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Safety of Influenza Vaccine Administration in Egg-Allergic Patients

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Safety of Influenza Vaccine Administration in Egg-Allergic Patients



WHAT'S KNOWN ON THIS SUBJECT: Current guidelines recommend that egg-allergic patients receive an influenza vaccine skin test before they receive an influenza vaccine.



WHAT THIS STUDY ADDS: The results of our study suggest that an influenza vaccine skin test may be safely removed from standard protocol, and egg-allergic patients without anaphylaxis to egg may be administered an influenza vaccine in a 2-dose, graded fashion without a vaccine skin test.

abstract

FREE

OBJECTIVE: Current guidelines recommend that egg-allergic patients receive an influenza vaccine skin test before the influenza vaccine. This study evaluated the safety of bypassing the skin test and administering graded doses of influenza vaccine to egg-allergic children.

METHODS: We conducted a retrospective chart-review study of egg-allergic patients aged 6 months to 18 years who received the vaccine skin test and/or a 2-dose graded influenza vaccine. Between influenza seasons 2002–2003 and 2006–2007, egg-allergic patients underwent a vaccine skin test before influenza vaccine administration. Starting in 2006–2007, the skin test was removed from our protocol and egg-allergic patients received the influenza vaccine in 2 graded doses. All vaccinated patients were observed for adverse reactions.

RESULTS: Two hundred sixty-one egg-allergic patients were evaluated for influenza vaccine administration, and 171 went on to receive the vaccine. Of the 56 patients who received the skin test before the influenza vaccine, 95% (exact 95% confidence interval [CI]: 85.1–98.9) tolerated the vaccine without a serious adverse reaction. This rate was unchanged after the vaccine skin test was removed from the protocol. Of the 115 patients who received the vaccine without a preceding skin test, 97% (exact 95% CI: 91.3–99.0) tolerated the vaccine without serious adverse reaction. The tolerance rate ratio was 1.01 (95% CI: 0.97–1.06).

CONCLUSION: The results of our study suggest that egg-allergic patients without anaphylaxis to egg may safely receive the influenza vaccine in a 2-dose, graded fashion without a vaccine skin test. *Pediatrics* 2010;125:e1024–e1030

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KEY WORDS

influenza vaccine, egg allergy, safety

ABBREVIATIONS

CDC—Centers for Disease Control and Prevention

CI—confidence interval

RAST—radioallergosorbent test

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Influenza is a major public health concern. Rates of hospitalization, outpatient visits, and prescribed antibiotics for children increase over the baseline rate during the influenza season.^{1,2} These rates are substantially increased in high-risk populations, such as those with asthma and concomitant food allergy.^{3–6} Annual influenza vaccination is recommended to protect children from the morbidity associated with influenza infection.^{7–9} Despite the benefits of decreased flu-like symptoms, outpatient visits, and hospitalizations, influenza vaccination rates are low.^{10,11} In select US cities, less than 20% to 30% of children receive the influenza vaccination.¹² This rate is likely lower for children with egg allergy, given conflicting recommendations regarding influenza vaccine in egg-allergic patients. On the one hand, in the 2009 *Red Book*,^{13,14} the American Academy of Pediatrics stated that children with severe allergic reactions to egg generally should not receive the influenza vaccine; on the other hand, it stated that these children may receive the influenza vaccine through a desensitization protocol after a positive vaccine skin test result. Furthermore, influenza vaccine manufacturers report egg allergy as a contraindication to influenza vaccine administration. In 2008, the Centers for Disease Control and Prevention (CDC) expanded the influenza vaccine recommendation to include all children between 6 months and 18 years of age.⁷ Given the prevalence of asthma^{15,16} and egg allergy¹⁷ in the US population, providers are faced with the challenge of administering egg-containing influenza vaccine to egg-allergic patients for whom the vaccine is indicated.

Various studies have emerged to assess influenza vaccine administration in egg-allergic patients. As early as the 1970s, study results indicated that patients with egg allergy should undergo

skin testing with the influenza vaccine.^{18–20} If the skin-test result were negative, the influenza vaccine could be safely administered. If the skin-test result were positive, the recommendation was not to administer the vaccine. Murphy and Strunk²¹ later suggested that egg-allergic patients with positive skin-test results could be safely administered the influenza vaccine through a protocol of multiple, graded injections. In a detailed guideline published in 2002, Zeiger²² recommended that individuals with histories of adverse reaction to egg and positive egg skin-test results receive the influenza vaccine skin tests (prick and intradermal) before vaccine administration. If the influenza vaccine skin-test results are negative, the vaccine may be administered in a single dose. If the skin-test results are positive, the vaccine may be administered in a 2-dose graded or desensitization protocol.^{22,23} In our study, we evaluated the safety of bypassing the vaccine skin test and administering the influenza vaccine in a graded, 2-dose fashion to egg-allergic children.

PATIENTS AND METHODS

Study Design

We performed a retrospective chart review of influenza vaccine administration to egg-allergic pediatric patients. This study was approved by the Children's Hospital Boston committee on clinical investigation. Data were collected retrospectively through review of both the electronic and hard-copy medical records during the influenza seasons of 2002–2003 through 2008–2009. For each influenza season, we identified patients who received the influenza vaccine skin test, the influenza vaccine in a graded fashion, or both.

Study Population

The study included patients between the ages of 6 months and 18 years with

egg allergy who received the influenza vaccine skin test and/or the graded influenza vaccine at the Children's Hospital Boston Allergy Program. The program is equipped with experienced staff and emergency supplies to manage serious adverse reactions and anaphylaxis should they arise. A history of egg allergy was confirmed in patients who received the graded influenza vaccine and was defined as (1) a positive egg skin-test or radioallergen sorbent test (RAST) result ($n = 167$) and allergic symptoms associated with probable or definite egg consumption or (2) significant RAST (>7 kU/L) or egg skin-test results (egg wheal reaction > 10 mm with appropriate positive and negative controls) but no documented allergic symptoms to egg ($n = 4$).^{24,25}

Patients with histories of recent egg-induced anaphylaxis were not immunized and, therefore, not included in the study. Patients who were eating egg-containing foods were given the full-dose vaccine and also not included in the study.

Vaccine Protocol

Between influenza seasons 2002–2003 and 2006–2007, patients with egg allergy underwent skin-prick testing with full-strength influenza vaccine. Patients with negative skin-test results received the vaccine under a 2-dose protocol (one-tenth of the recommended dose, followed by nine-tenths of the recommended dose); those with positive skin-test results had vaccine administration deferred in most cases. Starting with influenza season 2006–2007, skin testing for the influenza vaccine was removed from our standard protocol, and most egg-allergic patients with clinical indications for influenza vaccination received the influenza vaccine under the 2-dose protocol (one-tenth dose, followed by a nine-tenths dose). Patients

were observed for 30 minutes after the one-tenth dose and 30 minutes after the nine-tenths dose. The egg-protein content of the influenza vaccine was not measured in our program or reported by the vaccine manufacturers.

Outcomes

All patients who received the influenza vaccine were observed for tolerance of the vaccine. Vaccine tolerance was defined as the lack of localized or systemic adverse reactions. Localized adverse reactions included wheal and flare limited to the site of injection. Systemic adverse reactions included urticaria, eczema exacerbation, and wheeze.

Statistical Analysis

The χ^2 and Fisher's exact tests were used to compare the demographics, atopic history, egg reaction, and egg-allergy test results between the vaccine skin-test and non-skin-test groups. To adjust for unbalanced baseline variables between the 2 groups, propensity scores were created through logistic regression. The vaccine-tolerance rates of the 2 groups and exact 95% confidence intervals (CIs) were calculated. The rate ratios of vaccine tolerance were estimated with the propensity scores adjustment. The 95% CIs for rate ratios were calculated to test for equivalence of the vaccine skin-test and non-skin-test groups. The χ^2 and Fisher's exact tests were used to test the factors that may predict an adverse reaction to the influenza vaccine. Odds ratios and 95% CIs of these factors were also calculated. A *P* value of $\leq .05$ was considered statistically significant. Analysis was conducted in SAS 9.2 (SAS Institute, Inc, Cary, NC).

RESULTS

Between influenza seasons 2002–2003 and 2008–2009, 261 patients with egg allergy were evaluated for influ-

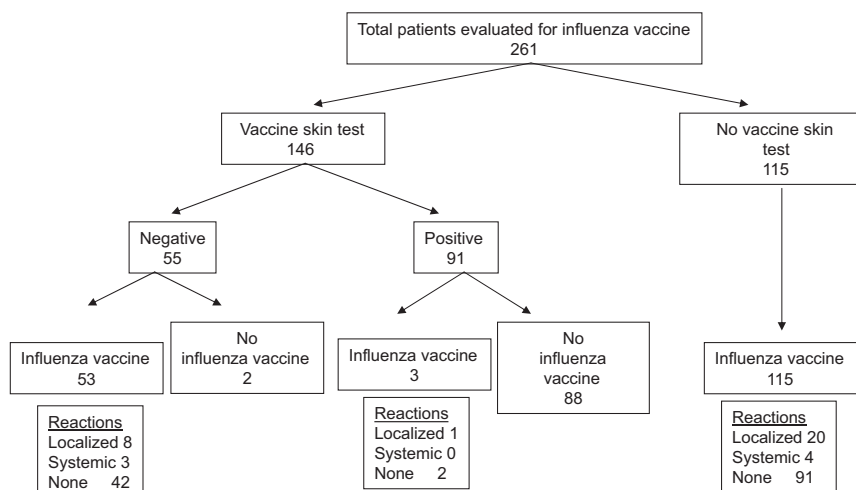


FIGURE 1
Flow diagram of study participants.

enza vaccine administration. Between influenza seasons 2002–2003 and 2006–2007, 146 patients received the influenza vaccine skin test. Ninety-one patients tested positive and 55 tested negative for a skin reaction. Subsequently, 56 patients who primarily tested negative for a skin reaction went on to receive the vaccine, whereas 90 patients who primarily tested positive for a skin reaction did not receive the vaccine. Between 2006–2007 and 2008–2009, the influenza vaccine skin test was removed from the standard protocol and 115 egg-allergic patients received the 2-dose graded influenza vaccine without the vaccine skin test (Fig 1).

Data from the 2 groups of vaccinated patients, those who received and those who did not receive the vaccine skin test, are compared in Table 1. The majority of patients in both groups were male (61% and 70%, respectively) and white (71% and 69%, respectively). In both groups, most patients had histories of multiple food allergies (91% and 84%, respectively) and atopic dermatitis (71% and 64%, respectively). The most common allergic reaction to egg was dermatologic (68% and 74%, respectively), which included hives, rash, swelling, or flare of eczema, fol-

lowed by gastrointestinal reactions (34% and 28%, respectively), which included abdominal pain, emesis, or diarrhea, and then by respiratory reactions (13% and 5%, respectively), which included wheezing, coughing, shortness of breath, or rhinitis. In these 2 groups, the mean egg skin-test wheal sizes were 11.2 and 12 mm, and the mean egg RAST results were 10.16 and 11.95 kU/L, respectively.

Significant differences between the 2 groups included mean age (6.2 years in the skin-test group vs 3.9 years in the non-skin-test group; *P* < .0001), history of asthma (77% in the skin-test group vs 50% in the non-skin-test group; *P* = .0007), and history of allergic rhinitis (73% in the skin-test group vs 33% in the non-skin-test group; *P* < .0001). These differences can be explained by the CDC change in influenza vaccine recommendation. During the period in which the influenza vaccine skin test was primarily performed (between 2002 and 2007), the influenza vaccine recommendation was limited to patients at high risk, such as those with asthma. This is likely reflected in the increased history of asthma and older average age in the cohort of patients who received the vaccine skin test. After the vaccine skin test was re-

TABLE 1 Characteristics of Skin-Test ($n = 56$) and Non–Skin-Test ($n = 115$) Groups

Characteristic	Skin-Test Group	Non–Skin-Test Group	<i>P</i>
Gender: male, <i>n</i> (%)	34 (60.7)	81 (70.4)	.2
Race, <i>n</i> (%)			.7
White	40 (71.4)	79 (68.7)	
Asian	1 (1.8)	8 (7)	
Black	6 (10.7)	7 (6.1)	
Hispanic	1 (1.8)	4 (3.5)	
Other	6 (10.7)	7 (6.1)	
Declined	2	10	
Atopic history, <i>n</i> (%)			
Asthma	43 (76.8)	57 (49.6)	.0007
Allergic rhinitis	41 (73.2)	38 (33)	<.0001
Atopic dermatitis	40 (71.4)	74 (64.3)	.4
Multiple food allergies	51 (91.1)	97 (84.4)	.2
Reaction to egg, <i>n</i> (%)			
Dermatologic	38 (67.9)	85 (73.9)	.4
Gastrointestinal	19 (33.9)	32 (27.8)	.4
Respiratory	7 (12.5)	6 (5.2)	.1 ^a
Other	3 (5.4)	5 (4.3)	.7 ^a
Age, average (95% CI), y	6.2 (5.1–7.2)	3.9 (3.3–4.5)	<.0001
Egg skin test, average wheal size (95% CI), mm	11.19 (7.67–14.71)	12 (10.27–13.73)	.7
Egg RAST, average level (95% CI), kU/L	10.16 (4.07–16.26)	11.95 (7.04–16.86)	.7
IgE, average level (95% CI), U/mL	609.6 (371.2–848.1)	628.1 (307.8–948.4)	.9

IgE indicates immunoglobulin E.

^a Fisher's exact test.

moved from our standard protocol in 2006, the CDC recommendation for influenza vaccination was incidentally

expanded to include all children between 6 months and 18 years of age. Therefore, the group of patients who

did not receive the vaccine skin test was likely to include those without history of asthma or allergic rhinitis and of younger age. Although these factors may be confounding variables, age, asthma, and allergic rhinitis were adjusted for through propensity scores in our multivariate analysis. Furthermore, univariate analysis demonstrated that these factors were not significantly associated with adverse reaction to the influenza vaccine (Table 2). These factors, therefore, were unlikely to be confounding variables in our study.

Of the 171 patients who received the influenza vaccine, 135 (79%) tolerated the vaccine without any adverse reaction, localized or systemic. The rate of vaccine tolerance without localized or systemic reactions was 78.6% (exact 95% CI: 65.6–88.4) in the group that received the vaccine skin test and 79.1% (exact 95% CI: 70.6–86.2) in the group that did not receive the vaccine skin test. The rate of vaccine tolerance

TABLE 2 Risk Factors for Adverse Reaction (Including Localized and Systemic)

Risk Factor	Adverse Reaction (<i>N</i> = 36)	No Reaction (<i>N</i> = 135)	Odds Ratio (95% CI)	Difference of Mean (95% CI)	<i>P</i>
Gender, <i>n</i> (%)					
Male	21 (58.3)	94 (69.6)	0.61 (0.29–1.30)	—	.2
Female	15 (41.7)	41 (30.4)			
Race, <i>n</i> (%)					.7
White	26 (72.2)	93 (68.9)	1.17 (0.52–2.65)	—	
Asian	3 (8.3)	6 (4.4)			
Black	0 (0)	13 (9.6)			
Hispanic	0 (0)	5 (3.7)			
Other	4 (11.1)	9 (6.7)			
Declined	3 (8.3)	9 (6.7)			
Atopic history, <i>n</i> (%)					
Asthma	19 (52.8)	81 (60)	0.75 (0.36–1.56)	—	.4
Allergic rhinitis	14 (38.9)	65 (48.2)	0.69 (0.32–1.45)	—	.3
Atopic dermatitis	24 (66.7)	90 (66.7)	1.00 (0.46–2.18)	—	>.999
Multiple food allergies	31 (86.1)	117 (86.7)	0.95 (0.33–2.77)	—	>.999 ^a
Reaction to egg, <i>n</i> (%)					
Dermatologic	24 (66.7)	99 (73.3)	0.73 (0.33–1.60)	—	.4
Gastrointestinal	13 (36.1)	38 (28.2)	1.44 (0.66–3.14)	—	.4
Respiratory	0 (0)	13 (9.6)	0.52 (0.06–4.39)	—	.07 ^a
Other	1 (2.8)	7 (5.2)	—	—	>.999 ^a
Age, average (95% CI), y	4.4 (2.99–5.79)	4.7 (4.11–5.28)	—	0.31 (–1.02–1.63)	.65
Egg skin test, average wheal (95% CI), mm	13.3 (9.92–16.75)	11.5 (9.73–13.21)	—	–1.86 (–5.65–1.93)	.3
Egg RAST level (95% CI), kU/L	14.30 (6.04–22.57)	10.54 (6.15–14.94)	—	–3.76 (–12.93–5.41)	.4
IgE level (95% CI), U/mL	914 (44.01–1783.8)	530 (371–689.1)	—	–383.9 (–923.3–155.5)	.2

— indicates not applicable. IgE, immunoglobulin E.

^a Fisher's exact test.

TABLE 3 Rate of Vaccine Tolerance in the Skin-Test Group (*n* = 56) Compared With the Non-Skin-Test Group (*n* = 115)

Outcome Variable	Skin-Test Group		Non-Skin-Test Group		Rate Ratio (95% CI) ^a
	<i>n</i>	% (Exact 95% CI)	<i>n</i>	% (Exact 95% CI)	
No localized or systemic reaction	44	78.6 (65.6–88.4)	91	79.1 (70.6–86.2)	1.12 (0.99–1.25)
No systemic reaction	53	94.6 (85.1–98.9)	111	96.5 (91.3–99.0)	1.01 (0.97–1.06)

^a Ratio with propensity score adjustment.

without systemic adverse reaction but including localized reaction was higher at 95% to 97%. In the vaccine skin-test group, 94.6% (exact 95% CI: 85.1–98.9) tolerated the vaccine without serious adverse reaction, whereas 96.5% (exact 95% CI: 91.3–99.0) of patients in the group that did not receive vaccine skin test tolerated the vaccine without serious adverse reaction. The rate ratio of tolerance without serious adverse reaction in the non-skin-test group compared with the skin-test group was 1.01 (95% CI: 0.97–1.06) (Table 3).

Of the 36 patients who had adverse reactions, 29 had localized reactions and 7 had systemic reactions. The localized reactions were wheals and flares limited to the sites of injection. Of the systemic reactions, 3 occurred in the group that received the vaccine skin test (3 of 56 [5.4%]) and 4 occurred in the group that did not receive the vaccine skin test (4 of 115 [3.5%]). Six systemic reactions occurred within 30 minutes after the one-tenth dose and included wheezing, eczema exacerbation, or hives on face/chest. These patients did not receive the subsequent nine-tenths dose. One systemic reaction of hives and facial flushing occurred >30 minutes after the nine-tenths dose. There were no anaphylaxis or multisystemic allergic reactions.

DISCUSSION

In our study, 95% of egg-allergic patients who received the vaccine skin test tolerated the influenza vaccine without any serious adverse reactions.

Despite removal of the vaccine skin test from the standard protocol, this rate of vaccine tolerance remained nearly the same at 97%. The tolerance rate in the skin-test group compared with the non-skin-test group was nearly equivalent, as demonstrated by the rate ratio of 1.01 and narrow 95% CI. The results of our study suggest that the influenza vaccine can be safely administered to egg-allergic patients in a 2-dose, graded fashion without the influenza vaccine skin test.

Our results are consistent with those of a multicenter controlled clinical trial of 207 patients by James et al²⁶ in which the authors concluded that the influenza vaccine could be administered safely to egg-allergic patients in a 2-dose injection protocol with vaccines containing no more than 1.2 µg/mL of egg protein. The influenza vaccine skin test was given to all patients with and without egg allergy before the vaccine. All patients with egg allergy, including 4 with positive skin-test responses, received the influenza vaccine without experiencing any significant adverse reactions, resulting in a 95% CI of 95.7%–100%. Eight egg-allergic subjects and 4 control subjects experienced some mild reactions during the 2-dose administration of the vaccine. In a more recent prospective study of 88 asthmatic patients, half of whom had egg allergy, Esposito et al²⁷ found that the influenza vaccine was tolerated without serious adverse reactions. Three patients developed immediate adverse reactions, including bronchospasm and erythema, and

15 patients developed localized reactions. All patients had negative vaccine skin-test results. Studies conducted more than 25 years ago demonstrated lower influenza vaccine tolerance rates between 71% and 87% by egg-allergic patients.^{18–20} These studies, however, were not designed specifically to examine the safety of skin-test removal from the influenza vaccine protocol for egg-allergic children.

The removal of the influenza vaccine skin test has many benefits for both the patient and clinical staff. First, the vaccine skin test itself requires additional patient and staff time for administration and observation. Second, before the vaccine skin test, patients are required to stop their long-acting antihistamine medications. During the time without their medications, patients are at risk for exacerbation of their atopic diseases. Third, the reliability of the influenza vaccine skin test in identifying patients at risk for adverse reactions has been questioned in previous studies.^{26,28} Wood et al²⁹ found that the interpretation of skin-test results for vaccines is often complicated by irritant reactions. The authors examined 20 healthy adults with no food- or drug-allergy history and administered vaccines, including the influenza vaccine, at varying strengths to assess the rate of irritant reactions. They found that with one-tenth and full-strength intradermal vaccine tests, irritant reactions were very common. Of the 20 subjects who received the intradermal 1:100 concentration, which is the concentration recommended for vaccine testing in egg-allergic patients before influenza vaccine administration, 3 had positive results. Although irritant reactions are not common, the authors concluded that clinicians should be aware that they may occur even at the 1:100 concentration. The study results suggest that false-

positive testing may occur with the influenza vaccine skin test.

In our study, 3 patients who had a positive vaccine skin-test result received and tolerated the influenza vaccine without serious adverse reactions. One of these patients had a small, localized reaction after the one-tenth dose but subsequently tolerated the nine-tenths dose without any reaction. Furthermore, of the 55 patients with negative skin-test results, 3 patients still developed mild systemic reactions to the influenza vaccine. Although this was a very small sample and not a primary aim of our study, these results, and those of previous studies, suggest that the vaccine skin test may not be reliable in distinguishing patients who are safe to receive the influenza vaccine from those who are unsafe to receive the vaccine.

Our study was limited by our modest sample size and the rare occurrence of a systemic reaction to the influenza vaccine, which affected the power of

our study. In addition, the discrepancy of the baseline prevalence of age, asthma history, and allergic-rhinitis history between our groups may have been a confounding variable. However, these variables were not statistically significant in affecting adverse reactions on the basis of univariate analysis (Table 1). Furthermore, these variables were adjusted for through propensity scores in the multivariate analysis. Therefore, these factors are unlikely to have affected the outcome of our study.

CONCLUSIONS

In our study, we evaluated the current protocol for influenza vaccine administration to egg-allergic patients. Our results suggest that the influenza vaccine skin test may be safely removed from the standard protocol, and that egg-allergic patients without anaphylaxis to egg may have the influenza vaccine administered in a 2-dose, graded fashion (one-tenth dose, followed by nine-tenths dose) by experienced staff

who are equipped to manage possible serious adverse reactions.

Areas for further research include a large, prospective, multicenter study to validate our findings, assess the safety of influenza vaccine in patients with anaphylactic reaction to egg, and identify risk factors that may predict adverse reaction to influenza vaccine in egg-allergic patients. In addition, a study of the safety of full-dose influenza vaccine administration may help increase the rate of influenza vaccination in egg-allergic patients.

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