Administering influenza vaccine to egg allergic recipients: a focused practice parameter update

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CLASSIFICATION OF RECOMMENDATIONS AND EVIDENCE

Category of evidence
Ia Evidence from meta-analysis of randomized controlled trials
Ib Evidence from at least one randomized controlled trial
IIa Evidence from at least one controlled study without randomization
IIb Evidence from at least one other type of quasiexperimental study
III Evidence from nonexperimental descriptive studies, such as comparative studies
IV Evidence from expert committee reports or opinions or clinical experience of respected authorities or both

Strength of recommendation
A Directly based on category I evidence
B Directly based on category II evidence or extrapolated from category I evidence
C Directly based on category III evidence or extrapolated from category I or II evidence
D Directly based on category IV evidence or extrapolated from category I, II, or III evidence
E Based on consensus of the Joint Task Force on Practice Parameters

EXECUTIVE SUMMARY

• The well-proven benefits of influenza immunization can now be made available to persons with a history of egg allergy. Individuals with diagnosed or suspected egg allergy who need an influenza vaccination should be evaluated by an allergist/immunologist for evaluation of egg allergy and for administration of the 2010-2011 trivalent influenza vaccine (TIV) if clinically indicated.

• Studies have suggested that influenza vaccines can be administered to patients with a history of anaphylaxis to egg without adverse effects. However, such studies are limited in number, and reactions to influenza vaccines in egg allergic persons can occur. Caution is warranted in patients with a history of anaphylaxis or where the severity of their clinical reactivity is uncertain, particularly when the ovalbumin content of the vaccine is unknown. Therefore, consultation with an allergist experienced in food allergy and anaphylaxis is strongly recommended.

• For the 2010-2011 influenza season, the routine practice of skin testing to the TIV is no longer recommended.

• Both the 2-dose (10%, 90%) and single-dose methods are appropriate for administering influenza vaccine to egg allergic individuals.

Egg allergic individuals can receive TIV without prior skin testing to the vaccine, with the vaccine being administered via a 2-step graded challenge: first administer 10% of the age-appropriate dose, with a 30-minute observation after administration for symptom development. If no symptoms develop, the remaining 90% can be administered, with a 30-minute observation for symptom development. The same TIV product brand should be used for booster vaccinations if possible, but it is not necessary to use the same lot.
Egg allergic individuals can receive TIV without prior skin testing to the vaccine as a single, age-appropriate dose without use of graded challenge. Individuals should be observed for 30 minutes after injection for evidence of a systemic reaction. The same TIV product brand should be used for booster vaccinations, but the same lot is not necessary.

INTRODUCTION
There was renewed interest in the safety of administering egg-containing immunizations to egg allergic children and adults during the global pandemic of the H1N1 influenza A virus in 2009-2010. The H1N1 influenza A vaccine, like the seasonal TIV, is grown on embryonated chicken eggs, leading to concern that residual contamination of ovalbumin (egg proteins) could provoke allergic reactivity in egg allergic individuals.

The 2010 influenza vaccine has incorporated the H1N1 strains, and thus a single influenza vaccine is being offered this season. In addition, several manufacturers now list the ovalbumin content of their influenza vaccine. However, other specific allergenic proteins or moieties that potentially could trigger allergic reactions in egg allergic individuals have not been identified.

Historically, although caution has been recommended in administering influenza vaccine to egg allergic individuals, previous experience suggests that many people with diagnosed or suspected egg allergy can receive influenza vaccination without serious reaction, if precautions are followed. Precautions that have been used include vaccine skin testing, administration via a 2-step graded dose challenging (10% followed by 90% of the age-appropriate dose after a brief observation period), or desensitization. In some circumstances, egg allergic individuals were advised not to receive the vaccine. Given the urgency to protect children last year from the global influenza pandemic, investigators have reexamined the safety of this vaccine in egg allergic individuals with significant changes in recommendations since the last influenza season. This practice parameter update offers guidance in how to evaluate and treat the patient with egg allergy.1

RECENT DEVELOPMENTS
Summary Statement 1. Egg allergic patients generally should receive influenza vaccinations because the risks of not vaccinating outweigh the risks of vaccinating. (A)

Within the past year, several studies have helped clarify ongoing questions about the vaccine’s safety in individuals with egg allergy of any severity, questioning the necessity of skin testing or optimal method of administration, including single-dose administration and 2-step graded dose protocols. Two groups separately analyzed the ovalbumin content of vaccine produced by several vaccine makers, for both H1N1 vaccine and TIV lots. These results showed that the analyzed TIV lots contained less than 1.2 μg/mL of ovalbumin, and the H1N1 vaccine lots contained less than 0.1 μg/mL.2,3 Previous investigation from the late 1990s demonstrated that TIV lots containing less than 1.2 μg/mL of ovalbumin were well tolerated in egg allergic individuals when administered after skin testing, using a 2-step graded challenge.4 Although there is no study that has demonstrated risk from vaccines containing ovalbumin above this level, many experts urged caution and possibly even withholding the vaccine with higher ovalbumin-containing lots.5,7 Many manufacturers have begun to list their ovalbumin content ranges on the package insert, which is of great utility in finding low ovalbumin-containing vaccine.7

Three studies in the past year have reexamined the approach to vaccinating egg allergic individuals with TIV. One retrospective study of 171 egg allergic individuals without a history of anaphylaxis or severe reactivity attributed to egg showed that the vaccine could be safely given using a 2-step graded challenge without vaccine skin testing. Seven patients (4%) developed systemic symptoms, and 17% reported localized symptoms.8 A large Canadian prospective study, using a unique squalene adjuvanted, low ovalbumin-containing H1N1 vaccine (containing <0.03 μg/mL of ovalbumin), showed that vaccine could be administered as a single, age-appropriate dose without prior vaccine skin testing in 758 egg allergic individuals without a history of severe reaction and 393 non–egg allergic control subjects; and by a 2-step graded challenge (without vaccine testing) in 72 egg allergic individuals with either a history of severe cardiovascular or respiratory symptoms from egg or uncontrolled asthma. In this study, 17 patients (2%) developed mild symptoms compared with 3.1% in the control group within the hour period of observation after vaccine administration, and there were no reports of anaphylaxis. A total of 13% reported mild symptom development, mostly gastrointestinal or mild respiratory (rhinitis) symptoms, by 24 hours after receiving their vaccination. On the basis of these favorable results, an additional 3,640 patients with self-reported egg allergy were then vaccinated according to the same protocol, with 69 (1.9%) developing symptoms consistent with an allergic reaction, including 2 individuals requiring epinephrine treatment.9

Lastly, a single-center, controlled, prospective study of H1N1 vaccination in 105 individuals with egg allergy of all severities, including 25 with a history of anaphylaxis to egg, and 19 non–egg allergic control subjects, demonstrated that vaccine skin testing was not predictive of vaccine tolerance, that use of a 2-step graded challenge was unnecessary irrespective of past reaction severity to egg, and that booster doses could be given from a different lot without vaccine skin testing. Three egg allergic patients (2.4%) and 1 control subject (5.2%) in this study developed symptoms, none consistent with an allergic reaction. This group further demonstrated...
that vaccine skin testing was likely to induce an irritant response with increasing vaccine ovalbumin content.\textsuperscript{10} Table 1 provides the breakdown of the types of reactions reported in the most recent studies.

Thus, the work from last season has shown both prospective and retrospective evidence that the influenza vaccine generally is well tolerated in egg allergic individuals, including limited data in those with a history of a severe allergic reaction to egg, and that vaccine skin testing is not necessary. Although there is still some historical debate about the safety of TIV in egg allergic individuals with a history of anaphylaxis or severe reaction to egg, 3 studies, each limited by low numbers of severely egg allergic individuals (n = 27, 72, and 25), have demonstrated 2 methods for vaccinating this subgroup.\textsuperscript{4,9,10} Although these results are promising, they must be interpreted cautiously given the sample size. A multicenter trial further evaluating this issue and comparing the methods for administering the vaccine is currently under way in the United States.

**EVALUATION OF EGG ALLERGY**

**Summary Statement 2.** Persons with a history of suspected egg allergy who need an influenza vaccination should be evaluated by an allergist/immunologist with expertise in food and vaccine allergy.

Persons with a history of suspected egg allergy who have an indication for influenza vaccination should first be evaluated by an allergist/immunologist with expertise in food and vaccine allergy. The reason to determine the egg allergy status of the patient is to confirm or refute the diagnosis of egg allergy and to assess the severity of prior reactions to egg. The evaluation for egg allergy includes a detailed history to assess the likelihood that the patient has had an IgE-mediated sensitivity to egg. If the clinical history is consistent with egg allergy, then skin prick testing to egg or specific in vitro IgE antibody testing for egg is indicated. With a convincing clinical history and evidence of specific IgE, the diagnosis may be confirmed, but in certain circumstances, oral food challenge to egg may be necessary. Patients with confirmed egg allergy can then receive influenza vaccine using one of the protocols detailed in the following section.

**GENERAL RECOMMENDATIONS FOR VACCINATING EGG ALLERGIC INDIVIDUALS WITH TIV**

The recent research summarized above has shown that the influenza vaccine can be administered to egg allergic individuals via a number of approaches. Although there may be no comparative studies that advocate the superiority of one approach over another, the time has passed when the vaccine should be withheld on account of an egg allergy, and physicians should be able to choose an approach with which they are comfortable to vaccinate these patients. In general, although there is no evidence that has conclusively shown that

### Table 1. Selected Major Published Studies Involving TIV and H1N1 Vaccine Administration to Egg Allergic Individuals

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>No. of patients</th>
<th>Patients with anaphylaxis to egg</th>
<th>Method</th>
<th>Vaccine</th>
<th>Protocol</th>
<th>No. of systemic reactions reported</th>
<th>No. of patients requiring epinephrine</th>
<th>No. of mild reactions reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>James et al*</td>
<td>1998</td>
<td>83</td>
<td>27</td>
<td>Prospective, controlled</td>
<td>TIV</td>
<td>2-Step graded challenge, with skin testing</td>
<td>0</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>Chung et al*</td>
<td>2010</td>
<td>171</td>
<td>0</td>
<td>Retrospective</td>
<td>TIV</td>
<td>2-Step graded challenge, no skin testing</td>
<td>7</td>
<td>Not listed</td>
<td>29</td>
</tr>
<tr>
<td>Gagnon et al*</td>
<td>2010</td>
<td>830a</td>
<td>72c</td>
<td>Prospective, controlled</td>
<td>H1N1</td>
<td>Single dose if no history of anaphylaxis; 2-step graded challenge without skin testing if have history anaphylaxis</td>
<td>21d</td>
<td>0</td>
<td>114</td>
</tr>
<tr>
<td>Greenhawt et al*</td>
<td>2010</td>
<td>3,600b</td>
<td>Not listed</td>
<td>Prospective, controlled</td>
<td>H1N1</td>
<td>Single dose if skin test result is negative; 2-step graded challenge if skin test result is positive</td>
<td>1</td>
<td>2e</td>
<td>69</td>
</tr>
</tbody>
</table>

Abbreviation: TIV, trivalent influenza vaccine.

* Reported as patients with confirmed egg allergy.

* Reported as additional patients with unconfirmed (eg, self-reported) egg allergy.

* Defined as having experienced a severe reaction to egg involving the cardiorespiratory system OR having uncontrolled asthma.

* Having signs or symptoms in more than 2 organ systems but not meeting Brighton Collaboration criteria for anaphylaxis used in this study.

* One individual described to have symptoms inconsistent with a severe or systemic reaction used self-injectable epinephrine.
egg ovalbumin is the antigen responsible for adverse reactions to TIV in egg allergic individuals, use of the lowest ovalbumin-containing vaccine is recommended. As stated earlier, most manufacturers list their ranges of ovalbumin for their vaccine lots, and studies last year confirmed the range is accurate.

Summary Statement 3. Skin testing (prick and/or intradermal) with the influenza vaccine itself in egg allergic individuals does not reliably identify patients who are at increased risk of reacting to the vaccine because of their egg allergy. (B)

For this influenza season, the routine practice of skin testing with the TIV in patients with a history of reactions to the vaccine is no longer recommended. Although skin testing has been used successfully in the past, recent data have indicated that neither skin prick testing nor intradermal skin testing using the vaccine is predictive of one’s ability to tolerate the vaccine, and testing was not necessary to administer a booster dose from a different lot than that used for the original dose. In 2 studies published this year, the vaccine was administered (and generally well tolerated) without the use of skin testing as both a single dose and as a 2-step graded challenge. Therefore, recent evidence no longer supports the use of skin testing as both a single dose and as a 2-step graded challenge. Therefore, recent evidence no longer supports the use of skin testing as both a single dose and as a 2-step graded challenge.

VACCINATION PROTOCOLS

Summary Statement 4. Administration of influenza vaccines to egg allergic individuals should be performed by clinicians experienced in recognizing and managing anaphylaxis and in a setting equipped to manage potential adverse reactions (including anaphylaxis).

Summary Statement 5. Egg allergic patients who receive influenza vaccine should be observed for at least 30 minutes after receiving the last dose of vaccine.

Summary Statement 6. Both the single-dose and 2-dose (10%, 90%) methods are appropriate for administering influenza vaccine to egg allergic individuals.

We advocate 1 of 2 approaches for administering the TIV during the 2010-2011 season, both of which have been used to provide TIV to egg allergic individuals.

First, egg allergic individuals can receive TIV without prior skin testing to the vaccine, with the vaccine being administered via a 2-step graded challenge. Administer 10% of the age-appropriate dose followed by a 30-minute observation period. If no symptoms develop during this 30-minute period, the remaining 90% can be administered followed by a 30-minute observation for symptom development. If a reaction is observed after the administration of 10% of the appropriate dose, in most cases no further administration of the vaccine should be given.

Second, egg allergic individuals can receive TIV without prior skin testing to the vaccine as a single, age-appropriate dose without use of graded challenge. Individuals should be observed for 30 minutes after injection for evidence of a systemic reaction.

For either approach, children who need a booster dose can receive this without prior vaccine skin testing and as a single dose, regardless of whether a different lot is used for the booster dose. It is recommended that the same vaccine brand be used if possible, however.

We recommend either of these approaches as an acceptable way to provide TIV to egg allergic vaccine recipients, which should allow for flexibility for patients and physicians. Both approaches are supported by recently published evidence that showed the vaccine could be given to egg allergic populations using either of these approaches. Although the evidence is clear that a 2-step approach generally is well tolerated, there is evidence that a single dose is sufficient for some egg allergic individuals and speculation that a single dose might have been sufficient in many of these 2-step recipients.

PATIENTS WITH A HISTORY OF ANAPHYLAXIS TO EGG

Summary Statement 7. A limited number of studies suggest that influenza vaccines can be administered to patients with a history of anaphylaxis to egg without adverse effect. However, such studies have involved small numbers of patients. Because reactions to influenza vaccines in egg allergic persons have been reported, caution is still warranted in such patients, especially those who have experienced more severe adverse reactions. (B)

There is no clear consensus on how to vaccinate individuals with a history of anaphylaxis or other severe allergic reactions to egg. The American Academy of Pediatrics Red Book recommends that for administration of TIV, “Children with known severe allergic reactions (e.g., hives, angioedema, allergic asthma, or systemic anaphylaxis) to chicken or egg proteins should not receive these vaccines, because both TIV and LAIV are developed with embryonated hen eggs.” However, as indicated above, many children with such histories have received the vaccine without incident. Two studies from last year’s influenza season showed that past reaction severity is not a risk factor for vaccination with either the H1N1 vaccine or TIV and that both the H1N1 vaccine and TIV were well tolerated when administered either as a 2-step graded challenge or as a single, age-appropriate dose. In one of these studies, neither skin testing nor other allergic comorbidity (e.g., asthma, atopic dermatitis, or other food allergy) was predictive of vaccine outcome. Both studies were limited, however, by small numbers of patients with a history of severe egg allergy.

For health care professionals more comfortable administering TIV with gradually increasing doses, multistep desensitization protocols for TIV administration have been previously recommended. Present evidence, however, suggests that more than a 2-step administration is unnecessary. In general, a 2-step protocol (10%, 90%) has been well tolerated and likely is sufficient (as opposed to a 5- or 6-step protocol).
However, 2-step vs multiple-step vaccine administration methods have not been directly compared in a formal study. Multiple-step desensitization protocols remain an option for health care professionals who have a particular concern about patients who have a history of anaphylaxis to TIV, H1N1 vaccine, or another egg-containing vaccine.

**OTHER CONSIDERATIONS**

In previous years, there has been concern that there could be significant differences in ovalbumin content among vaccine lots. Thus, it was recommended that patients who needed a booster dose receive this from the same lot to which they were initially tested or be retested if a different lot was to be used. Data from last year’s vaccine lots did not reveal large differences in ovalbumin content, and one study found that no reactions resulted from deliberate administration of a different lot without testing. Repeat testing for different lots remains an option, but only for those seeking the most conservative approach. On the other hand, it is still recommended that the same vaccine brand be used for booster immunizations if possible.

It is strongly recommended that any health care professional administering vaccinations have proper resuscitative equipment available in the office to manage potential anaphylaxis and that all patients receiving a vaccine be observed for some time after vaccination. Several recent US studies have used an observation period of 30 minutes, although an earlier study used a 60-minute observation period. The Canadian study described above used a 60-minute observation period after the last dose, although this study involved a unique adjuvant in the vaccine, which may explain the time selected. In the 2 patients in this study who required epinephrine, symptoms developed within 30 minutes, although 17 additional patients reported less severe symptoms during the 60-minute interval. The choice of 30 minutes is consistent with the currently recommended observation interval for receiving subcutaneous immunotherapy.

This year (2010-2011), most manufacturers have listed an upper limit of ovalbumin content per 0.5-mL dose of TIV. Table 2 details these stated ovalbumin levels as listed in the package inserts for the various approved vaccines. This table is provided as a reference to help clarify the approximate ovalbumin content per dose and to help better guide the selection of the product to use in the egg allergic patient, according to age-recommended indications for use of the particular vaccine brand. In considering the individual vaccine product selection and the 2 approaches to administering the vaccine described above, the Canadian study provided evidence that lower-risk egg allergic patients were able to successfully receive a low ovalbumin-containing product as a single dose. Furthermore, in that same study, higher-risk patients (based on past egg allergy severity) were able to receive the same low ovalbumin-containing vaccine given as a 2-step graded challenge. Such “risk stratification” is a reasonable approach. However, in 2 studies, the authors were able to administer vaccine with higher ovalbumin content to both higher- and lower-risk patients using either the single-step or the 2-step approach, highlighting that neither approach is superior at the present time.

**CONCLUSION**

There has been tremendous growth during the past year in demonstrating that the TIV and H1N1 vaccine are safe for egg allergic individuals to receive. Although a few concepts bear further study, such as the safety of these vaccines in individuals with severe allergy to egg, it appears that most egg allergic patients can receive influenza vaccination if desired. Although no particular approach to administering the vaccine has been shown to be the safest and most effective, several methods for providing this service exist. Health care professionals should no longer withhold the influenza vaccine because a patient has egg allergy and should feel comfortable selecting from the 2 strategies outlined above for administering the influenza vaccine.

**CONTRIBUTORS**

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Table 2. Approved 2010-2010 Influenza Vaccines Ovalbumin Content Levels

<table>
<thead>
<tr>
<th>Product</th>
<th>Manufacturer</th>
<th>Age range</th>
<th>Ovalbumin content listed in package insert1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Afluria</td>
<td>CSL Biotherapies (Merck)</td>
<td>≥9 y</td>
<td>≤1 μg</td>
</tr>
<tr>
<td>Agriflu</td>
<td>Novartis</td>
<td>≥18 y</td>
<td>&lt;0.4 μg</td>
</tr>
<tr>
<td>Fluarix</td>
<td>GlaxoSmithKline</td>
<td>≥3 y</td>
<td>≤0.05 μg</td>
</tr>
<tr>
<td>FluLaval</td>
<td>ID Biomedical Corp of Quebec (GSK)</td>
<td>≥18 y</td>
<td>≤1 μg</td>
</tr>
<tr>
<td>FluMist (nasal)</td>
<td>MedImmune</td>
<td>2-49 y</td>
<td>Level not listed</td>
</tr>
<tr>
<td>Fluvirin</td>
<td>Novartis</td>
<td>≥4 y</td>
<td>≤1 μg</td>
</tr>
<tr>
<td>Fluzone, Fluzone HD</td>
<td>Sanofi Pasteur</td>
<td>≥6 mo</td>
<td>Level not listed</td>
</tr>
</tbody>
</table>

1 All levels per 0.5-mL dose.
This document was developed by a Working Group under the aegis of the Joint Task Force on Practice Parameters, which has published 26 practice parameters and updated parameters for the field of allergy/immunology (these can be found online at www.jcaai.org).

REFERENCES


Reprint requests:
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