ORIGINAL ARTICLES

Does influenza vaccination prevent asthma exacerbations in children?

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Objective: Influenza can exacerbate asthma, particularly in children. The effectiveness of influenza vaccine in preventing influenza-related asthma exacerbations, however, is not known. We evaluated influenza vaccine effectiveness in protecting children against influenza-related asthma exacerbations.

Study design: We conducted a population-based retrospective cohort study with medical and vaccination records in 4 large health maintenance organizations in the United States during the 1993-1994, 1994-1995, and 1995-1996 influenza seasons. We studied children with asthma who were 1 through 6 years of age and who were identified by search of computerized databases of medical encounters and pharmacy dispensings. Main outcome measures were exacerbations of asthma evaluated in the emergency department or hospital.

Results: Unadjusted rates of asthma exacerbations were higher after influenza vaccination than before vaccination. After adjustment was done for asthma severity by means of a self-control method, however, the incidence rate ratios of asthma exacerbations after vaccination were 0.78 (95% CI: 0.55 to 1.10), 0.59 (0.43 to 0.81), and 0.65 (0.52 to 0.80) compared with the period before vaccination during the 3 influenza seasons.

Conclusions: After controlling for asthma severity, we found that influenza vaccination protects against acute asthma exacerbations in children. (J Pediatr 2001;138:306-10)

Viral respiratory tract infections, including influenza, can exacerbate asthma, particularly in children.[1] It has been estimated that 24% to 85% of all asthma attacks in children are associated with viral respiratory tract infections.[2,3] Influenza infection in children with asthma causes wheezing and results in increased hospitalizations for exacerbations of asthma.[4] The Advisory Committee for Immunization Practices, the American Academy of Pediatrics, and the Second Expert Panel for the Diagnosis and Management of Asthma recommend annual influenza vaccination for children with asthma to protect them against complications of influenza infection such as pneumonia.[5-7] Despite the recommendations, a minority of children with asthma receive an annual influenza vaccination.[8,9] One important reason for not vaccinating children with asthma against influenza is uncertainties about the benefits of vaccination in this population.[2] Although influenza vaccination has been shown to result in production of protective levels of antibodies in children with asthma,[10] no evidence exists on the effectiveness of influenza vaccine in preventing influenza-related asthma exacerbations. It has even been suggested that influenza vaccination may increase the risk of asthma exacerbations.[11,12] Our objective was to study the effectiveness of influenza vaccine in protecting children against influenza-related asthma exacerbations.

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ED	Emergency department
HMO	Health maintenance organization
VSD	Vaccine Safety Datalink

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Submitted for publication May 17, 2000; revision received Sept 12, 2000; accepted Oct 5, 2000.

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9/21/112168

doi:10.1067/mpd.2001.112168

METHODS

We conducted a retrospective cohort study with the Vaccine Safety Datalink, a computerized, linked database on immunizations, medical encounters, and demographic information.[13] VSD contains data on more than 1,000,000 children enrolled in 4 large health maintenance organizations located on the West Coast of the United States. We analyzed 3 consecutive influenza seasons (October 1 through April 30) between 1993 and 1996. At the time of our analysis, data were available from 3 HMOs for the 1993-1994 and 1994-1995 influenza seasons and from all 4 HMOs for the 1995-1996 influenza season.

We restricted the study to children 1 through 6 years of age because of the difficulty in differentiating between asthma and bronchiolitis in children younger than 1 year of age.[14] To be included in the study, children had to have been continuously enrolled in the HMO from at least May 1 through October 1 of the year encompassing the start of a particular influenza season. The asthma case definition had to be met before May 1 of the year in which the influenza season began. During the period from May 1 through October 1 of each season, we estimated severity of asthma, a potential confounder in the analysis.

Asthma Case Definition

To identify children with asthma, we searched computerized outpatient clinic, hospital, emergency department, and pharmacy files. Cases had to meet at least one of the following criteria: (1) at least 1 International Classification of Diseases, Ninth Revision (ICD-9) code for asthma (493) and at least 1 dispensing of any asthma medication, (2) at least 1 dispensing of a β-agonist drug and at least 1 for cromolyn, or (3) 5 or more dispensings of any asthma medication. We adapted this definition from a previous study conducted at one of the HMOs participating in the VSD.[15] Asthma medications included β-agonists (inhaled or oral), theophylline, corticosteroids (inhaled, oral, or injectable), cromolyn, adrenergic drugs not elsewhere specified, and unclassified asthma medications.

Table I. Characteristics of children with asthma by influenza season, Vaccine Safety Datalink

	Influenza season		
	1993-1994*	1994-1995*	1995-1996†
No. of children with asthma	22,231	38,669	70,753
Sex			
Female, n (%)	9,235 (41.5)	16,115 (41.7)	29,908 (42.3)
Male, n (%)	12,996 (58.5)	22,554 (58.3)	40,845 (57.7)
Age (y)			
1-2, n (%)	6,845 (30.8)	11,112 (28.7)	18,712 (26.5)
3-4, n (%)	7,982 (35.9)	14,419 (37.3)	26,200 (37.0)
5-6, n (%)	7,404 (33.3)	13,138 (34.0)	25,841 (36.5)
Vaccinated, n (%)	2,315 (10.4)	3,397 (8.8)	6,315 (8.9)
One dose, n (%)	1,630 (7.4)	2,723 (7.1)	5,029 (7.1)
Two doses, n (%)	684 (3.0)	671 (1.7)	1276 (1.8)

*Three HMOs.
†Four HMOs.

Definition of Asthma Exacerbation

An asthma exacerbation was defined as a hospitalization or ED visit for asthma identified from the computerized HMO databases.

Statistical Analysis

Studies analyzing drug effectiveness are often biased by "confounding by indication or severity."[16] In our cohort, children who had more severe asthma were more likely to be vaccinated against influenza,[17] thus potentially biasing our analysis in the direction of a spurious association between influenza vaccination and acute asthma attacks. We used 2 different methods to control for such confounding: a traditional cohort analysis adjusted for asthma severity and a self-control analysis.

Traditional Cohort Analysis

In the first analysis we included all children with asthma. During each influenza season, we computed incidence rates of asthma exacerbations according to vaccination status. Postvaccination incidence rates were determined by dividing the total number of exacerbations after vaccination by the total postvaccination person-time. The unexposed incidence rate was calculated by dividing the number of exacerbations by the total person-time in vaccinated children before vaccination plus the total person-time in unvaccinated children. Because children younger than 9 years of age who are vaccine naive for the first time in their life require 2 doses to be fully immunized, we measured the postvaccination intervals after the last dose of vaccine. In the analysis involving the entire cohort of children with asthma, we used unconditional Poisson regression models to estimate incidence rate ratios of asthma exacerbations adjusted for severity of asthma and for sex, age, HMO, preventive care practices, and seasonal fluctuations in asthma exacerbations. To control for severity of asthma, we used the number of inhaled β-agonist dispensings and the number of hospitalizations and ED visits for asthma during the 6 months before the influenza season (May 1 through Sep-

Table II. Traditional cohort analysis of asthma exacerbations after influenza vaccination by influenza season, Vaccine Safety Datalink

	Influenza season		
	1993-1994	1994-1995	1995-1996
Incidence rate (95% CI)*			
Vaccinated†	17.1 (14.9-19.6)	13.3 (11.7-15.1)	14.5 (13.3-15.9)
Comparison‡	3.9 (3.6-4.2)	3.9 (3.7-4.2)	4.9 (4.7-5.2)
Crude rate ratio (95% CI)	4.4 (3.8-5.2)	3.4(2.9-3.9)	2.9 (2.7-3.2)
Adjusted rate ratio§ (95% CI)	2.2 (1.8-2.6)	1.5 (1.3-1.7)	1.4 (1.2-1.5)
P value	.0001	.0001	.0001

*Unadjusted rate per 1000 child-months (95% CI).
†Period after influenza vaccination.
‡Before vaccination or unvaccinated.
§Adjusted with unconditional Poisson regression for HMO, sex, age, previous use of β-agonists and cromolyn, previous hospitalizations and emergency department visits for asthma, and 2-week periods of calendar time from October 1 through April 30 of each season.

Table III. Self-control analysis of asthma exacerbations after influenza vaccination by influenza season, Vaccine Safety Datalink

	Influenza season		
	1993-1994*	1994-1995*	1995-1996†
No. of cases‡	577	969	2,075
No. of asthma exacerbations	710	1,146	2,564
Follow-up time (child-months)	3,904	6,520	14,067
Adjusted incidence rate ratio	0.78	0.59	0.65
(95% CI)§	(0.55-1.10)	(0.43-0.81)	(0.52-0.80)
P value	.15	.001	.0001

*Three HMOs.
†Four HMOs.
‡Children with asthma who had at least one asthma exacerbation during the influenza season.
§Incidence rate ratio (95% CI) of asthma exacerbation occurring after influenza vaccination compared with the period before vaccination in the same individual; estimated by conditional Poisson regression models stratified by individual child and adjusted for 2-week periods of calendar time from October 1 through April 30 of each season.

tember 30). We grouped the numbers of inhaled β-agonist dispensings, hospitalizations, and ED visits into categories with sufficient numbers of children to allow meaningful comparisons. The use of β-agonists was categorized as 0, 1, 2, or 3 dispensings. Hospitalizations and ED visits were dichotomized (0, 1). Because children with better adherence to preventive care practices are more likely to be vaccinated, we also adjusted for preventive care practices with frequency of cromolyn dispensings (0, 1) during the 6 months before the influenza season.

Self-Control Analysis

In this analysis we included only children who had at least one asthma exacerbation and had been vaccinated during the influenza season of interest. To estimate the effectiveness of vaccine in preventing asthma exacerbations, we compared the incidence of exacerbations after vaccination with the incidence before vaccination in the same child. We used a conditional Poisson regression model[18,19] to estimate incidence rate ratios of asthma exacerbations. To adjust for seasonal fluctuations in asthma exacerbations, the model included terms for 2-week intervals of calendar time. Because the self-control method uses individuals as their own controls, it implicitly controls for potential confounders such as asthma severity that may be difficult to measure or that may not have been measured.[18-20] To perform the analyses, we used the SAS GENMOD procedure for unconditional Poisson regression. For conditional Poisson regression, we developed a special-purpose program with SAS Interactive Matrix Language.[21]

RESULTS

Depending on the influenza season, between 22,231 and 70,753 children with asthma were included in the analysis (Table I). During all seasons, fewer girls than boys were found to have asthma, and the ages of the patients were fairly evenly distributed. Only 9% to 10% of the children were vaccinated against influenza in any given year. Most of the vaccinations were given in October and November, and asthma exacerbations peaked in December (data not shown).

In the unadjusted full cohort analysis that compared influenza exacerbation rates after vaccination with rates in unvaccinated children or rates before vaccination among those who were vaccinated, vaccination was associated with an elevated exacerbation rate during each influenza season (Table II). When we adjusted for asthma severity and other variables, the relative risks decreased but still remained significantly elevated above 1.0. In the self-control analysis, in which risks of asthma exacerbation were compared before and after vaccination within the same individual, the rate ratios were <1.0 during each of the influenza seasons (Table III).

DISCUSSION

We found that the apparent effectiveness of influenza vaccination against

asthma exacerbations is highly confounded by asthma severity. In the traditional cohort analysis, in which vaccinated children were compared with unvaccinated children, we found that vaccination was associated with an increased risk of asthma exacerbations. Adjusting the cohort analysis for measures of asthma severity and other potential confounders decreased the relative risks, but risks remained significantly elevated. We suspected that we had not adequately controlled residual confounding with crude measures of asthma severity. In the self-control analysis, which controls for asthma severity on an individual level, influenza vaccination decreased the risk of asthma exacerbations by as much as 22% to 41%. These findings lend further support to the current recommendation to vaccinate children with asthma against influenza. Hospitalizations and ED visits account for 70% of the asthma-related expenditures in the United States.[22] According to our study results, vaccinating all children with asthma could prevent 59% to 78% of asthma hospitalizations and ED visits during influenza seasons.

Confounding by severity (or indication) is a well-recognized obstacle in studying the effectiveness of medications.[23] Vaccinated children have higher rates of asthma exacerbations because they tend to have more severe asthma.[17] The self-control method addressed this problem by comparing incidence rates of asthma exacerbations before and after influenza vaccination in the same person.

Among the potential limitations of our study is the validity of our case definition of asthma. In previous studies various combinations of ICD-9 codes and medications have been used to identify cases of asthma.[14,15,24] Osborne et al[15] have demonstrated high specificity and sensitivity of asthma case-finding algorithms similar to ours. Given the low influenza vaccination coverage, the completeness of our computerized vaccination data could also be questioned. Previous quality control checks in the Vaccine Safety Datalink, however, have shown that between 78% and 89% of influenza vaccinations recorded in paper medical records were captured by the automated vaccination databases.[25] Furthermore, the 10% vaccination coverage in our population is consistent with studies by other investigators.[8] Another potential concern is that our results could be explained by seasonal variability in incidence of asthma exacerbations. However, we adjusted for seasonal incidence of asthma by dividing the influenza season into 2-week periods of calendar time. It could be argued that the substantial decrease in the incidence of severe asthma exacerbations after influenza vaccination may be explained by changes in the intensity of asthma over time. Exacerbations of asthma are usually followed by periods of better control of asthma symptoms. If the exacerbations prompt health care providers to vaccinate children, then the following decrease of asthma symptoms would be falsely attributed to vaccination. However, in another study[9] we examined the incidence of asthma exacerbations within 2 weeks before and after influenza vaccinations, and we did not find a peak of asthma exacerbations before the influenza vaccination. Finally, the populations in the HMOs are not fully representative of the general US population in that they tend to have higher levels of education and socioeconomic status.

Our self-control results suggest that influenza vaccination may protect against asthma attacks during influenza seasons. This apparent protective effect is consistent with a good match between the wild and vaccine viral strains during the analyzed influenza seasons.[26-28] For example, in the 1995-1996 influenza season, 67% of A/H3N2 wild influenza virus isolates were similar to the A/Johannesburg/33/94 (H3N2) influenza vaccine strain, 91% of the wild A/H1N1 viruses were similar to the A/Texas/36/91 (H1N1) vaccine strain, and 98% of the B isolates were similar to the B/Beijing/184/93 vaccine strain.[28]

In conclusion, our study suggests that influenza vaccination is associated with a decreased incidence of asthma exacerbations in children throughout the influenza season. The effectiveness of influenza vaccine in preventing asthma exacerbations was 78%, 59%, and 65% in the 1993-1994, 1994-1995, and 1995-1996 influenza seasons, respectively. We are not certain whether the degree of protective effectiveness against asthma exacerbations that we observed can be completely accounted for by protection against influenza. A nonspecific immunologic effect of the vaccine, or vaccination as a marker of health care, resulting in lower incidence of asthma attacks, may be other possible explanations of the strong protective effect observed in our study.

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