

SAFE ADMINISTRATION OF SEASONAL INFLUENZA VACCINE TO CHILDREN WITH EGG ALLERGY OF ALL SEVERITIES

Egg allergy is the second most common pediatric food allergy, affecting approximately 1.3% of US children.¹ The Centers for Disease Control and Prevention recommend that egg allergic children should not routinely receive seasonal trivalent influenza vaccine (TIV); however, opinions among allergists are changing, and recent data indicate the need to question this recommendation.^{2,3} A retrospective review⁴ demonstrated safe 2-step administration of TIV, without vaccine pretesting, in egg allergic children without a history of egg-induced anaphylaxis. Another group safely administered adjuvant, low-dose ovalbumin containing H1N1 vaccine, without pretesting, to nonanaphylactic egg allergic children as a single dose or as a 2-step graded challenge to 72 individuals with a history of a severe egg allergy or poorly controlled asthma.⁵ Our group safely administered H1N1 vaccine to children with egg allergy of any severity (including anaphylaxis) through either single or 2-step (10%, 30-minute observation; 90%, 30-minute observation) dosing and found skin testing did not predict vaccination outcome.⁶

We conducted an institutional review board-approved retrospective review of TIV immunization patterns for egg allergic children ages 6 to 36 months seen at the University of Michigan Allergy Clinics from October 2004 to February 2009. Potential study participants were identified from the *International Classification of Diseases, Ninth Revision (ICD-9)* code (v15.03) and validated by medical record review. We also prospectively studied TIV administration in a group of egg allergic children enrolled in an institutional review board-approved study of H1N1 vaccine.⁶ Informed consent was obtained from all prospective study participants. Data analyzed included demographics, skin and ImmunoCAP tests to egg (Phadia US Inc, Portage, Michigan), TIV skin tests, symptoms of the most severe egg reaction, atopic comorbidities, administration details for TIV immunization, and TIV reactions. Data were analyzed using SAS statistical software, version 9.2 (SAS Institute Inc, Cary, North Carolina).

Of 193 potential egg allergic patients in the retrospective review, 140 met inclusion criteria (6–36 months at first immunization or testing, objective evidence of egg allergy, seen during TIV immunizing season). Subsequent immunizations were evaluated only for trending of practice patterns. Booster vaccines were not analyzed. Of the 140 patients, 135 received TIV; none had significant complications. Five (4%) were not vaccinated per physician or parent preference after a positive TIV skin test result. There were no differences in comorbidities of asthma and egg-induced anaphylaxis between the egg allergic children who were (135) and were not (5) vaccinated. During the 5-year retrospective review, the likelihood of receiving single-dose vaccine increased significantly ($P < .006$, Fig 1). Twenty-eight of 135 children (21%) safely received their first TIV without prior skin testing. Of 17 children with documented anaphylaxis to egg, 14 (82%) safely received TIV: 2 with positive skin test results to TIV, 9 with negative skin test results, and 3 with no pretesting. Three did not receive the vaccine because of physician or parent preference. There were only minor reactions reported in 7 patients, none of whom had a history of anaphylaxis (wheal or erythema at the injection site, a few hives, and diarrhea).

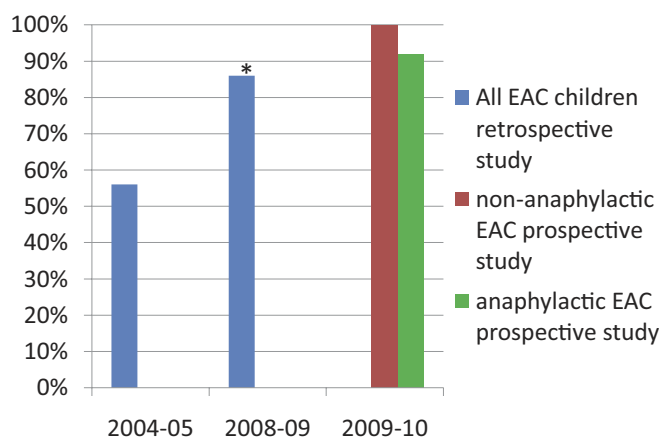


Figure 1. Administration of full-dose trivalent influenza vaccine (TIV) as a single shot. *In the retrospective study, the likelihood of receiving a single shot at initial TIV immunization increased significantly over time ($P = .006$). EAC indicates egg allergic children.

We prospectively evaluated 69 egg allergic children and 14 non-egg allergic children during the 2009 to 2010 influenza immunization season: 34 egg allergic children (49%) received full-strength skin prick testing to TIV, with 6 positive test results (18%). If TIV test results were positive, vaccine was administered in 2 steps; all boosters were administered as a single dose. Overall, 68 of 69 egg allergic children tolerated single-dose administration of TIV as either a first or booster dose. One of 13 anaphylactic patients received 2-stage dosing and did not require a booster (Figure). There were no serious allergic reactions to TIV, but 2 egg allergic children had lip or mouth itching and scattered hives and 2 non-egg allergic controls had hives and fever or rash. No patient with a history of egg-induced anaphylaxis had even a minor reaction to the TIV.

In the prospective study, 0.5-mL samples from available seasonal influenza lots were sent to the Allergic Diseases Research Laboratory at the Mayo Clinic for analysis of ovalbumin content, which ranged from 0.3 to 1.087 $\mu\text{g/mL}$.⁷ There was no correlation of ovalbumin content with reactions. Historically, we have always used Sanofi-Pasteur TIV.

In summary, we demonstrated, both retrospectively and prospectively, that TIV can safely be given to egg allergic children, including those with past egg-induced anaphylaxis. We concur that TIV skin testing is not necessary.^{4–6} We propose that egg allergic children will tolerate TIV given as a single dose; 68 of 69 of our prospective patients tolerated this, including 12 of 13 with a history of anaphylaxis. In our retrospective review, by the 2008–2009 influenza season, 87% of egg allergic children received TIV as a single dose. We found no difference in TIV tolerance between egg allergic children with and without a history of egg-induced anaphylaxis. Although we conclude that TIV is safe for single-dose administration in egg allergic children irrespective of past reaction severity, these numbers are small and are currently being reevaluated in a randomized, placebo-controlled study of severely egg allergic individuals.

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CONTACT URTICARIA TO RAW ARUGULA AND PARSLEY

A 24-year-old woman with a history of seasonal rhinoconjunctivitis presented with severe angioedema of the lips and tongue, associated with oropharyngeal pruritus and choking sensation, which developed approximately 5 minutes after the ingestion of a few raw arugula leaves. The acute reaction was successfully managed at an emergency unit with intramuscular epinephrine (0.5 mL of a 1:1,000 solution) and intravenous administration of chlorpheniramine. A similar episode occurred 2 months earlier after she ate a pizza with tomato and raw arugula. Moreover, the patient reported previous episodes characterized by lip angioedema after the consumption of foods containing raw parsley, as well as the occurrence of itchy erythematous-edematous lesions of the hands after contact with uncooked leaves of the specified vegetables. On the other hand, the patient did not report any symptoms after the ingestion of cooked parsley or arugula.

Skin prick tests (SPTs) were performed with common airborne allergens and with a large panel of commercial food extracts (Lofarma, Milan, Italy). The SPT result was assessed as positive if the wheal diameter was 3 mm or larger than that of the negative controls. Positive results were observed with *Parietaria*, *Dermatophagoides pteronyssinus*, cat dander, and grass. Furthermore, prick-prick testing was performed with leaves of arugula and parsley and showed strong positive results, eliciting a wheal of 12 mm for the former and 11 mm for the latter. Ten healthy volunteers tested with the same procedure had negative results. Specific IgE for parsley (2.39 kUA/I), *D pteronyssinus*, grass, and *Parietaria* were detected by ImmunoCAP, whereas specific IgE test results for rBet v 1 were negative. IgE antibodies for arugula have not been investigated because the ImmunoCAP test for this vegetable is not available.

Parsley and arugula leaves were extracted as previously described by Bjorksten et al.¹ Protein content was determined according to Bradford² using a commercial BioRad Protein Assay Dye Reagent (BioRad, Milan, Italy) and bovine serum albumin as reference standard. The protein concentration was 1.1 mg/mL and 931 µg/mL for parsley and arugula extracts, respectively.

Parsley and arugula extracts were dialyzed extensively against double distilled water, lyophilized, and then dissolved in prick solution (0.68% sodium chloride, 0.275% sodium bicarbonate, 50% glycerol, and 0.4% phenol) at a concentration of 80 µg/mL. The SPTs performed with both allergen extracts showed a strong positive reaction, with a 12-mm wheal for the parsley extract and a 10-mm wheal for the arugula extract. Extracts at 1:10 dilution showed positive reactions, with a wheal of 8 mm for both vegetables. Ten healthy volunteers tested with the same procedures had negative results.

Parsley and arugula extracts were mixed with lithium dodecyl sulfate sample buffer (Nupage Bis-Tris; Invitrogen, Milan, Italy) and 5% β-mercaptoethanol. The samples were then denatured by heating at 100°C for 10 minutes. Electrophoresis of both extracts (25 µg per lane) was performed in a 10% polyacrylamide precast gel (Nupage Bis-Tris) at 180 mA for 1 hour. The gel was stained with a colloidal blue staining kit (Invitrogen). Immunoblotting showed no IgE reactivity in the patient's serum.

Eruca sativa, commonly known as arugula, rocket, or roquette, is an edible annual plant that belongs to the family Brassicaceae or Cruciferae and is used as a leaf vegetable, either raw or cooked, in some Mediterranean countries, especially Italy. Parsley (*Petroselinum crispum*) is a herbaceous plant widely used in cooking that belongs to the Apiaceae family, which is not botanically related to Brassicaceae.

Allergic reactions to the ingestion of these vegetables seem to be rare. Previous reports have described the occurrence of urticaria-angioedema after eating parsley.³ In 1 case IgE reactivity against a 12-kDa lipid transfer protein was demonstrated by immunoblotting.⁴ Regarding arugula, a case documented the occurrence of IgE-mediated urticaria after eating or skin contact with this vegetable.⁵ Another report described a patient sensitized to *Eruca sativa* who developed intraoral and respiratory symptoms after its ingestion.⁶ In our case, contact urticaria to both vegetables was established based on history, positive SPT results, and positive ImmunoCAP results for the parsley. The patient appeared to tolerate the ingestion of cooked arugula and parsley, as frequently observed in patients with fruit-pollen syndrome.⁷ Immunoblotting assay failed to detect any IgE reactivity against the protein components of each vegetable in the patient's serum. A possible explanation of the difference between ImmunoCAP and immunoblotting could be that the extract sample for immunoblotting was previously heated (5 minutes at 100°C). We cannot exclude that this treatment can alter allergenic epitopes, which consequently makes them no more recognizable by IgE testing of the patient's serum.

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