ORIGINAL CONTRIBUTION

Does Influenza Vaccination Exacerbate Asthma?

Analysis of a Large Cohort of Children With Asthma

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Context: Although influenza vaccination is recommended for children with asthma, only a minority are vaccinated. One reason for low influenza vaccine coverage among children with asthma may be concern that influenza vaccination may induce an exacerbation of asthma.

Objective: To evaluate the safety of influenza vaccination in children with asthma, we studied the incidence of hospitalizations and emergency department visits for asthma following influenza vaccination.

Design: Retrospective cohort study–analysis of population-based computerized medical and vaccination records.

Setting: Four large health maintenance organizations on the West Coast of the United States.

Subjects: Children with asthma 1 through 6 years of age, identified by search of computerized databases of medical encounters and pharmacy prescriptions.

Main Outcome Measures: Exacerbations of asthma.

Results: In unadjusted analyses vaccination was associated with high rates of asthma exacerbations. However, after adjusting for asthma severity using a self-control method, the incidence rate ratios of asthma exacerbations after vaccination were 0.58 (95% confidence interval, 0.36-0.95), 0.74 (95% confidence interval, 0.47-1.17), and 0.98 (95% confidence interval, 0.76-1.27) during the 3 influenza seasons.

Conclusions: After controlling for asthma severity, we found that influenza vaccination does not result in acute asthma exacerbations in children. Concern about possible exacerbation of asthma is not a valid reason to not vaccinate children with asthma against influenza.

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ASTHMA IS a large and growing health problem,[1-4] especially in children.[5-8] It is the most common cause of hospitalization in children,[9] with rates increasing in recent decades.[10] Asthma may be precipitated by viral infections of the upper respiratory tract, including influenza.[11-16] Influenza infection can cause exacerbations of wheezing[14] and life-threatening bronchial obstruction in children.[17] Health authorities in many countries recommend annual influenza vaccination for patients with asthma.[18-20] Despite these recommendations, only a few children with asthma receive an annual influenza vaccination.[21-24]

One reason for low influenza vaccine coverage among children with asthma may be concern that influenza vaccination may induce an exacerbation of asthma.[23,25,26] The evidence that influenza vaccine exacerbates asthma is conflicting. Observational[27-31] and placebo-controlled studies[32-34] conducted to date have been small and the results have been inconsistent.

To evaluate the safety of influenza vaccination in children with asthma, we studied the incidence of hospitalizations and emergency department (ED) visits for asthma following influenza vaccination at 4 large health maintenance organizations (HMOs).

RESULTS

Table 1 gives, for each of the 3 influenza seasons, the number of children who met our asthma case definition and their demographic characteristics.

Among all children with asthma, the crude rates of asthma exacerbations (per

METHODS

We conducted a retrospective cohort study using the Vaccine Safety Datalink.[35] The Vaccine Safety Datalink is a computerized, linked database on immunizations, medical encounters, and demographic information on more than 1 million children enrolled in 4 large HMOs on the West Coast of the United States. We studied 3 influenza seasons: 1993-1994, 1994-1995, and 1995-1996. We defined the period from October 1 through April 30 as the influenza season. 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 did not have access to pharmacy prescription data for the fourth HMO for 1993-1994 or 1994-1995.

The study was restricted to children 1 through 6 years of age because of the difficulty in differentiating between asthma and bronchiolitis in infants younger than 1 year.[36] Eligible children had to meet our asthma case definition before May 1 of the year in which the influenza season began and had to have been continuously enrolled in the HMO from at least May 1 through October 1 of that year.

ASTHMA CASE DEFINITION

To identify children with asthma, we searched computerized outpatient clinic, hospital, ED, and pharmacy files. A case had to meet 1 of the following criteria since the beginning of HMO membership: (1) at least 1 *International Classification of Diseases, Ninth Revision (ICD-9)*[37] code 493 and at least 1 prescription for any asthma medication; or (2) at least 1 prescription for a β-agonist drug and at least 1 for cromolyn; or (3) 5 or more prescriptions for any asthma medication. This definition was adapted from a previous study conducted at one of the HMOs.[38] Asthma medications included: β-agonists (inhaled or oral), theophyllin, corticosteroids (inhaled, oral, or injectable), cromolyn, adrenergic drugs not elsewhere specified, and unclassified asthma medications.

STATISTICAL ANALYSIS

The main outcome measure was the number of acute asthma exacerbations, defined as hospitalizations or ED visits for asthma and identified from computerized HMO databases on medical encounters. Influenza vaccination data came from computerized vaccination databases. We computed incidence rates of asthma exacerbations by dividing the total number of exacerbations by the person-time contributed by each subject during periods of interest throughout each influenza season. In our primary analysis, we compared crude incidence rates of asthma exacerbations that occurred in vaccinated children within 2 weeks after vaccination to the background incidence rates of asthma exacerbations that occurred in unvaccinated children and in vaccinated children outside the postvaccination risk intervals. Since some children require 2 doses of vaccine to be fully immunized, we measured the 2-week postvaccination intervals after each dose of vaccine. We used a 2-week risk interval, but since some previous studies have reported asthma exacerbations within 48 hours after vaccination, we also evaluated a 2-day risk interval.

Controlling for severity of asthma in our analysis was very important to avoid "confounding by indication."[39-41] This bias arises because the tendency to receive influenza vaccination increases with the severity of asthma.[42] Such confounding, if uncontrolled, can result in a spurious association between influenza vaccination and acute asthma attacks. We used 2 different methods to control for confounding by indication. We first used unconditional Poisson regression models to estimate incidence rate ratios of asthma exacerbations adjusted for sex, age, HMO, severity of asthma, preventive care practices, and seasonal fluctuations in asthma exacerbations. 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 September 30) to adjust for asthma severity. The use of β-agonists was categorized as 0, 1, 2, or 3 or more dispensings. Hospitalizations and ED visits were dichotomized (0 and ≥1). To adjust for preventive care practices, we used frequency of cromolyn dispensings (0 and ≥1) during the 6 months prior to the influenza season.

We conducted a second analysis using a self-control design, including only children who had at least 1 asthma exacerbation during the influenza season of interest. Each child was treated as a separate stratum, and incidence rates of asthma exacerbations within 2 weeks after vaccination were compared with other intervals for the same child. We used a conditional Poisson regression model[43,44] to estimate incidence rate ratios. We included terms for 2-week intervals of calendar time throughout the entire influenza season to adjust for seasonal changes in asthma exacerbation incidence. Since the method uses individuals as their own controls, it implicitly controls for many potential confounders, such as asthma severity.[43-45] We also performed self-control analysis using a 2-day risk interval. Separately, we performed a self-control analysis including only children with severe asthma (with ≥3 dispensings of a β-agonist or at least 1 hospitalization or ED visit for asthma).

We used the SAS GENMOD procedure for unconditional Poisson regression, and we wrote a special-purpose program using SAS Interactive Matrix Language for conditional Poisson regression.[46]

1000 child-months) during each influenza season were 5.00 (95% confidence interval [CI], 4.64-5.38) in 1993-1994, 4.61 (95% CI, 4.35-4.89) in 1994-1995, and 5.64 (95% CI, 5.43-5.86) in 1995-1996. In vaccinated children, the asthma attack rates showed no obvious relation to influenza vaccination (**Figure**).

Table 1. 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	9235 (41.5)	16 115 (41.7)	29 908 (42.3)
Male	12 996 (58.5)	22 554 (58.3)	40 845 (57.7)
Age, y			
0-2	6845 (30.8)	11 112 (28.7)	18 712 (26.5)
3-4	7982 (35.9)	14 419 (37.3)	26 200 (37.0)
5-6	7404 (33.3)	13 138 (34.0)	25 841 (36.5)
Follow-up time, child-months	142 026	248 434	454 619
No. of asthma exacerbations	710	1146	2564
Total No. of vaccinated children	**2315** (10.4)	**3397** (8.8)	**6315** (8.9)
1 dose received	1630 (7.4)	2723 (7.1)	5029 (7.1)
2 doses received	684 (3.0)	671 (1.7)	1276 (1.8)
≥3 doses received	1	3	10

*Values expressed as number (percentage) unless otherwise indicated.
†Data available for 3 health maintenance organizations.
‡Data available for 4 health maintenance organizations.

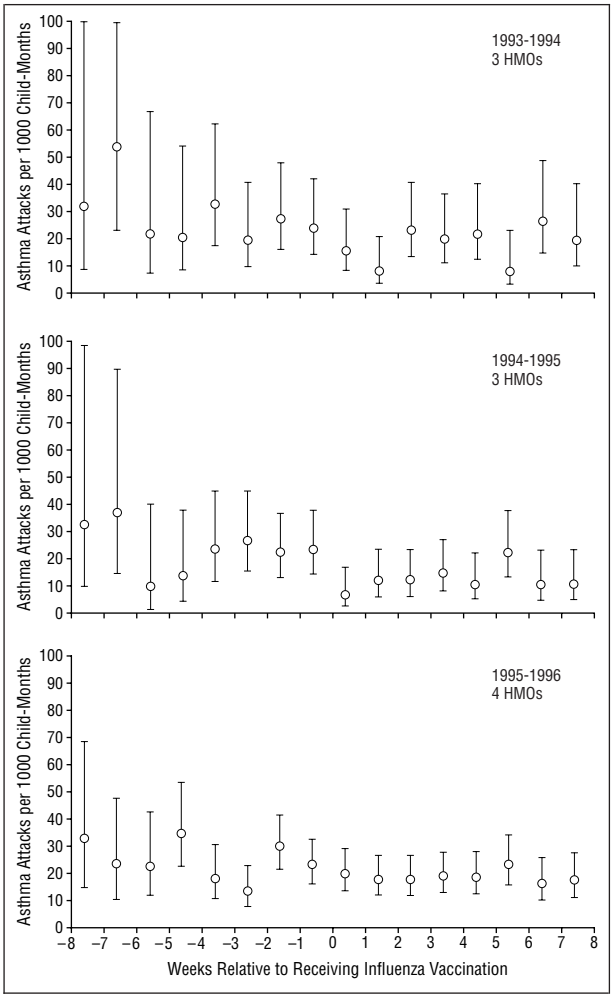
In the first analysis, the crude incidence rates of asthma exacerbations within 2 weeks after vaccination were 2 to 3 times higher than the crude rates in unvaccinated children throughout the influenza season and in vaccinated children during periods outside the 2-week postvaccination interval (**Table 2**). After adjustment for sex, age, HMO, calendar time, asthma severity, and preventive care practices, the incidence rate ratios of asthma exacerbation within 2 weeks after influenza vaccination decreased but remained slightly elevated, and the increase in risk was statistically significant in the 1995-1996 season. Results using a 2-day risk interval were consistent with the 2-week interval results. The adjusted rate ratios of asthma exacerbation within 2 days after vaccination in the full cohort analysis were 0.55 (95% CI, 0.09-1.71), 1.34 (95% CI, 0.48-2.91), and 1.15 (95% CI, 0.60-1.98) in consecutive influenza seasons. The adjusted rate ratios of asthma exacerbation in children with severe asthma (≥3 prescriptions for a β-agonist or with at least 1 hospitalization or ED visit) were 0.87 (95% CI, 0.39-1.66), 0.35 (95% CI, 0.11-0.83), and 1.34 (95% CI, 0.91-1.89) in consecutive influenza seasons.

In the self-control analysis, in which the risk of asthma exacerbation in vaccinated children within 2 weeks after vaccination was compared with periods outside this interval, none of the incidence rate ratios were greater than 1.0 (**Table 3**). Using a 2-day risk interval, the adjusted rate ratios in the self-control analysis were 0.34 (95% CI, 0.08-1.37), 0.96 (95% CI, 0.40-2.36), and 0.83 (95% CI, 0.45-1.50) in each of the influenza seasons. The adjusted rate ratios of asthma exacerbation in children with severe asthma (≥3 prescriptions for a β-agonist or with at least 1 hospitalization or ED visit) were 0.67 (95% CI, 0.41-1.14), 0.74 (95% CI, 0.44-1.23), and 1.02 (95% CI, 0.78-1.35) in consecutive influenza seasons.

COMMENT

After controlling for confounding by asthma severity, we found that influenza vaccination did not lead to an acute exacerbation of asthma within 2 days or 2 weeks after vaccination. In the past, a few anecdotal reports and physiologic studies have sustained concerns about asthma exacerbation.[23,26] Several small studies failed to find any harmful effects on lung function after vaccination.[29,31,47-49] However, 2 investigators have reported exacerbations of asthma following influenza vaccination.[50,51] Furthermore, some authors described increased bronchial responsiveness after influenza vaccination.[28,52] Bell et al[27] observed a significantly increased use of bronchodilating drugs and a decrease in the peak expiratory flow rate 48 hours after vaccination.

Results from controlled clinical trials also have been inconsistent. Campbell and Edwards[53] in a crossover trial observed significant reductions in peak expiratory flow with no increase in symptoms during the week after influenza vaccination, but they examined adults and their sample size was small (28 individuals). Kava et al[32] showed no increased need for bronchodilators up to 21 days after influenza immunization of 16 adults. Stenius-Aarniala et al[33] in a study of 318 adults (161 with asthma) did not find a significant difference in clinical symptoms, medication use, or peak expiratory flow between vaccinated patients and placebo recipients. De Jongste et al[30] showed increased bronchial responsiveness to histamine after administration of live, but not after inactivated, influenza vaccine to asth-



Incidence rates of acute asthma attacks during weeks before and after influenza vaccination for 3 influenza seasons. The period from October 1 through April 30 was defined as the influenza season. Data were available from 3 health maintenance organizations (HMOs) for the 1993-1994 and 1994-1995 influenza seasons and from all 4 health maintenance organizations for the 1995-1996 influenza season. Access to pharmacy prescription data from the fourth health maintenance organization for 1993-1994 and 1994-1995 was unavailable.

matic children. Recently, Nicholson et al[34] in a crossover study among 255 adults with asthma demonstrated a fall in peak expiratory flow after influenza vaccination, but the effect became insignificant after patients with common colds were removed from the analysis.

Regardless of possible subclinical physiological effects on pulmonary function, the results of our study indicate that influenza vaccination does not result in clinically meaningful exacerbations of asthma symptoms in children. The crude risk of asthma exacerbation within 2 weeks after influenza vaccination was 2 to 3 times higher than the risk in unvaccinated children or during periods outside the 2-week interval after vaccination. These crude results, however, were confounded by severity of asthma since children with more severe asthma are more likely to be vaccinated against influenza.[42] After adjustment for asthma severity and other potential confounders in unconditional Poisson regression models, the incidence rate ratios of asthma exacerbation within 2 weeks after immunization decreased to between 1 and 1.39, depending on the influenza season. The relative risks for the 1993-1994 and 1994-1995 influenza seasons were not statistically significant; however, the relative risk for the 1995-1996 influenza season was significant (1.39; 95% CI, 1.08-1.77). Using a self-control method, which more fully adjusts for asthma severity, resulted in incidence rate ratios of asthma exacerbation that were all at or below 1.0. Almost all previous studies of the safety of influenza vaccination have had observation periods of 2 weeks or less after vaccination.[27,28,30,33,34] We also analyzed asthma exacerbations occurring within a 2-day risk interval, and we did not detect any increased risk of asthma exacerbation within this shorter interval. We also performed separate analyses of children with severe asthma and did not find an increased risk of asthma exacerbations following influenza vaccination.

The difference between the relative risks computed based on the traditional cohort analysis and the self-control analysis results from the differences in method.

Table 2. Full Cohort Analysis of Asthma Exacerbations Within 2 Weeks of Influenza Vaccination, by Influenza Season, Vaccine Safety Datalink

	Influenza Season		
	1993-1994	1994-1995	1995-1996
Incidence rate (95% confidence interval [CI])*			
Vaccinated†	12.34 (7.77-19.58)	10.12 (6.53-15.69)	18.20 (14.32-23.12)
Comparison‡	4.92 (4.57-5.30)	4.57 (4.31-4.84)	5.54 (5.32-5.76)
Crude rate ratio (95% CI)	2.51 (1.51-3.88)	2.22 (1.38-3.35)	3.29 (2.55-4.15)
Adjusted rate ratio§ (95%CI)	1.00 (0.60-1.56)	1.09 (0.67-1.67)	1.39 (1.08-1.77)
P	.99	.71	.01

**Unadjusted rate per 1000 child-months (95% CI).*
†Two-week period following influenza vaccination.
‡Outside the 2-week period or unvaccinated.
§Adjusted using unconditional Poisson regression for health maintenance organization, sex, age, prior use of β-agonists and cromolyn, prior hospitalizations and emergency department visits for asthma, and 2-week periods of calendar time from October 1 through April 30 of each season.

Table 3. Self-control Analysis of Asthma Exacerbations During the 2-Week Period After Influenza Vaccination, by Influenza Season, Vaccine Safety Datalink

	Influenza Season		
	1993-1994	1994-1995	1995-1996
No. of cases*	577	969	2075
Follow-up time, child-months	3904	6520	14 067
No. of asthma exacerbations	710	1146	2564
Adjusted incidence rate ratio (95% CI)†	0.58 (0.36-0.95)	0.74 (0.47-1.17)	0.98 (0.76-1.27)
P	.03	.20	.90

**Children with asthma who had at least 1 asthma exacerbation during the influenza season.*

†Incidence rate ratio (95% confidence interval [CI] of asthma exacerbation occurring during the 2-week period after influenza vaccination compared with other periods 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 influenza season.

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The 2 approaches analyze different populations. In the traditional cohort analysis, vaccinated children were compared with unvaccinated children. In the self-control analysis, only children with at least 1 asthma exacerbation were analyzed. In this method, the incidence of asthma exacerbations within the 2-week period after vaccination was compared with the incidence outside this risk interval in the same child. The self-control method adjusts for asthma severity on an individual level, using individuals as their own controls. The method controls for many other potential confounders that may be difficult to measure or that may not have been measured.[43,44]

Although ours was an observational study, it had many advantages over previous studies, including: (1) it was population based, (2) the sample size was large enough to detect even small differences in risk (eg, we could have detected a relative risk of 1.25 with 90% power), (3) the results were consistent across 3 different influenza seasons, and (4) there was rigorous statistical adjustment for asthma severity and other potential confounding factors.

There were, however, some limitations to our study. First, we know that there were some errors in our computerized vaccination data, but these were not large. Quality control analyses in the Vaccine Safety Datalink have shown that between 78% and 89% of influenza vaccinations recorded in the medical records were captured by the automated vaccination databases.[54] Another concern might be that we used hospitalizations and ED visits as surrogate measures of asthma exacerbation, thus limiting our analysis to more severe exacerbations. Our asthma case definition could also be questioned. A universal asthma case definition is difficult to design,[55] and others also have relied on *ICD-9* codes[36,37,56-58] and asthma medication data[38,56,59] to define asthma cases. A case definition similar to ours was previously shown to have high sensitivity and positive predictive value.[38]

Another potential source of bias may have occurred if the vaccination was postponed in cases where a child had been recently hospitalized for asthma. To explore this possibility we computed the incidence of acute asthma attacks during 2-month periods before and after an influenza vaccination. The rates showed no obvious relation to influenza vaccination (Figure).

We used prescriptions for asthma medications as one of the measures of asthma severity. We believe that the number of prescriptions provides an accurate reflection of asthma severity because of the uniformity of asthma management in the HMOs. All the HMOs participating in the study have guidelines for asthma management that are reinforced through continual quality control monitoring.

We excluded children younger than 1 year in our analysis because of the difficulty in differentiating asthma and bronchiolitis in this age category. We have performed a subanalysis including these children, and the results were consistent with the results of the analysis of children 1 through 6 years of age (data not shown).

CONCLUSIONS

In this large, population-based, observational study, we found that influenza vaccination does not result in acute asthma exacerbations in children. Concern about possible exacerbation of asthma is not a valid reason to not vaccinate children with asthma against influenza. We observed a decrease in the incidence of asthma exacerbations within 2 weeks after influenza vaccination during all analyzed influenza seasons that was statistically significant during the 1993-1994 influenza season (relative risk 0.58; 95% CI, 0.36-0.95). The results raise the question whether influenza vaccination may cause a decrease in the incidence of asthma attacks beyond the 2 weeks (ie, vaccination may provide long-term protection against asthma exacerbations). We are exploring this possibility in a separate analysis.

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The authors have no commercial, proprietary, or financial interest in the products or companies described in this article.

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