et al. Oral oseltamivir treatment of influenza in children. *Pediatr Infect Dis J.* 2001;20(2):127–133
44. Winther B, Block SL, Reisinger K, Dutkowski R. Impact of oseltamivir treatment on the incidence and course of acute otitis media in children with influenza. *Int J Pediatr Otorhinolaryngol.* 2010;74(6):684–688
45. Short KR, Diavatopoulos DA, Thornton R, et al. Influenza virus induces bacterial and nonbacterial otitis media. *J Infect Dis.* 2011;204(12):1857–1865
46. Hersh AL, Herigon JC, Ampofo K, Pavia AT, Newland JG. Rapid increase in use of antiviral therapy for hospitalized children with influenza during the 2009 H1N1 epidemic. *Pediatr Infect Dis J.* 2011;30(10):895–897
47. Centers for Disease Control and Prevention. 2011–2012 influenza antiviral medications. Available at: www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm. Accessed April 23, 2012
48. Singleton RJ, Bulkow LR, Miernyk K, et al. Viral respiratory infections in hospitalized and community control children in Alaska. *J Med Virol.* 2010;82(7):1282–1290

49. Jansen RR, Wieringa J, Koekkoek SM, et al. Frequent detection of respiratory viruses without symptoms: toward defining clinically relevant cutoff values. *J Clin Microbiol.* 2011;49(7):2631–2636
50. Sanghavi SK, Bullotta A, Husain S, Rinaldo CR. Clinical evaluation of multiplex real-time PCR panels for rapid detection of respiratory viral infections. *J Med Virol.* 2012; 84(1):162–169
51. Advani S, Sengupta A, Forman M, Valsamakis A, Milstone A. Detecting respiratory viruses in asymptomatic children [published online ahead of print June 25, 2012]. *Pediatr Infect Dis J.* doi:10.1097/INF.0b013e318265a804
52. Zaman K, Roy E, Arifeen SE, et al. Effectiveness of maternal influenza immunization in mothers and infants [published correction appears in *N Engl J Med.* 2009; 360(6):648]. *N Engl J Med.* 2008;359(15): 1555–1564
53. Benowitz I, Esposito DB, Gracey KD, Shapiro ED, Vázquez M. Influenza vaccine given to pregnant women reduces hospitalization due to influenza in their infants. *Clin Infect Dis.* 2010;51(12):1355–1361
54. Eick AA, Uyeki TM, Klimov A, et al. Maternal influenza vaccination and effect on influenza virus infection in young infants. *Arch Pediatr Adolesc Med.* 2011;165(2):104–111
55. Poehling KA, Szilagyi PG, Staat MA, et al; New Vaccine Surveillance Network. Impact of maternal immunization on influenza hospitalizations in infants. *Am J Obstet Gynecol.* 2011;204(6 suppl 1):S141–S148

(Continued from first page)

Dr Poehling contributed to the conceptualization and design of the study, interpreted the data, drafted the initial manuscript, and approved the final manuscript as submitted. Drs Edwards and Griffin substantially contributed to conception and design, acquisition of data, and interpretation of data; revised the article critically for important intellectual content; and approved the final version as submitted. Drs Szilagyi and Weinberg contributed to the conceptualization of the study and review and edits of drafts and revisions, and approved the final manuscript as submitted. Drs Staat and Iwane made substantial contributions to the conception and design and interpretation of the data, reviewed and revised the manuscript, and approved the final manuscript as submitted. Dr Snively provided input on data analysis and presentation of results, critically reviewed and edited the manuscript, and approved the final manuscript as submitted. Ms Suerken contributed to the analysis and interpretation of data, critically reviewed the manuscript, and approved the final manuscript as submitted. Dr Hall helped coordinate and supervise personnel collecting data and supervised the laboratory testing at 1 site, reviewed and revised the manuscript, and approved the final manuscript as submitted. Dr Chaves contributed to the conception and design of the analysis and interpretation of results and has critically reviewed and approved the submitted manuscript. Dr Zhu contributed to the analysis and interpretation of data, critically reviewed the manuscript, and approved the final manuscript as submitted. Ms McNeal performed the laboratory assays to acquire the data for the Cincinnati site, critically reviewed the manuscript, and approved the final manuscript as submitted. Dr Bridges made substantial contribution(s) to conception and design of the study/surveillance network, interpretation of data, review and revision of drafts for important intellectual content, and final approval of the version to be submitted for publication.

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

www.pediatrics.org/cgi/doi/10.1542/peds.2012-1255

doi:10.1542/peds.2012-1255

Accepted for publication Sep 19, 2012

Address correspondence to Katherine A. Poehling, MD, MPH, Department of Pediatrics, Wake Forest School of Medicine, Medical Center Blvd, Winston-Salem, NC 27157. E-mail: kpoehlin@wakehealth.edu

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

Copyright © 2013 by the American Academy of Pediatrics

FINANCIAL DISCLOSURE: Dr Edwards received grant support from Novartis (for meningococcus); Dr Hall was a consultant for MedImmune (for respiratory syncytial virus [RSV]) and a past consultant for GlaxoSmithKline (for RSV); Dr Staat received research support and was a consultant for MedImmune (for RSV); Dr Weinberg was a consultant for MedImmune and speaker's bureaus of Merck & Co., GlaxoSmithKline, and Sanofi Pasteur; and Dr Poehling received research support from BD Diagnostics. The other authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: The primary support for the NVSN was the US Centers for Disease Control and Prevention (cooperative agreement numbers U38/CCU217969, U38/CCU417958, U38/CCU522352, U01/IP000017, U01/IP000022, and U01/IP000147). In addition, Dr Poehling received research support from Wachovia Research Fund and National Institute of Allergy and Infectious Diseases (grant R01 AI079226). Funded by the National Institutes of Health (NIH).