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Safe administration of the seasonal trivalent influenza vaccine to children with severe egg allergy

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Background: Anaphylaxis to egg or severe egg allergy has been considered a contraindication to receiving trivalent seasonal influenza vaccine (TIV).

Objective: To evaluate the safety of TIV among severely egg allergic children.

Methods: A 2-phase, multicenter study at 7 sites was conducted between October 2010 and March 2012. Inclusion criteria included a history of a severe reaction, including anaphylaxis, to the ingestion of egg and a positive skin test result or evidence of serum specific IgE antibody to egg. Phase 1 consisted of a randomized, prospective, double-blind, placebo controlled trial of TIV administration to egg allergic children, using a 2-step approach; group A received 0.1 mL of influenza vaccine, followed in 30 minutes if no reaction with the remainder of an age-appropriate dose, whereas group B received an injection of normal saline followed in 30 minutes if no reaction with the full 100% of the age-appropriate dose. Phase 2 was a retrospective analysis of single dose vs split-dose administration of TIV in eligible study participants who declined participation in the randomized controlled trial.

Results: Thirty-one study participants were prospectively evaluated in the randomized controlled trial (group A, 14; group B, 17); 45.1% had a history of anaphylaxis after egg ingestion. A total of 112 participants were retrospectively evaluated (87 with the single dose and 25 with the split dose); 77.6% of participants had a history of anaphylaxis after egg ingestion. All participants in both phases received TIV without developing an allergic reaction.

Conclusion: TIV administration is safe even in children with histories of severe egg allergy. Use of 2-step split dosing appears unnecessary because a single dose was well tolerated.

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Introduction

Trivalent seasonal influenza vaccine (TIV) is grown in embryonated chicken eggs and contains residual amounts of ovalbumin, a major egg allergen.¹ Historically, this has raised concern regarding the safety of TIV in egg allergic children (EAC), given the theoretic possibility that vaccination could provoke an allergic reaction.^{2–4} Influenza A is responsible for approximately 294,128 annual hospitalizations, 21,156 of these in children younger than 5 years.⁵ It is estimated that approximately 1.5% of children have egg allergy and that approximately one-third of food allergic children also have asthma.⁶ Thus, there is a large group of children who are not being

vaccinated because they are egg allergic who remain susceptible to the morbidity of influenza disease.

For many years, TIV was simply withheld from EAC.³ Since 1998, however, some reports have described EAC, usually without a history of severe reactivity, who have received TIV uneventfully. Many of these studies required that the patient have a negative TIV skin test result, the vaccine lot contain a low amount of ovalbumin, and/or the dose be administered in 2 or more graded steps.^{2,5,7} In the last 3 years, 8 groups reexamined the safety of TIV in EAC. The cumulative result of these studies has demonstrated that the risk of reaction to TIV (or H1N1 monovalent influenza vaccine) in EAC is exceptionally low, that the ovalbumin content of recent years' vaccines are consistently low, and that neither skin testing nor split-dosing strategies were necessary to safely provide these vaccines to EAC.^{7–14} Although these studies demonstrated that influenza vaccine was safe for subgroups of EAC with severe allergy (totaling 241 cumulative patients), no widespread data exist that this practice is safe or that graded dosing is necessary. Recent guidelines from the Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices (ACIP) were updated to recommend influenza vaccination of some EAC, namely, those with "only hives" after egg ingestion, but that they be observed for 30 minutes afterward. However, the guidelines recommend that EAC with more severe allergy be referred to an allergist for further evaluation before vaccination.¹⁵ The purpose of this study was to investigate the safety of TIV in EAC with severe allergy.

Methods

This study was conducted from October 2010 through March 2012 at 7 institutions: University of Michigan, Children's Hospital of Pittsburgh of University of Pittsburgh Medical Center, Children's Hospital of Philadelphia, Scripps Clinic, Mayo Clinic, University of Texas Southwestern, and Children's National Medical Center. It consisted of 2 phases; phase 1 was a randomized controlled trial (RCT), whereas phase 2 was a retrospective, observational trial. The study was registered with www.clinicaltrials.gov (NCT01264601) and was approved by the University of Michigan institutional review board and the institutional review boards of the respective sites.

In the RCT portion, eligible participants were enrolled after a parent or guardian provided informed consent. Written assent was additionally provided by children aged 14 to 17 years. Parents were asked to fill out a questionnaire detailing their child's history of past reactions to the ingestion of egg and any prior seasonal or H1N1 influenza vaccines. This information was verified by medical record review. In addition, the most recent egg skin test and serum egg protein specific IgE (sIgE; egg white, as well as ovalbumin and ovomucoid if available) were also obtained through medical record review. Study participants were randomized at the time of enrollment to 1 of 2 dosing regimens via an electronic list, with stratification per participating site. Randomization number packets were distributed to each site in envelopes and assigned consecutively to patients after obtaining consent. Patients and site investigators were masked and remained so through the study analysis. Two different regimens for immunization were assigned: group A received a graded challenge consisting of 0.1 mL of influenza vaccine, followed in 30 minutes if no reaction with the remainder of the age-appropriate dose (either 0.15 mL or 0.4 mL); group B received a full TIV dose for age in 1 injection but received a 0.1-mL 0.9% saline sham first dose to maintain the appearance of receiving a graded challenge. All study participants requiring a booster received it as a single dose if the initial immunization was tolerated and by graded challenge if any allergic reaction was noted to

develop. No participant received TIV skin testing before vaccination.

For the retrospective, observational phase (initiated in February 2011), participants were enrolled based on preidentified lists of RCT-eligible patients at each institution. These individuals either declined enrollment in the RCT and received TIV at their allergist's office or had already received their TIV at their primary care physician's office when contacted, despite the prior ACIP contraindication. Parents of the EAC were contacted to verify that the child received TIV and in what venue if this was not identifiable from review of the medical record. The same inclusion and exclusion criteria were followed as in the RCT, and informed consent or written assent was obtained. In addition, the same questionnaire was completed by the parents, and the same patient medical record review was performed as the RCT.

All participants in the prospective phase were observed for 30 minutes after each dose of the protocol. Doses were to be withheld until further assessment by a masked physician if any patient demonstrated symptoms of allergic reactivity. All patients in the retrospective phase were observed for 30 minutes after vaccination as well. Patients were given a discharge sheet for the purposes of follow-up of symptom development during the next 48 hours, containing their study number, site code, and 3 means of communicating with the investigators (e-mail, fax, or voice mail) to report symptoms up to 48 hours after vaccination. Patients requiring a booster returned per established recommendation at a minimum of 30 days after receiving initial the vaccine. All vaccine was supplied per the individual sites, and all sites used Fluzone (Sanofi Pasteur, Swiftwater, Pennsylvania). Fluzone is reported by the manufacturer to have an ovalbumin content of approximately 0.1 µg per 0.5-mL dose.¹

Inclusion criteria for enrollment in either phase included the following: (1) egg allergy defined by allergic reaction to an observed egg challenge OR history strongly suggestive of clinical allergy within 4 hours of ingestion AND egg sIgE above 0.70 kUA/L OR egg skin prick test wheal 3 mm greater than the negative control (or 2+ score if wheal size not available); AND (2) a documented history of anaphylaxis by established criteria after egg ingestion, verified through medical record review¹⁶; OR (3) a severe allergic reaction to egg defined as a history of severe hives, angioedema, or asthma attributable to egg allergy.²

Thus, patients needed to fulfill criteria for both egg allergy and for either anaphylaxis or a severe allergic reaction to be included in the study (ie, both 1 and either 2 or 3).

Exclusion criteria included (1) egg sensitization only (ie, detectable sIgE or positive skin test result without a history of clinical reactivity to the ingestion of egg or children who did not fulfill requirements for both egg allergy AND anaphylaxis or severe allergic reaction; (2) prolonged use of immunosuppressive medication, including high dose corticosteroids for longer than 6 months; (3) prior history of egg allergy, with the child now tolerating the ingestion of egg directly; (4) history of active or resolved eosinophilic esophagitis; and (5) cardiac disease, known tumor under treatment, or pregnancy.

Symptom development for all doses of influenza vaccine were compared between groups for the RCT and by single vs 2-step dose protocol for the retrospective phase, using a Fisher exact test and Kruskal-Wallis test. Logistic regression was used to determine a relationship between patient specific variables and odds of symptom development. All data were analyzed using Stata IC statistical software, version 12 (StataCorp, College Station, Texas).

Results

A total of 143 patients were enrolled between October 2010 and March 2012. Demographics and baseline characteristics of the

Table 1
Baseline population demographics

Demographic	Phase 1 (RCT)			Phase 2 (retrospective)		
	Group A (n=14)	Group B (n=17)	Total (n=31)	Single dose (n=87)	Split dose (n=25)	Total (n=112)
Age at diagnosis, median, mo	11	12	12	12	12	12
Egg skin test wheal, median, mm (n=101)	6	9	7	7	4	7
slgE by ImmunoCAP, median, kUA/L						
Egg white (n=89)	16.2	5.3	6.4	9.53	14.05	8.69
Ovalbumin (n=39)	10.45	4.52		4.81		5.48
Ovomucoid (n=39)	7	2.83		2.92		3.03
Prior TIV, %	78.6	68.8	73.3	86.7	13.3	88.2
Prior H1N1, %	43.8	56.2	55.2	56.1	19.6	52.6
Male, %	42.1	57.9	63.3	79.7	20.3	75.5
History of anaphylaxis to egg, %	42.8	47.0	45.1	82.7	44.0	77.6
Baked egg tolerant, %	35.7	29.4	32.3	29.6	43.5	33.8
Other atopic disease, %						
Atopic dermatitis	71.4	47.0	58.0	47.1	80.0	54.5
Asthma	28.5	41.2	35.5	45.9	32	42.9
Allergic rhinitis	35.0	17.6	25.8	46.5	8.0	31.3
Other food allergy	50.0	70.6	61.3	47.1	68.0	51.8

Abbreviations: slgE, specific IgE; RCT, randomized controlled trial; TIV, trivalent seasonal influenza vaccine.

Group A received TIV as a 2-step graded challenge; group B received TIV as a single dose with a preceding 0.1-mL saline sham dose.

patients' egg allergy, by protocol, are described in Table 1. Table 2 details the symptoms of the most severe reactions to egg ingestion. A total of 31 patients were enrolled in the RCT portion. A total of 112 patients were enrolled in the observational, retrospective study, including 87 patients (77.7%) who received TIV via single injection. No significant allergic reactions or IgE-mediated symptoms directly attributable to TIV vaccination were reported within either phase of the study. Seven of the 31 RCT patients (22.6%) observed or reported some degree of mild, transient induration at the injection site (4 in group A and 3 in group B). No additional local or systemic reactivity was observed or reported among the recipients requiring a booster dose of TIV.

Three adverse events occurred in the RCT phase but were deemed unrelated to administration of TIV and verified as such by the study's data safety monitoring board and the University of Michigan institutional review board. These events consisted of the following: (1) a 3-year-old girl with underlying milk and egg allergy developed anaphylaxis within several minutes of consuming a packaged chocolate sauce labeled as containing both milk and egg, occurring approximately 24 hours after vaccination; (2) a 2-year-old boy with a history of recurrent vomiting and allergy to milk, egg, and peanut vomited once in the office approximately

28 minutes after his vaccination, after vigorously running around the examination room, but was otherwise playful and had no other symptoms of IgE-mediated reactivity; and (3) a 12-year-old boy, receiving his first ever TIV, reported tachycardia 24 hours after receiving TIV but had no symptoms noted during his observation period or later that same day/night. Per the principal investigators at the site (University of Michigan), these events were believed to be unrelated to the study.

Discussion

We demonstrate, through 2 distinct study methods, that TIV administration to EAC with severe allergy is safe and that graded dosing methods are not necessary. This is the first study, to our knowledge, to specifically investigate the tolerability of children with severe allergic reactions to egg and compare dosing methods. No allergic reactions, mild or severe, occurred in any EAC, irrespective of protocol. Therefore, we conclude that no significant difference exists between single and 2-step graded dosing of TIV and that TIV is safe to provide as a single dose to EAC with severe allergy, including those with a history of anaphylaxis to the ingestion of egg. The degree of egg protein sensitization or presence of other allergic comorbidities did not affect TIV tolerability in these children. Although the number of patients in the RCT was small, we believe it is valid given identical results in the larger observational, retrospective study. We believe these findings support further revision of the ACIP guidelines to recommend that children with egg allergy of any severity, including anaphylaxis, should receive TIV as a single injection with a 30-minute observation period and do not require referral to an allergist for influenza vaccination.

These findings are consistent with the cumulative data regarding safe TIV administration to EAC noted in 8 studies between 1998 and 2012.^{4,6–10,12,13} In these studies, subgroups of children with severe egg allergy (total n=241) were vaccinated by either single or graded dosing and incurred no adverse events. The current study is the first to singularly focus on the safety and tolerability of TIV in EAC with severe allergy and compare dosing strategy and finds that these children tolerate the vaccine given as a single dose without reactions.

The Fluzone brand of influenza vaccine used in this study, as well as other TIV marketed in the United States during the period of the trial, contain very low amounts of egg protein measured as ovalbumin¹ based on assays performed by both the vaccine makers and independent research groups.^{17–19} It is not clear what

Table 2
Symptoms of the most severe reaction to egg ingestion among study participants

Symptom	Phase 1 (RCT), No. (%)		Phase 2 (retrospective), No. (%)	
	Group A (n=14)	Group B (n=17)	Single dose (n=87)	Split dose (n=25)
Localized urticaria	5 (35.7)	6 (35.2)	9 (10.5)	9 (36.0)
Systemic urticaria	5 (35.7)	9 (52.9)	35 (40.7)	10 (40.0)
Oral/facial angioedema	6 (42.8)	5 (29.4)	17 (19.8)	10 (40.0)
Throat itching	3 (21.4)	3 (17.6)	5 (5.8)	3 (12.0)
Throat swelling	2 (14.3)	1 (5.9)	2 (2.3)	1 (4.0)
Stridor	1 (7.1)	2 (11.7)	2 (2.3)	0
Cough	3 (17.6)	10 (11.6)	10 (11.6)	4 (16.0)
Dyspnea	2 (14.3)	1 (5.9)	8 (9.3)	1 (4.0)
Wheezing	2 (14.3)	2 (11.7)	8 (9.3)	1 (4.0)
Hypotension	1 (7.1)	1 (5.9)		
Vomiting	9 (64.3)	10 (58.8)	44 (51.2)	13 (52.0)
Abdominal pain	3 (21.4)	2 (11.7)	11 (12.8)	2 (8.0)

Abbreviation: RCT, randomized controlled trial.

Group A received trivalent seasonal influenza vaccine as a 2-step graded challenge; group B received trivalent seasonal influenza vaccine as a single dose with a preceding 0.1-mL saline sham dose.

constitutes a “safe” ovalbumin level. In 1998, James et al.⁷ noted that 83 EAC safely received a 2-step graded challenge to the Parke Davis brand of TIV, which contained up to 1.2 µg/mL of ovalbumin. This level has since become an arbitrary threshold below which TIV administration to EAC was deemed safe. However, this level was just what happened to be in the vaccine used in that trial and not a designated study outcome. Although ovalbumin levels up to 1.2 µg/mL were well tolerated in that study,⁷ and even up to 1.4 µg/mL in another study,¹⁴ it has never been demonstrated that higher levels of ovalbumin were not. However, no TIV currently marketed in the United States contains more than approximately 0.2 µg/mL of ovalbumin.^{1,17–19} Because these levels could potentially change in the future, physicians are still advised to check the ovalbumin content in each year’s influenza vaccines. This information can be found in package inserts or by contacting the manufacturers. Also, the Centers for Disease Control and Prevention will likely continue to include this information in recommendations issued annually before influenza season. Thus, as long as the ovalbumin content remains at present levels, a particular brand of influenza vaccine should be chosen based on its approved age range because all have acceptably low levels of ovalbumin.

This study has several limitations. During the trial significant changes in practice recommendations in providing TIV to EAC were published.^{15,20} Foremost, this affected children with a history of developing hives attributable to egg ingestion. At the initiation of the trial, it was recommended by both the ACIP and the American Academy of Pediatrics (AAP) Committee on Infectious Diseases (Red Book) that persons with generalized urticaria not receive TIV. At the midpoint of the trial, the updated recommendations from the ACIP and AAP advised that such children could receive TIV with a 30-minute observation period afterward and that this could occur at their primary care physician’s office. Only 8 patients were enrolled who had a history of only hives to egg and no other symptoms. This represented only 5.6% of total enrollment and had no effect on the overall study outcome, given that all patients tolerated the vaccine. Of these 8, 1 patient received the 2-step graded dose as part of the RCT, and 4 additionally received TIV via the 2-step graded dose in the retrospective arm. In addition, the recommendations also changed at the midpoint of the trial pertaining to single vs 2-step graded dose administration of TIV, and graded dose administration was no longer advocated.^{15,20} This likely influenced low enrollment rates in the RCT portion to recruit individuals for a study involving a 2-step procedure, when the practice parameters stated that TIV could be received in a single dose. The observational arm was implemented in anticipation that the changes in guidelines would create recruitment issues and provides crucial supporting evidence, identical to the RCT findings. However, the observational arm provided results further bolstering the safety of this procedure, with the finding that 17 of 17 individuals who received their TIV as a single dose at the primary care physician’s office did so without incident. Other limitations of the study include selection bias in that all patients were cared for at academic medical centers, that there may have been bias in the observational arm in the selection of patients to receive graded challenges, and that many individuals had safely received TIV or H1N1 previously (although this only serves to underscore that the vaccine is safe in this population).

Overall, we demonstrate in a multicentered trial with both randomized, prospective, placebo-controlled data and retrospective, observational data that EAC with severe allergy, including those with a history of anaphylaxis to egg ingestion, can safely receive TIV. The method of vaccine administration—single-dose vs 2-step graded challenge—was tolerated equally in both the prospective and retrospective groups, and thus single-dose administration is safe and appropriate. This is the first study, to our knowledge, to exclusively evaluate dosing methods in EAC with severe allergy. No allergic reactions were attributable to TIV,

despite level of sensitization to egg protein or other allergic comorbidity. These data are similar to the 241 previously published cases of EAC with severe allergy studied as subgroups of 8 investigations between 1998 and 2012, which also demonstrated TIV was safe in this population. Thus, there are now 384 cases of severe allergy in EAC receiving TIV that have been studied both prospectively and retrospectively, across 9 studies, and the outcomes have been identical. The practice of administering TIV to EAC, irrespective of reaction severity, is safe, and TIV can be administered as a single dose. Current ACIP and AAP recommendations state that EAC with severe allergy (ie, those having more than hives only after egg ingestion) should be referred to an allergy specialist for further evaluation before influenza vaccination. However, these children tolerate the influenza vaccine, and allergy referral poses a barrier to their being vaccinated. Thus, it would seem that EAC with allergy of any severity can be safely vaccinated in a primary care setting, with the only precaution being they be observed for 30 minutes after receiving the vaccine.

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