The New England Journal of Medicine

VOLUME 342 JANUARY 27, 2000 NUMBER 4

THE EFFECT OF INFLUENZA ON HOSPITALIZATIONS, OUTPATIENT VISITS, AND COURSES OF ANTIBIOTICS IN CHILDREN

KATHLEEN MALETIC NEUZIL, M.D., M.P.H., BEVERLY G. MELLEN, PH.D., PETER F. WRIGHT, M.D., EDWARD F. MITCHEL, JR., M.S., AND MARIE R. GRIFFIN, M.D., M.P.H.

ABSTRACT

Background Despite high annual rates of influenza in children, influenza vaccines are given to children infrequently. We measured the disease burden of influenza in a large cohort of healthy children in the Tennessee Medicaid program who were younger than 15 years of age.

Methods We determined the rates of hospitalization for acute cardiopulmonary conditions, outpatient visits, and courses of antibiotics over a period of 19 consecutive years. Using the differences in the rates of these events when influenzavirus was circulating and the rates from November through April when there was no influenza in the community, we calculated morbidity attributable to influenza. There was a total of 2,035,143 person-years of observation.

Results During periods when influenzavirus was circulating, the average number of hospitalizations for cardiopulmonary conditions in excess of the expected number was 104 per 10,000 children per year for children younger than 6 months of age, 50 per 10,000 per year for those 6 months to less than 12 months, 19 per 10,000 per year for those 1 year to less than 3 years, 9 per 10,000 per year for those 3 years to less than 5 years, and 4 per 10,000 per year for those 5 years to less than 15 years. For every 100 children, an annual average of 6 to 15 outpatient visits and 3 to 9 courses of antibiotics were attributable to influenza. In winter, 10 to 30 percent of the excess number of courses of antibiotics occurred during periods when influenzavirus was circulating.

Conclusions Healthy children younger than one year of age are hospitalized for illness attributable to influenza at rates similar to those for adults at high risk for influenza. The rate of hospitalization decreases markedly with age. Influenza accounts for a substantial number of outpatient visits and courses of antibiotics in children of all ages. (N Engl J Med 2000; 342:225-31.)

ACUTE respiratory disease is the most common reason for outpatient visits and hospitalizations among children in the United States.[1] The majority of these illnesses are precipitated by viral infection. Influenza is a common disease of childhood; during epidemics, the rates of attack may exceed 40 percent in preschool children and 30 percent in school-age children.[2-8] Furthermore, children have an important role in the spread of influenza, because school-age children are the main channel through which influenza is introduced into households.[3,6,7]

Influenza vaccines are given infrequently to healthy children despite the high rates of attack in children and despite the important role of children in the transmission of viruses. One obstacle to the use of vaccines is the perception that influenza is a benign disease in children. Data on mortality, commonly used to estimate the effect of influenza in adults, are insensitive indicators of the effect of influenza in children.[9-11] Furthermore, the contribution of other respiratory viruses, such as respiratory syncytial virus, to morbidity from acute cardiopulmonary conditions is greater in children than adults.[12,13] Despite these difficulties, population-based studies of influenza epidemics have reported higher than expected, or excess, numbers of hospitalizations for acute respiratory disease[12,14] and outpatient visits among children.[15]

The evidence that an investigational, intranasal, live attenuated influenzavirus vaccine is safe, well tolerated, and effective in healthy children increases the attractiveness of expanding the coverage of influenza vaccines to include all children.[16,17] Whether such a

From the Department of Medicine, University of Washington School of Medicine, and the Department of Veterans Affairs, Puget Sound Health Care System — both in Seattle (K.M.N.); and the Departments of Preventive Medicine (B.G.M., E.F.M., M.R.G.), Pediatrics (P.F.W.), and Medicine (M.R.G.), Vanderbilt University School of Medicine, Nashville. Address reprint requests to Dr. Neuzil at the Department of Veterans Affairs, Puget Sound Health Care System, Division of Infectious Diseases 111, 1660 S. Columbian Way, Seattle, WA 98108-1595, or at kneuzil@u.washington.edu.

change in policy is made depends on the degree to which the vaccine is expected to reduce the severe and costly outcomes of the disease and to be cost effective. We undertook a study to evaluate the effect of influenza on children by assessing a wide spectrum of illnesses in a large cohort of healthy children over several influenza seasons.

METHODS

Study Design

We performed a retrospective cohort study of healthy children younger than 15 years of age to determine the rates of hospitalization for acute cardiopulmonary conditions, outpatient visits, and courses of antibiotics over a period of 19 consecutive years. To calculate morbidity attributable to influenza, we used annual differences between the rates of these events when influenzavirus was circulating and the rates of these events during winter months when there was no influenza in the community.

Sources of Data and Definitions of Seasons

Tennessee Medicaid files for 1973 through 1993 included dates of enrollment in Medicaid, demographic characteristics, and medical services reimbursed by Medicaid, including dates of medical service received in the hospital or on an outpatient basis, associated diagnoses and procedures, and detailed information on prescriptions filled. We linked Medicaid files to birth certificates, from which we determined the date of birth and maternal characteristics, and to death certificates, which included the date of death and coded underlying cause of death.[18,19]

We defined the influenza season as the period in each year of the study from November 1 through April 30 that included the dates of the first and last isolation of influenzavirus in middle Tennessee as determined by surveillance in a Vanderbilt University–based pediatric population.[13] These seasons showed reasonable concordance with the timing of excess numbers of deaths from pneumonia and influenza that were estimated for 11 cities in Tennessee and surrounding states that participate in the Centers for Disease Control and Prevention 121 City Surveillance System.[20] We defined the peri-influenza season as the period each year from November 1 through April 30 in which there was no influenza activity; the rates from this period served as the base-line values for the analyses. Two of the 19 years studied (1978–1979 and 1979–1980) were determined to have had no influenza season, because of low influenza activity (fewer than five viral isolates), so that all winter months constituted the peri-influenza season.

The peak season for the respiratory syncytial virus was defined as the period from the identification on or after November 1 of the first of two consecutive isolates of respiratory syncytial virus (identified within 30 days of each other) until the identification before or on April 30 of the last of two consecutive isolates. We defined the summer season as the period each year from May 1 through October 31.

Study Population

The study included children younger than 15 years of age who were enrolled in Tennessee Medicaid at birth or for at least one year. Since the number of children who were not white or black was small, we excluded these children. Children entered the study on the first day after June 30, 1974, on which they met criteria for enrollment and were followed until the development of a high-risk condition, loss of coverage by Medicaid, 15 years of age, death, or June 30, 1993.

Because our study was designed to evaluate healthy children, we used information from computerized Medicaid files and birth-certificate records to identify and exclude children at high risk for influenza-related complications. Children were determined to be at high risk if they were institutionalized or disabled, weighed less than 2500 g at birth and were younger than one year (these children could be included after one year of age if they had no other high-risk condition), or had been given a diagnosis or prescription medication that indicated a high-risk condition in the year before entry into the study. High-risk conditions were considered to be congenital heart disease and other selected cardiac conditions, bronchopulmonary dysplasia, hospitalization for respiratory conditions, asthma, cystic fibrosis, sickle cell disease, diabetes mellitus, infection with the human immunodeficiency virus, cancer, chronic use of oral corticosteroids, and chronic renal disease. The remaining children were considered to be at low risk for influenza-related complications and were the focus of our analysis.

We ascertained the following characteristics of the children in our study: age group (younger than 6 months, 6 months to less than 12 months, 1 year to less than 3 years, 3 years to less than 5 years, and 5 years to less than 15 years), sex, residence (urban [four largest cities in Tennessee], other standard metropolitan statistical area, or rural), and race (black or white). The number of living siblings was obtained from the birth certificates of children younger than three years of age. This variable was not included for older children.

Study Outcomes

Study outcomes were hospitalization for or death from pneumonia, influenza, acute respiratory conditions other than pneumonia or influenza, nonacute respiratory conditions other than pneumonia or influenza, and heart failure or myocarditis. Secondary outcomes were the total number of outpatient visits and the number of antibiotic prescriptions filled.

Statistical Analysis

Crude rates of hospitalization were calculated by dividing the number of hospitalizations for acute cardiopulmonary conditions during influenza seasons by the age-specific person-years during influenza seasons; these rates were expressed per 10,000 person-years. Rates were similarly calculated for the peri-influenza season, the summer season, and all seasons combined. Differences between these crude rates during influenza and peri-influenza seasons were calculated as measures of risk attributable to influenza.

Standardized versions of these differences between rates, which account for variation in hospitalization rates between years and between other strata, were calculated with the use of strata based on age group, study year, race, and residence as well as strata-specific differences in rates. The standardized rate of hospitalizations attributable to influenza was defined as the weighted average of the strata-specific differences in rate, with use of the corresponding strata-specific person-years in all seasons combined as the weights.

The excess number of hospitalizations per 10,000 persons per year was estimated separately in all strata by multiplying the strata-specific differences in rate by the proportion of days of the corresponding study years accounted for by the respective influenza season. Standardized estimates were calculated with a weighted average of strata-specific values, as was done for the standardized differences in rate. The two years in which there was no influenza season were included in all calculations. We elected to include as stratifying variables study year, race, residence, and age group. The inclusion of the other variables resulted in no change of more than 0.5 in any age-specific estimate of annual excess numbers of hospitalizations, and they were therefore excluded. Confidence intervals were calculated as previously described.[21]

To estimate the overall excess rate of hospitalizations in winter as compared with summer, the excess rate of hospitalizations in winter that were not associated with influenza was added to the excess rate of hospitalizations attributable to influenza and then standardized as described above, with use of a zero weight when no excess rate of hospitalizations in winter was observed. Excess rates of hospitalizations in winter that were attributable to factors other than influenza (e.g., other respiratory viruses) were estimated with use of strata-specific differences in rate between peri-influenza seasons and summer seasons. The proportion of the overall rate of excess hospitalizations in winter attributable to influenza was calculated for each age group. Rates, differences in rate, excess rates

TABLE 1. RATES OF HOSPITALIZATION FOR ACUTE CARDIOPULMONARY CONDITIONS ATTRIBUTABLE TO INFLUENZA.

AGE	NO. OF PERSON-YEARS	NO. OF HOSPITALIZATIONS FOR ACUTE CARDIOPULMONARY CONDITIONS PER 10,000 PERSON-YEARS				NO. OF INFLUENZA-ATTRIBUTABLE HOSPITALIZATIONS PER 10,000 PERSON-YEARS*		AVERAGE EXCESS NO. OF HOSPITALIZATIONS PER 10,000 CHILDREN PER YEAR (95% CI)†
		INFLUENZA SEASON	PERI-INFLUENZA SEASON	SUMMER	TOTAL	CRUDE	STANDARDIZED‡	
<6 mo	117,205	1964	1497	608	1146	467	449	103.8 (89.0–118.6)
6 to <12 mo	82,997	1117	854	403	675	263	233	49.6 (35.3–63.8)
1 to <3 yr	324,900	464	387	233	325	77	79	18.6 (14.2–23.0)
3 to <5 yr	302,344	232	193	138	173	39	43	8.6 (4.9–12.3)
5 to <15 yr	1,207,697	120	105	86	98	15	22	4.1 (2.8–5.5)

*Values are differences in rates between the influenza season and the peri-influenza season (the base-line values).

†Values are weighted averages of annual excess hospitalizations for a population of 10,000 persons within the specified age group. The excess hospitalizations were calculated for each stratum by multiplying the stratum-specific difference in hospitalization rate by the proportion of the study year covered by the influenza season. CI denotes confidence interval.

‡The weighted average differences in rate between the influenza season and the peri-influenza season were calculated with stratum-specific person-years in all seasons as weights; strata were defined by age group, study year, race, and residence.

of events, and proportions of excess rates of hospitalizations in winter attributable to influenza were calculated similarly for outpatient visits and courses of antibiotics.

We performed another analysis to assess the effect of respiratory syncytial virus seasons on our results. We calculated crude and standardized differences in rates by subtracting rates of hospitalizations, outpatient visits, and courses of antibiotics during peri-influenza seasons from rates during influenza seasons, excluding all person-time and events during respiratory syncytial virus seasons.

RESULTS

Children at low risk for influenza-related complications accounted for 91 percent of all children younger than 15 years of age who were enrolled in the Tennessee Medicaid program, and they contributed 2,035,143 person-years during the 19 years of the study. By definition, 50 percent of person-time occurred during summer seasons; 19 percent occurred during influenza seasons, and 31 percent during peri-influenza seasons. The mean duration of the influenza season was 63 days (range, 0 to 119), and the mean duration of the peak season for respiratory syncytial virus was 68 days (range, 6 to 125). The peak season for respiratory syncytial virus overlapped the influenza season an average of 27 days per year (range, 0 to 83) and occurred with a similar frequency during the influenza and peri-influenza seasons.

The demographic characteristics of the children in the study reflected those of children in the Medicaid population; 51 percent were male, and 60 percent were black. The age distribution was as follows: 6 percent were younger than 6 months, 4 percent were 6 months to less than 12 months, 16 percent were 1 year to less than 3 years, 15 percent were 3 years to less than 5 years, and 59 percent were 5 years to less than 15 years. There were changes in the demographics of the study population over the 19 years of study due to changes in Medicaid eligibility requirements. The total enrollment for children younger than 15 years decreased slightly over the first nine years of the study and then increased steadily, with a more marked increase in younger children. The last seven years of the study constituted 50 percent of the total person-years, ranging from 46 percent of total person-years in those 5 years to less than 15 years of age to 64 percent of total person-years in those younger than 6 months of age. In addition, the percentage of the population made up of blacks decreased from 69 percent in the first year to 47 percent in the last.

We identified 46,690 hospitalizations for acute cardiopulmonary conditions during the entire study period, 28 percent of which occurred during an influenza season. For all age groups, the rates of hospitalization were higher during the influenza season than during the peri-influenza season (Table 1). In all seasons, the rates of hospitalization were highest for children younger than six months of age, and rates decreased with increasing age. Using the rate of hospitalization during the peri-influenza season as the base-line rate of hospitalization in winter, we calculated the rate of hospitalization attributable to influenza by subtracting the hospitalization rate during the peri-influenza season from the hospitalization rate during the influenza season. After adjustment for the duration of each influenza season, these rates translated into average excess numbers of hospitalizations for acute cardiopulmonary conditions that ranged from 4 to 104 per 10,000 children annually. Another analysis, in which all person-time and events during respiratory syncytial virus seasons were excluded, yielded similar results (Table 2).

We identified 154 deaths from selected acute cardiopulmonary conditions during the 19 years of the

TABLE 2. RATES OF HOSPITALIZATION FOR ACUTE CARDIOPULMONARY CONDITIONS ATTRIBUTABLE TO INFLUENZA, WITH PERSON-TIME AND EVENTS DURING RESPIRATORY SYNCYTIAL VIRUS SEASONS EXCLUDED.

AGE	NO. OF PERSON-YEARS	NO. OF HOSPITALIZATIONS FOR ACUTE CARDIOPULMONARY CONDITIONS PER 10,000 PERSON-YEARS		NO. OF INFLUENZA-ATTRIBUTABLE HOSPITALIZATIONS PER 10,000 PERSON-YEARS*	
		INFLUENZA SEASON	PERI-INFLUENZA SEASON	CRUDE	STANDARDIZED†
<6 mo	68,959	1779	1207	572	538
6 to <12 mo	48,651	1023	730	293	227
1 to <3 yr	197,334	441	336	105	101
3 to <5 yr	184,860	247	194	53	55
5 to <15 yr	759,063	127	112	15	25

*Values are differences in rates between the influenza season and the peri-influenza season (the base-line values).

†The weighted average differences in rate between the influenza season and the peri-influenza season were calculated with stratum-specific person-years in all seasons as weights; strata were defined by age group, study year, race, and residence.

study; 87 deaths (56 percent) occurred among children younger than one year of age. For all ages combined and for all years, the excess number of deaths from cardiopulmonary conditions was 0.077 per 10,000 children (95 percent confidence interval, 0.001 to 0.154).

Trends for secondary outcomes were similar to those for hospitalizations for acute cardiopulmonary conditions (Fig. 1). The frequencies of both outpatient visits and courses of antibiotics were higher during the influenza season than the peri-influenza season for all age groups. The number of outpatient visits attributable to influenza-associated illness was highest in children 6 months to less than 12 months of age and ranged from 6 to 15 per 100 children. The number of courses of antibiotics attributable to influenza-associated illness ranged from 3 to 9 per 100 children. An analysis in which respiratory syncytial virus seasons were excluded yielded similar results (data not shown).

For children younger than three years of age, the rates of all outcomes were consistently higher in winter than in summer. Among children younger than 6 months, 6 months to less than 12 months of age, and 1 year to less than 3 years of age, influenza accounted for 19 percent, 18 percent, and 20 percent of the excess number of hospitalizations in winter, respectively; 24 percent, 23 percent, and 35 percent of the excess number of outpatient visits in winter; and 10 percent, 14 percent, and 20 percent of the excess number of courses of antibiotics in winter. Among older children, there was more variation in the rates of hospitalization and outpatient visits, with no consistent excess in winter. However, the number of antibiotic prescriptions filled for older children was consistently higher in winter than in summer. The courses of antibiotics attributable to influenza-associated illness accounted for 26 percent and 30 percent of the excess number of courses of antibiotics prescribed for children 3 years to less than 5 years of age and 5 years to less than 15 years of age, respectively, in winter.

DISCUSSION

In this large, retrospective cohort study, we found that among healthy children younger than 15 years of age, there were excess numbers of hospitalizations for acute cardiopulmonary conditions, excess numbers of outpatient visits, and excess numbers of antibiotic prescriptions filled during the periods when influenzavirus was circulating in the community between 1974 and 1993. These outcomes were observed among children of all ages. Deaths were rare in these healthy children, and most deaths occurred in those younger than one year of age. The estimate of the excess number of deaths due to influenza was 8 per million children younger than 15 years of age (95 percent confidence interval, 0.1 to 15 per million).

Excess rates of hospitalization for acute cardiopulmonary conditions during influenza season were most frequent in children younger than one year of age and were less frequent with increasing age. Although these results, from a group of children enrolled in Medicaid, may not be generalizable to other populations, two prior studies of excess rates of hospitalization in different populations yielded similar estimates. In Houston, estimated rates of hospitalization attributable to influenza ranged from 51 to 160 per 10,000 children younger than 1 year of age, 26 to 45 per 10,000 children 1 to 4 years of age, and 3 to 7 per 10,000 children 5 to 19 years of age.[12] In a large prepaid group practice, the excess rates of hospitalization of low-risk children during two influenza seasons were 10 per 10,000 children younger than 4 years of age and 2 per 10,000 children 5 to 14 years of age.[14]

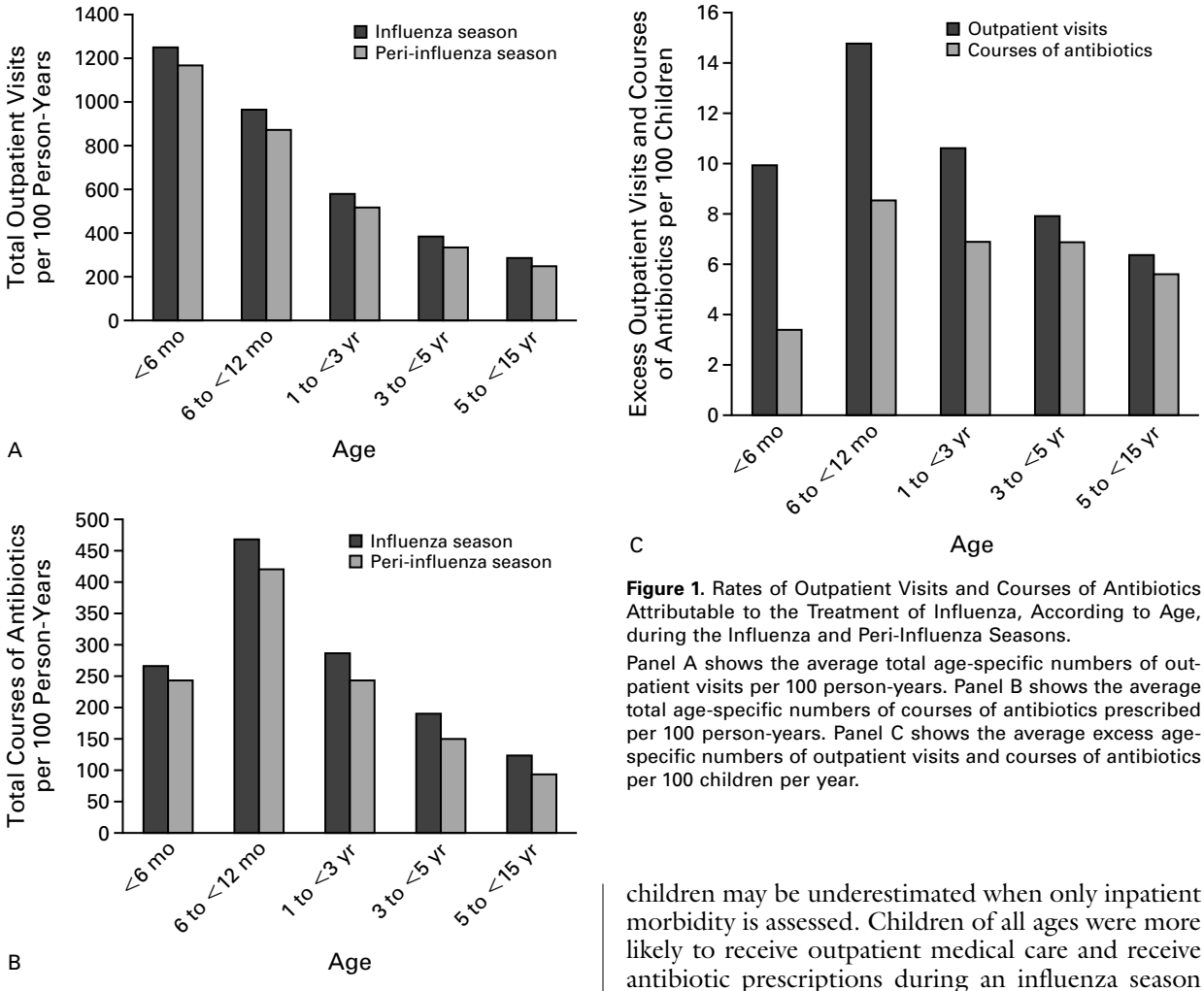

Figure 1. Rates of Outpatient Visits and Courses of Antibiotics Attributable to the Treatment of Influenza, According to Age, during the Influenza and Peri-Influenza Seasons.

Panel A shows the average total age-specific numbers of outpatient visits per 100 person-years. Panel B shows the average total age-specific numbers of courses of antibiotics prescribed per 100 person-years. Panel C shows the average excess age-specific numbers of outpatient visits and courses of antibiotics per 100 children per year.

These findings argue for the designation of children younger than one year of age as being at high risk for influenza. The excess rate of hospitalization in this age group is similar to rates in adults for whom an influenzavirus vaccine is recommended.[12,22-24] An inactivated influenzavirus vaccine is poorly immunogenic in children younger than six months of age and is not approved for children in this age group. Likewise, investigational, monovalent live attenuated influenzavirus vaccines were well tolerated but not consistently immunogenic in small numbers of children younger than six months of age.[25,26] Until better vaccines are available, stronger recommendations should be considered for immunizing family members of children younger than one year of age. Further research is needed to determine whether broadening the coverage of the influenzavirus vaccine to include pregnant women will provide protection to the infant through the transfer of maternal antibody.[27,28]

Our results indicate that the effect of influenza on children may be underestimated when only inpatient morbidity is assessed. Children of all ages were more likely to receive outpatient medical care and receive antibiotic prescriptions during an influenza season than at other times during the winter when influenzavirus was not circulating in the community. Excess numbers of outpatient visits ranged from 6 to 15 per 100 children. We evaluated excess numbers of antibiotic prescriptions as a more specific indicator of outpatient infections; these ranged from 3 to 9 per 100 children. Our data suggest that influenza accounts for up to 35 percent of the excess number of outpatient visits in winter in children younger than 3 years of age and 10 to 30 percent of the excess use of antibiotics in winter in children younger than 15 years of age.

Increased use of an influenzavirus vaccine in healthy children could reduce the number of outpatient visits and the use of antibiotics during winter months. Randomized, controlled trials have demonstrated that both inactivated and cold-adapted influenzavirus vaccines prevent influenza-like illness in children.[16,17] In two randomized, placebo-controlled studies, children younger than three years of age who received inactivated influenzavirus vaccine had a 31 to 36 percent lower incidence of acute otitis media during subsequent influenza A epidemics than children who were not vaccinated.[29,30] A cold-adapted, trivalent intrana-

sal influenzavirus vaccine reduced the incidence of febrile otitis media by 30 percent and the incidence of any febrile illness with concomitant use of antibiotics by 29 percent in children 15 to 71 months old.[17]

The main strengths of our study were the large number of children in a well-defined population, the use of more than one outcome, and the length of the study period. Previously published prospective studies, which used active virologic surveillance to define influenza-associated outcomes, involved small numbers of children over a limited number of influenza seasons or were hospital-based. Morbidity from influenza varies markedly from season to season,[9,12,22,31] and the severity of any given season cannot be predicted in advance. Thus, recommendations regarding influenza immunization should consider morbidity over a period of several years.

A potential confounding factor in this observational study is the contribution of other respiratory viruses, particularly respiratory syncytial virus, to the morbidity among the children in our cohort. The effect of respiratory syncytial virus is most problematic in younger children, in whom it is thought to cause the greatest morbidity.[13,32-35]

Three lines of evidence suggest that respiratory syncytial virus was not a serious confounder. First, the analysis in which respiratory syncytial virus seasons were excluded yielded similar results. Second, influenza accounted for 20 percent of the excess number of hospitalizations in winter in the children less than three years old, which is consistent with the finding that respiratory syncytial virus, not influenza, is the most frequent cause of lower respiratory tract disease that leads to hospitalization in infants and young children.[13,32-35] Third, our estimates are corroborated by the findings of a 20-year hospital-based study in which 10 to 36 percent of children younger than six years of age who were hospitalized with respiratory illness during the peak month of influenza season had laboratory-confirmed influenzavirus infection.[31] Other respiratory viruses that cause morbidity in young children, such as parainfluenza viruses, may be less likely to occur when influenzavirus is circulating in the community.[32,36] If these viruses contribute to morbidity during the peri-influenza season, our analysis may have underestimated the effect of influenza.

The cost, inconvenience, and safety of yearly immunization must be considered before expanded strategies for immunization can be recommended. Our study of excess numbers of hospitalizations, outpatient visits, and courses of antibiotics quantifies an effect of influenza on healthy children and suggests that the increased use of influenza vaccines in this population could have substantial benefits. Strategies designed to control epidemics of influenza must also focus on healthy schoolchildren and children in day care because of their role in the transmission of disease.[3,6]

Supported in part by a cooperative agreement with the Centers for Disease Control and Prevention (U50/CCU41398-01).

We are indebted to Juliette Thompson and Sharon Tollefson for their role in influenzavirus surveillance; to Drs. Edgar K. Marcuse and Thomas G. Boyce for helpful suggestions on the manuscript; and to Cindy Naron for editorial assistance.

REFERENCES

1. National Center for Health Statistics. Current estimates from the National Health Interview Survey, 1994. Vital and health statistics. Series 10. No. 193. Washington, D.C.: Government Printing Office, 1995. (DHHS publication no. (PHS) 96-1521.)
2. Glezen WP, Keitel WA, Taber LH, Piedra PA, Clover RD, Couch RB. Age distribution of patients with medically-attended illnesses caused by sequential variants of influenza A/H1N1: comparison to age-specific infection rates, 1978-1989. Am J Epidemiol 1991;133:296-304.
3. Longini IM Jr, Koopman JS, Monto AS, Fox JP. Estimating household and community transmission parameters for influenza. Am J Epidemiol 1982;115:736-51.
4. Wright PF, Ross KB, Thompson J, Karzon DT. Influenza A infections in young children: primary natural infection and protective efficacy of live-vaccine-induced or naturally acquired immunity. N Engl J Med 1977;296:829-34.
5. Wright PF, Thompson J, Karzon DT. Differing virulence of H1N1 and H3N2 influenza strains. Am J Epidemiol 1980;112:814-9.
6. Glezen WP, Couch RB. Interpandemic influenza in the Houston area, 1974-76. N Engl J Med 1978;298:587-92.
7. Fox JP, Hall CE, Cooney MK, Foy HM. Influenzavirus infections in Seattle families, 1975-1979. I. Study design, methods and the occurrence of infections by time and age. Am J Epidemiol 1982;116:212-27.
8. Monto AS, Sullivan KM. Acute respiratory illness in the community: frequency of illness and the agents involved. Epidemiol Infect 1993;110:145-60.
9. Simonsen L, Clarke MJ, Williamson GD, Stroup DF, Arden NH, Schonberger LB. The impact of influenza epidemics on mortality: introducing a severity index. Am J Public Health 1997;87:1944-50.
10. Perrotta DM, Decker M, Glezen WP. Acute respiratory disease hospitalizations as a measure of impact of epidemic influenza. Am J Epidemiol 1985;122:468-76.
11. Glezen WP, Payne AA, Snyder DN, Downs TD. Mortality and influenza. J Infect Dis 1982;146:313-21.
12. Couch RB, Kasel JA, Glezen WP, et al. Influenza: its control in persons and populations. J Infect Dis 1986;153:431-40.
13. Fisher RG, Gruber WC, Edwards KM, et al. Twenty years of outpatient respiratory syncytial virus infection: a framework for vaccine efficacy trial. Pediatrics 1997;99:E7.
14. Mullooly JP, Barker WH. Impact of type A influenza on children: a retrospective study. Am J Public Health 1982;72:1008-16.
15. Glezen WP, Paredes A, Taber LH. Influenza in children: relationship to other respiratory agents. JAMA 1980;243:1345-9.
16. Edwards KM, Dupont WD, Westrich MK, Plummer WD Jr, Palmer PS, Wright PF. A randomized controlled trial of cold-adapted and inactivated vaccines for the prevention of influenza A disease. J Infect Dis 1994;169:68-76.
17. Belshe RB, Mendelman PM, Treanor J, et al. The efficacy of live attenuated, cold-adapted, trivalent, intranasal influenzavirus vaccine in children. N Engl J Med 1998;338:1405-12.
18. Ray WA, Griffin MR. Use of Medicaid data for pharmacoepidemiology. Am J Epidemiol 1989;129:837-49.
19. Piper JM, Mitchel EF Jr. Prenatal exposure to prescribed drugs in Tennessee Medicaid, 1983-1988. Paediatr Perinat Epidemiol 1991;5:402-9.
20. Simonsen L, Clarke MJ, Stroup DF, Williamson GD, Arden NH, Cox NJ. A method for timely assessment of influenza-associated mortality in the United States. Epidemiology 1997;8:390-5.
21. Rothman KJ, Greenland S. Modern epidemiology. 2nd ed. Philadelphia: Lippincott-Raven, 1998.
22. Neuzil KM, Reed GW, Mitchel EF Jr, Griffin MR. Influenza-associated morbidity and mortality in young and middle-aged women. JAMA 1999;281:901-7.
23. Barker WH, Mullooly JP. Impact of epidemic type A influenza in a defined adult population. Am J Epidemiol 1980;112:798-811.
24. Glezen WP, Decker M, Joseph SW, Mercready RGJ. Acute respiratory disease associated with influenza epidemics in Houston, 1981-1983. J Infect Dis 1987;55:1119-26.
25. Karron RA, Steinhoff MC, Subbarao EK, et al. Safety and immunogenicity of a cold-adapted influenza A (H1N1) reassortant virus vaccine

administered to infants less than six months of age. Pediatr Infect Dis J 1995;14:10-6.
26. Clements ML, Makhene MK, Karron RA, et al. Effective immunization with live attenuated influenza A virus can be achieved in early infancy. J Infect Dis 1996;173:44-51.
27. Neuzil KM, Reed GW, Mitchel EF, Simonsen L, Griffin MR. Impact of influenza on acute cardiopulmonary hospitalizations in pregnant women. Am J Epidemiol 1998;148:1094-102.
28. Puck JM, Glezen WP, Frank AL, Six HR. Protection of infants from infection with influenza A virus by transplacentally acquired antibody. J Infect Dis 1980;142:844-9.
29. Clements DA, Langdon L, Bland C, Walter E. Influenza A vaccine decreases the incidence of otitis media in 6- to 30-month-old children in day care. Arch Pediatr Adolesc Med 1995;149:1113-7.
30. Heikkinen T, Ruuskanen O, Waris M, Ziegler T, Arola M, Halonen P. Influenza vaccination in the prevention of acute otitis media in children. Am J Dis Child 1991;145:445-8.
31. Kim HW, Brandt CD, Arrobio JO, Murphy B, Chanock RM, Parrott RH. Influenza A and B virus infection in infants and young children during the years 1957-1976. Am J Epidemiol 1979;109:464-79.
32. Glezen WP, Denny FW. Epidemiology of acute lower respiratory disease in children. N Engl J Med 1973;288:498-505.
33. Foy HM, Cooney MK, McMahan R, Grayston JT. Viral and mycoplasmal pneumonia in a prepaid medical care group during an eight-year period. Am J Epidemiol 1973;97:93-102.
34. Kim HW, Arrobio JO, Brandt CD, et al. Epidemiology of respiratory syncytial virus infection in Washington, D.C. I. Importance of the virus in different respiratory tract disease syndromes and temporal distribution of infection. Am J Epidemiol 1973;98:216-25.
35. Brandt CD, Kim HW, Arrobio JO, et al. Epidemiology of respiratory syncytial virus infection in Washington, D.C. 3. Composite analysis of eleven consecutive yearly epidemics. Am J Epidemiol 1973;98:355-64.
36. Monto AS, Cavallaro JJ. The Tecumseh study of respiratory illness. II. Patterns of occurrence of infection with respiratory pathogens, 1965-1969. Am J Epidemiol 1971;94:280-9.