

THE SAFETY OF INACTIVATED INFLUENZA VACCINE IN ADULTS AND CHILDREN WITH ASTHMA

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ABSTRACT

Background Influenza causes substantial morbidity in adults and children with asthma, and vaccination can prevent influenza and its complications. However, there is concern that vaccination may cause exacerbations of asthma.

Methods To investigate the safety of the inactivated trivalent split-virus influenza vaccine in adults and children with asthma, we conducted a multicenter, randomized, double-blind, placebo-controlled, crossover trial in 2032 patients with asthma (age range, 3 to 64 years). The order of injection of vaccine and placebo was assigned randomly, with a mean of 22 days between the injections. Each day during the two weeks after each injection, the patients recorded peak expiratory flow rates, symptoms thought to be related to the injection, use of asthma medications, unscheduled health care visits for asthma, and asthma-related absences from school or work. The primary outcome measure was an exacerbation of asthma in the two weeks after the injections.

Results The frequency of exacerbations of asthma was similar in the two weeks after the influenza vaccination and after placebo injection (28.8 percent and 27.7 percent, respectively; absolute difference, 1.1 percent; 95 percent confidence interval, -1.4 percent to 3.6 percent). The exacerbation rates were similar in subgroups defined according to age, severity of asthma, and other factors. Among symptoms thought to be associated with the injection, only body aches were more frequent after the vaccine injection than after placebo injection (25.1 percent vs. 20.8 percent, $P < 0.001$).

Conclusions The inactivated influenza vaccine is safe to administer to adults and children with asthma, including those with severe asthma. Given the morbidity of influenza, all those with asthma should receive the vaccine annually. (N Engl J Med 2001;345:1529-36.)

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OUTBREAKS of influenza are associated with substantial adverse effects, including time lost from work or school, pneumonia, and hospitalization, especially among people who have chronic diseases such as asthma.¹⁻⁴ Infection with influenzavirus makes people with asthma more susceptible to bronchoconstriction, exacerbations of asthma, and even prolonged declines in lung function.⁵ Influenza is a common reason for hospitalization in children with asthma.^{3,6-8} Immunization is 70 to 90 percent effective in preventing influenza when the strains included in the vaccine match the

strains in circulation.⁹⁻¹³ Some reports suggest that vaccination reduces morbidity in patients with asthma, and immunization is widely recommended for all such patients.¹³⁻¹⁷ However, reviews of the literature have found that there is inconclusive evidence of the safety of the influenza vaccine in patients with asthma.¹⁸⁻²¹

Currently, fewer than 10 percent of patients with asthma receive the influenza vaccine, as compared with 68 percent of the portion of the general population that is older than 65 years — another group for which annual immunization is recommended.^{7,17,22} Among the reasons given for the low rates of vaccination are an aversion to injections and fears that the vaccine is not safe.^{19,22-27} Because of these issues, the American Lung Association Asthma Clinical Research Centers conducted a randomized, controlled trial to evaluate the safety of the influenza vaccine in patients with asthma.

METHODS**Participants**

Between September 15 and November 30, 2000, a total of 2032 patients were recruited from 19 centers. Eligible patients ranged in age from 3 to 64 years, had physician-diagnosed asthma, had been taking prescribed treatment for asthma within the preceding 12 months, and had stable asthma. Stable asthma was defined by the absence of visits to the emergency department, hospitalization, increased doses of systemic corticosteroids, or urgent visits to a health care provider for asthma in the two weeks before enrollment. All patients or their parents gave written informed consent. Patients were excluded if they were allergic to egg products or thimerosal, were unable to use the peak flowmeter properly (if they were older than five years of age), did not have a telephone, had a history of the Guillain-Barré syndrome, had had an influenza vaccination within the preceding six months, had had a febrile illness (temperature, $\geq 38.0^{\circ}\text{C}$) within 24 hours before enrollment, or had any other condition that in the opinion of the investigator might put a patient at risk or interfere with his or her participation in the study.

Study Design and Treatment

The study design was a randomized, double-blind, crossover trial in which each eligible patient was assigned to receive an injection of influenza vaccine and an injection of placebo in random order (vaccine followed by placebo or placebo followed by vaccine), with four weeks between injections. Two syringes containing either heat-killed trivalent split-virus influenza type A and B vaccine (Fluzone, Aventis-Pasteur) or an identical-appearing placebo

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saline solution were packaged into consecutively numbered kits and labeled as either the first or second injection by a central pharmacy according to an assignment list prepared by the data-coordinating center. Randomization of the injection order was carried out with use of a permuted-block design with a block size of six; assignments were not stratified according to the enrolling center. The contents of the syringes were not divulged until the trial was completed.

Before randomization, all patients completed a questionnaire that included questions about demographic characteristics; smoking history; age at onset of asthma; hospitalizations; unscheduled health care visits for asthma or courses of oral corticosteroids during the preceding 12 months; current asthma medications; average daily use of albuterol for the relief of symptoms during the 2 weeks before randomization; current symptoms, as assessed by the Asthma Symptom Utility Index²⁸; and history of influenza vaccination, including any adverse reactions. For 14 days after each injection, patients completed a diary recording peak expiratory flow rates in the morning with use of a peak flowmeter (Mini-Wright flowmeter, Ferraris Medical) at least six hours after any inhalation of bronchodilator rescue medication, asthma symptom score,²⁹ use of asthma medications, use of corticosteroids, unscheduled contact with a health care provider (telephone calls or visits) for asthma, absences from school or work due to asthma, and symptoms thought to be associated with the vaccine or placebo injection (reactogenicity).

The Asthma Symptom Utility Index²⁸ is derived from a 10-item questionnaire completed by the patient. Scores range from 0 to 1, with higher scores indicating fewer symptoms. The asthma symptom score is a four-level classification based on the frequency of episodes of asthma, limitations of activities, and interruptions in sleep. Scores range from 0 to 3, with higher scores indicating more symptoms.

The study was approved by the local institutional review boards at each clinical center and at the data-coordinating center. The study was also approved by an independent data and safety monitoring committee, which met once before the trial began, to approve the study protocol, and once during the trial, to review safety data.

Outcome Measures

The primary outcome measure was an exacerbation of asthma within 14 days after an injection, defined as the occurrence of one or more of the following: a decrease of at least 30 percent in the peak expiratory flow rate from the second-highest morning peak expiratory flow rate measured during the study (the "personal best" flow rate), an increase in the daily use of bronchodilator rescue medication (e.g., albuterol) above the average use reported in the two weeks before randomization (four or more puffs of a bronchodilator from a metered-dose inhaler or two or more uses of nebulized albuterol for the relief of symptoms), an increase in the use of systemic corticosteroids for asthma or the addition of systemic corticosteroids to the treatment regimen, or the unscheduled use of health care for the treatment of asthma, including a visit to the emergency department, hospitalization, or a visit or a telephone call to a health care provider.

Other outcome measures included a decrease of at least 20 percent in the peak expiratory flow rate from the personal-best rate during the 14 days after each injection, the average morning peak expiratory flow rate, symptoms thought to be associated with the vaccine or placebo injection (rhinitis, sore throat, cough, headache, body aches, fever, chills, and fatigue), the number of days without symptoms of asthma, the amount of time lost from work or school because of illness, and an increase in the dose of a current medication used for the long-term control of asthma or the addition of such a medication to the treatment regimen.

Statistical Analysis

The study was designed to include 2000 patients in order to provide the statistical power to reject at a level of 95 percent confidence the hypothesis that the rate of exacerbations of asthma in the three days after the injection of influenza vaccine was more than 6 percentage points higher than the rate after the placebo

injection, with a one-sided type I error rate of 5 percent. A two-group test of the equivalence of binomial proportions was used,³⁰ and the values were based on published rates of exacerbations of asthma in the three days after vaccine injection and placebo injection of 4.7 percent and 1.2 percent, respectively.² The sample size was chosen to allow for the possibility of a carryover effect of vaccinations; if a carryover effect was detected, only the data obtained after the first injection would be used. In the absence of a carryover effect, the power of the study exceeded 99 percent. We reduced the possibility of a carryover effect of vaccination during the two-week follow-up measures by using a four-week period between the two injections.

Each outcome measure was analyzed according to the intention-to-treat principle, and the analyses included all patients who received both injections and for whom complete data on outcome measures were available for both follow-up periods. The range of equivalence of the rates of exacerbations of asthma after vaccine injection and after placebo injection was determined from the difference in the rates and in the associated 95 percent exact confidence intervals for the difference in paired binomial proportions.^{31,32} If the upper bound of the 95 percent confidence interval was less than the prespecified limit of 6 percentage points, the rates during the two periods were considered equivalent. The differences in the rates and 95 percent confidence intervals during the follow-up periods were examined in subgroups of patients defined according to demographic characteristics, the presence or absence of obesity, smoking status, number of symptoms of asthma, medication use, and lung function to determine whether the finding of equivalence was consistent among the subgroups. Conditional logistic-regression analysis was used to test for interactions, in order to determine whether the difference in rates between vaccine injection and placebo injection varied according to subgroups.³³ Other asthma-related and vaccine-related measures during the 14-day period after each injection were analyzed with use of McNemar's test for paired binary categorical variables (with the chi-square statistic) and the Wilcoxon signed-rank test for continuous variables.³¹ Possible carryover effects of the order of the injections were also examined with the use of conditional logistic-regression models. All P values are two-sided. All data analyses were performed with SAS software, version 8.0.³⁴

RESULTS

Of the 2032 patients who were enrolled and assigned to receive vaccine and placebo injections, 2009 (98.9 percent) received both injections, 1952 (96.1 percent) received both injections and completed both 14-day post-injection diaries, and 1865 (91.8 percent) had peak expiratory flow rates measured during both periods (the daily measurement of peak expiratory flow rate was not required in patients who were three to five years old). The mean time between injections was 22 days. A broad cross section of adults and children with asthma was enrolled (Table 1). There were more boys than girls and more women than men enrolled, as would be expected on the basis of the age and sex distribution of asthma in the United States.^{29,36} The scores on the Asthma Symptom Utility Index and the frequency of symptoms of asthma suggested that, at base line, most patients had mild-to-moderate persistent asthma; however, there was substantial variability.

The overall rates of exacerbations of asthma during the 14 days after vaccine injection and the 14 days after placebo injection were equivalent (28.8 percent and 27.7 percent, respectively; absolute difference,

TABLE 1. BASE-LINE CHARACTERISTICS OF THE PATIENTS.*

CHARACTERISTIC	ADULTS (N=1240)	CHILDREN (N=712)	TOTAL (N=1952)
Age at randomization — yr	42.4±12.2	9.4±3.8	30.4±18.8
Sex — no. (%)			
Female	924 (74.5)	283 (39.7)	1207 (61.8)
Male	313 (25.2)	427 (60.0)	740 (37.9)
Data missing	3 (0.2)	2 (0.3)	5 (0.3)
Race or ethnic group — no. (%)			
White	835 (67.3)	431 (60.5)	1266 (64.9)
Black	275 (22.2)	204 (28.7)	479 (24.5)
Hispanic	80 (6.5)	40 (5.6)	120 (6.1)
Other	44 (3.5)	31 (4.4)	75 (3.8)
Data missing	6 (0.5)	6 (0.8)	12 (0.6)
Smoking history — no. (%)			
Current smoker	93 (7.5)	1 (0.1)	94 (4.8)
Former smoker	329 (26.5)	4 (0.6)	333 (17.1)
Never smoked	813 (65.6)	706 (99.2)	1519 (77.8)
Data missing	5 (0.4)	1 (0.1)	6 (0.3)
Exposure to secondhand smoke — no. (%)			
Exposed	509 (41.0)	240 (33.7)	749 (38.4)
Data missing	19 (1.5)	16 (2.12)	35 (1.8)
Asthma characteristics			
Age at onset of asthma — yr	21.5±16.9	3.3±3.0	14.9±16.1
≥1 Unscheduled health care visits for asthma in previous 12 mo — no. (%)	511 (41.2)	419 (58.8)	930 (47.6)
≥1 Course of oral corticosteroids in previous 12 mo — no. (%)	500 (40.3)	387 (54.4)	887 (45.4)
Use of inhaled short-acting β-agonist ≥2 times/wk — no. (%)	558 (45.0)	269 (37.8)	827 (42.4)
Asthma Symptom Utility Index†	0.82±0.18	0.87±0.15	0.84±0.17
Peak expiratory flow rate			
Liters/min	399±117	281±102	359±125
Percent of predicted value‡	89.7±23.4	103.0±22.0	93.9±23.8
Daily asthma treatment — no. (%)			
Inhaled long-acting β-agonist	449 (36.2)	139 (19.5)	588 (30.1)
Leukotriene modifier	328 (26.5)	273 (38.3)	601 (30.8)
Inhaled corticosteroid	684 (55.2)	369 (51.8)	1053 (53.9)
Oral corticosteroid	30 (2.4)	8 (1.1)	38 (1.9)

*Plus-minus values are means ±SD. Of the 2032 patients who were enrolled, 1952 (96.1 percent) received both injections and completed both 14-day post-injection diaries and 1865 (91.8 percent) had peak expiratory flow rates measured in both periods. The percentages of missing data were less than 5 percent except in the case of peak expiratory flow rate and percent of predicted peak flow rate, for which data were missing for 12.2 percent and 21.5 percent of children, respectively. Seventy-eight of the 88 children with missing data on peak flow rate and 129 of the 154 children with missing data on predicted peak flow rate were three to five years of age.

†The Asthma Symptom Utility Index²⁸ is derived from a 10-item questionnaire completed by the patient. Scores range from 0 to 1, with higher scores indicating fewer symptoms.

‡Values are based on the predicted peak expiratory flow rate described by Hankinson et al.³⁵

1.1 percent; 95 percent confidence interval, -1.4 percent to 3.6 percent) (Table 2). The most common types of exacerbation were an increase in the use of rescue medications and a decrease of 30 percent or more in the peak expiratory flow rate from the personal-best value. The daily mean peak expiratory flow rates were similar after vaccine injection and placebo injection (Fig. 1A), as were the percentages of patients who were using bronchodilator rescue medication to control their asthma (Fig. 1B). When the frequency of exacerbations of asthma within three days after injection was assessed, the patterns were

similar after vaccine and placebo injections (Table 2 and Fig. 1).

The frequency of exacerbations varied considerably among the subgroups that were categorized according to demographic characteristics, smoking status, asthma symptoms before enrollment, and lung function; however, none of the differences in values after vaccine and placebo injections were significant. All 95 percent confidence intervals were consistent with the conclusion that there was no difference in the rates after vaccine injection and placebo injection (Table 3). In a few cases the upper bound of the 95

TABLE 2. FREQUENCY OF EXACERBATIONS OF ASTHMA WITHIN 3 AND 14 DAYS AFTER VACCINE AND PLACEBO INJECTIONS.

EVENT	NO. OF PATIENTS IN ANALYSIS*	VACCINE INJECTION	PLACEBO INJECTION	ABSOLUTE DIFFERENCE (95% CI)†	
				percent	
New or increased use of oral corticosteroids					
Within 3 days after injection	1952	2.0	2.0	0.1	(-0.8 to 0.9)
Within 14 days after injection	1952	5.3	5.1	0.2	(-1.2 to 1.6)
Unscheduled use of health care for asthma symptoms					
Within 3 days after injection	1952	1.3	1.8	-0.5	(-1.3 to 0.3)
Within 14 days after injection	1952	5.5	5.1	0.4	(-1.0 to 1.8)
Increased use of rescue medication					
Within 3 days after injection	1858	6.1	6.5	-0.4	(-1.9 to 1.1)
Within 14 days after injection	1858	15.2	14.5	0.7	(-1.5 to 2.8)
≥30% decrease in peak expiratory flow rate from personal best‡					
Within 3 days after injection	1861	7.5	8.2	-0.8	(-2.3 to 0.8)
Within 14 days after injection	1865	16.7	16.6	0.1	(-1.8 to 2.0)
Any of the above§					
Within 3 days after injection	1952	12.7	13.8	-1.1	(-3.0 to 0.9)
Within 14 days after injection	1952	28.8	27.7	1.1	(-1.4 to 3.6)

*The number of patients is the number who received, in random order, both injections (vaccine and matching placebo) and who had complete data regarding the event during both post-injection periods. Data on increased use of rescue medications were missing for 94 patients because of missing data on their use just before the injections. Data on peak flow rates in the first three days after each injection were missing for 91 patients, 78 of whom were children three to five years of age. Data on peak flow rates for the 14 days after each injection were missing for 87 patients, 77 of whom were children three to six years of age.

†The 95 percent confidence intervals (CIs) are the exact confidence intervals for the difference in paired binomial proportions.³²

‡Personal best was defined as the second highest peak flow measurement recorded in the patient's asthma diary during the 14 days after the vaccine or placebo injection.

§The occurrence of any of the listed events within 14 days after injection was the primary outcome measure. The individual components of an exacerbation of asthma do not add up to the overall percentage of events because some patients had more than one event.

percent confidence interval extended beyond the limit of equivalence of 6 percentage points owing to the small size of some subgroups.

There was no significant difference between vaccine injection and placebo injection in other asthma-related outcomes, including the number of symptom-free days, daily symptom score, the percentage of patients with a decrease in the peak expiratory flow rate of at least 20 percent from personal-best values, the rate of new or increased use of medication for the long-term control of asthma, or the percentage of patients who missed one or more days of work or school (Table 4). Patients reported body aches more frequently after vaccine injection than after placebo injection (25.1 percent vs. 20.8 percent, $P < 0.001$), but the frequency of other symptoms thought to be associated with treatment was similar (Table 4).

DISCUSSION

The main finding of this controlled study is that influenza vaccination does not worsen asthma. This

finding should be reassuring to patients and to their physicians, and it provides evidence that the current guidelines for the immunization of patients with asthma are safe.²³ We could not identify any subgroup based on the severity of asthma or demographic characteristics in which influenza vaccine increased the rate of exacerbations of asthma over the rate associated with the placebo injection. As expected, there were slightly more symptoms, such as headache, body aches, and chills, in the first 72 hours after the administration of the vaccine than after the administration of placebo.

Our findings fail to confirm the results of an earlier double-blind, placebo-controlled, crossover trial of adults with asthma.²¹ The previous study was smaller (262 patients), had a shorter period of observation (72 hours), used two types of influenza vaccine (a trivalent split-virus preparation and a surface-antigen preparation), and reported only eight exacerbations of asthma. The length of observation in our study was 14 days, thereby enabling us to detect potential-

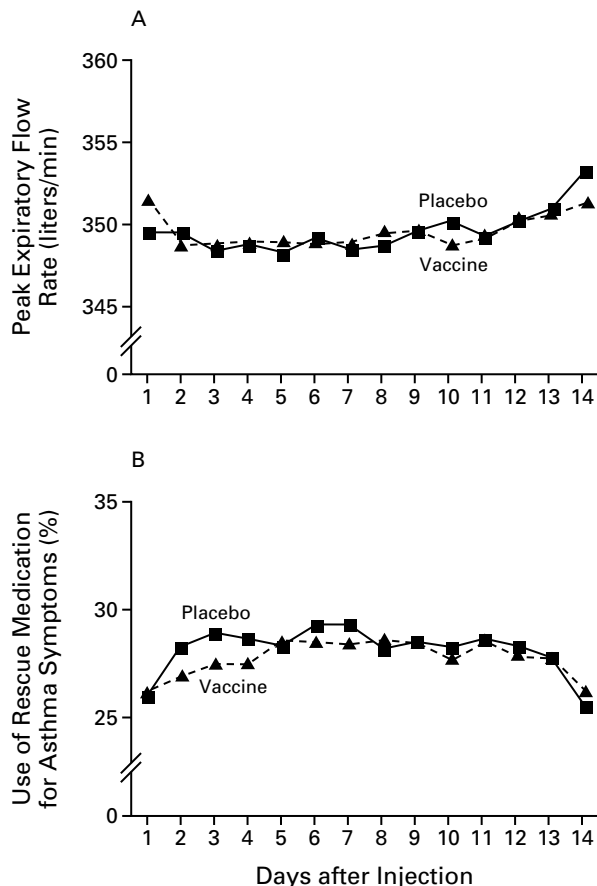


Figure 1. Daily Mean Peak Expiratory Flow Rates (Panel A) and Percentage of Patients Who Used Rescue Medication to Control Asthma (Panel B) during the Two Weeks after Vaccine and Placebo Injections.

The peak flow rate was measured each morning at least six hours after any inhalation of rescue medication. Of the 2032 randomized patients, only those who received, in random order, both injections (vaccine and matching placebo) and who had complete data on the mean daily peak expiratory flow rate (1756 patients) and the use of rescue medication (1858 patients) in the 14 days after each injection were included. There was no significant difference after vaccine injection and placebo injection in the mean daily peak expiratory flow rates ($P=0.92$) or in the percentage of patients who were using rescue medication ($P=0.20$ by conditional logistic regression for the vaccine–placebo paired response).³³

ly delayed reactions to the vaccine. We also found no difference in the frequency of asthma symptoms in the first three days after vaccine injection and placebo injection.

Our finding of rates of exacerbations of asthma of 13.2 percent and 28.2 percent within 3 and 14 days after injection, respectively, was higher than expected on the basis of the findings of Nicholson et al.²¹ The

higher rates in our study can be explained by the broader criteria we used. The frequency of exacerbations in our study is consistent with the results of a survey of the general population of patients with asthma in the United States.^{16,38} In that survey, 41 percent of respondents reported symptoms of asthma frequent enough for them to be classified as having moderate or severe persistent asthma.^{16,38} This high rate of spontaneous exacerbations, as well as the high rate of symptoms in our study even after placebo injection, may contribute to the oft-held belief that immunization induces symptoms.

A recent retrospective cohort study from the Centers for Disease Control and Prevention evaluated the frequency of exacerbations of asthma in children after influenza vaccination at four large health maintenance organizations.³⁹ The results conflicted, depending on the method used to adjust for the severity of asthma. In a traditional cohort–control analysis, controlling for the use of β -agonists and cromolyn, previous hospitalizations, and visits to the emergency department for asthma, the investigators found a substantially increased risk of an exacerbation of asthma after vaccination across three influenza seasons (adjusted relative risk, 1.4 to 2.2). However, when they compared data before and after vaccination in subjects with at least one exacerbation of asthma, they found a significant reduction in the risk of exacerbations (adjusted relative risk, 0.59 to 0.78). These conflicting results reflect the difficulty in accurately controlling for asthma severity with the use of retrospective measures, given the seasonal variation in the severity of asthma and the selection bias attributable to the selection of vaccine recipients in a nonrandomized study. We found that patients with more symptoms were more likely to have an exacerbation than those with fewer symptoms, but there were no differences in the frequency of exacerbations of asthma after vaccine injection and after placebo injection among patients with more severe asthma. Therefore, we conclude that inactivated influenza vaccine is safe in patients with more severe asthma.

Our study demonstrates the effectiveness of large, simple clinical trials that address an important public health issue. A recent systematic review of the literature evaluating the safety of influenza vaccination in patients with asthma was inconclusive.¹⁸ Unlike smaller studies, ours found no significant increase in the risk of an exacerbation of asthma after influenza vaccination in a diverse population of adults and children with asthma. One potential limitation of our study is that the majority of our patients were recruited from the clinic populations of pulmonary and allergy specialists in academic referral centers, so our study sample may represent patients with more severe asthma than in the general population. However, many of our patients had mild-to-moderate asthma, and we found no trends related to the severity of asthma; hence,

TABLE 3. VARIATIONS IN THE FREQUENCY OF EXACERBATIONS OF ASTHMA DURING THE 14 DAYS AFTER VACCINE AND PLACEBO INJECTIONS IN VARIOUS SUBGROUPS.

SUBGROUP	NO. OF PATIENTS IN ANALYSIS*	VACCINE INJECTION	PLACEBO INJECTION	ABSOLUTE DIFFERENCE (95% CI)†
				percent
Age at randomization				
≤17 yr	712	33.6	33.0	0.6 (−3.8 to 4.9)
≥18 yr	1240	26.1	24.6	1.5 (−1.6 to 4.4)
Sex				
Female	1207	28.7	27.6	1.1 (−2.1 to 4.2)
Male	740	28.9	27.8	1.1 (−3.0 to 5.1)
Race or ethnic group				
Black	479	39.2	37.2	2.1 (−3.5 to 7.6)
Hispanic	120	25.0	29.1	−4.2 (−13.8 to 6.2)
White	1266	25.3	24.0	1.3 (−1.7 to 4.2)
Other	75	28.0	26.7	1.3 (−13.0 to 15.4)
Obesity classification‡				
Obese	638	30.6	31.0	−0.5 (−5.0 to 4.1)
Nonobese	1276	27.9	25.9	2.0 (−1.0 to 5.0)
Smoking status				
Smoker	94	37.2	39.4	−2.1 (−16.4 to 12.5)
Nonsmoker	1852	28.4	27.2	1.2 (−1.3 to 3.7)
Daily use of inhaled corticosteroids				
Yes	1053	30.3	29.5	0.8 (−2.7 to 4.2)
No	891	27.0	25.6	1.5 (−2.2 to 5.0)
Asthma Symptom Utility Index§				
≤0.75	469	38.0	37.5	0.4 (−5.1 to 6.0)
>0.75	1455	25.8	24.4	1.4 (−1.4 to 4.2)
Peak expiratory flow rate¶				
≤80% of predicted value	423	35.0	33.6	1.4 (−4.3 to 7.1)
>80% of predicted value	1340	26.1	25.1	1.0 (−1.9 to 3.9)
FEV ₁ ¶				
≤80% of predicted value	332	30.7	31.6	−0.9 (−7.2 to 5.4)
>80% of predicted value	637	25.4	22.4	3.0 (−1.1 to 7.0)
FVC¶				
≤80% of predicted value	228	33.3	31.1	2.2 (−5.9 to 10.1)
>80% of predicted value	738	25.5	23.8	1.6 (−2.1 to 5.3)

*The number of patients is the number who received, in random order, both injections (vaccine and matching placebo) and who had complete data regarding the event during both post-injection periods.

†The 95 percent confidence intervals (CIs) are the exact confidence intervals for the difference in paired binomial proportions.³¹

‡Obesity was defined as a body-mass index (the weight in kilograms divided by the square of the height in meters) of more than 30 in the case of adults and a value that was above the 95th percentile for age in the case of children.³⁷

§The Asthma Symptom Utility Index²⁸ is derived from a 10-item questionnaire completed by the patient. Scores range from 0 to 1, with higher scores indicating fewer symptoms.

¶Values for forced expiratory volume in one second (FEV₁) and forced vital capacity (FVC) are based on the predicted peak expiratory flow rate, FEV₁, and FVC described by Hankinson et al.³⁵

our findings can be extrapolated to patients with less severe disease. Another potential limitation of our study is that it was conducted during only one influenza season, with just one preparation of vaccine. It is possible that other formulations of influenza vaccine might have different effects. We emphasize that our findings cannot be extrapolated to cold-attenuated live influenza vaccines that may become available in the future.^{40,41}

In summary, we found that in a large, diverse group of adults and children with asthma, influenza vaccination is safe. Since fewer than 10 percent of patients with asthma are vaccinated against influenza, we encourage the promotion of programs that emphasize the importance of this vaccine in patients with asthma.^{19,27} Strategies such as patient-reminder systems, educational interventions, and reminders to health care providers can help increase compliance

TABLE 4. FREQUENCY OF SECONDARY OUTCOMES DURING THE 14 DAYS AFTER VACCINE AND PLACEBO INJECTIONS.*

OUTCOME	NO. OF PATIENTS IN ANALYSIS†	VACCINE INJECTION	PLACEBO INJECTION	P VALUE‡
Asthma-related outcomes				
No. of symptom-free days	1851	10.4±4.7	10.4±4.7	0.91
Daily symptom score§	1851	0.3±0.4	0.3±0.5	0.98
Daily peak flow rate (liters/min)	1865	347±119	347±118	0.31
≥20% decrease in peak flow rate from personal best (%)¶	1865	37.6	36.5	0.31
New or increased use of asthma medication (%)	1952	7.0	5.7	0.075
≥1 Day's absence from work or school (%)	1952	6.7	6.7	1.00
Injection-associated symptoms (%)				
Rhinitis	1952	44.8	45.0	0.87
Sore throat	1952	28.3	28.7	0.77
Cough	1952	46.1	45.7	0.74
Headache	1952	39.6	37.8	0.14
Myalgia	1952	25.1	20.8	<0.001
Chills	1952	12.2	11.1	0.23
Fever	1952	5.1	5.0	0.87
Fatigue	1952	27.9	28.6	0.51

*Plus-minus values are means ±SD.

†The number of patients is the number who received, in random order, both injections (vaccine and matching placebo) and who had complete data regarding the event during both post-injection periods. Data on peak flow rates were missing for 87 patients, 77 of whom were children three to five years of age.

‡Two-sided P values comparing vaccine with placebo are based on the Wilcoxon signed-rank test for quantitative measures and on McNemar's test for paired proportions (with the chi-square statistic) for categorical measures.³¹

§The asthma symptom score is a four-level classification based on the frequency of asthma episodes, limitations of activities, and interruptions in sleep. The score ranges from 0 to 3, with higher scores indicating more symptoms.

¶Personal best was defined as the second-highest peak flow measurement recorded in the patient's asthma diary during the 14 days after the vaccine injection or placebo injection.

||New or increased use was defined by an increase in the dose of a medication used for the long-term control of asthma or the addition of such a drug to the treatment regimen.

with current immunization recommendations.⁷ Given the substantial effects of influenza in patients with asthma, the efficacy of the inactivated vaccine, and the safety of the vaccine in these patients, health care providers should urge patients with asthma to be immunized and thus reduce the morbidity and mortality associated with influenza in this population.

Supported by grants from the American Lung Associations of Alabama, Central Florida, Colorado, Delaware, Eastern Missouri, Finger Lakes (New York), Georgia, Gulfcoast Florida, Hudson Valley (New York), Illinois, Indiana, Louisiana, Maine, Metropolitan Chicago, Michigan, Mid-Ohio, Minnesota, Nashua-Suffolk (New York), New Hampshire, New York City,

North Carolina, Northeast Florida, Ohio, Oklahoma, Pennsylvania, South Florida, Southeast Florida, Texas, Vermont, Western Missouri, Wisconsin, Greater Norfolk County (Massachusetts), Hawaii, Middlesex County (Massachusetts), New York State, Northern Rockies, Queens (New York), Western Massachusetts, and Virginia; Baylor College of Medicine; the Thalheim Family; Duke University; the Ernest N. Morial Asthma, Allergy, and Respiratory Disease Center; the Merck Foundation; and Glaxo-SmithKline.

Drs. Fish and Wise have received honorariums or consulting fees from Aventis, the parent company of Aventis-Pasteur, the manufacturers of Fluzone, the influenza vaccine used in the study. Aventis-Pasteur did not provide any support for the study, and the influenza vaccine used in the study was purchased from Aventis-Pasteur by Asthma Clinical Research Centers.

APPENDIX

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