

Establishing the Safety of Influenza Vaccine in Egg-Allergic Individuals

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Abstract

Trivalent influenza vaccine is grown in chick embryos and contains residual egg protein (ovalbumin). Historically, trivalent influenza vaccine (TIV) has been contraindicated in egg-allergic individuals (EAI) and the vaccine was withheld in many of these individuals due to the ovalbumin. However, protocols were developed that allowed EAIs to safely receive TIV, including stepwise desensitization, vaccine skin testing, and use of low ovalbumin containing vaccine. In the past 3 years, several groups have systematically disproven that EAI are at any increased risk for an allergic reaction than the general population and withholding TIV is not necessary. To date, approximately 4,315 patients have safely received 4,872 total doses of TIV, including 656 EAI with severe egg allergy (including anaphylaxis to egg) who safely received 740 doses of TIV. Thus, it is as safe to provide TIV to EAI as providing it to a non-EAI. This article will trace the evolution of this practice.

CME EDUCATIONAL OBJECTIVES

1. Understand that trivalent influenza vaccine is safe for patients with egg allergy, including patients with severe egg allergy.
2. Understand that egg-allergic patients no longer require any special precautions to safely receive trivalent influenza vaccine.
3. Recognize that the Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices advises that most egg-allergic patients can now receive trivalent influenza vaccine from their primary care physician.

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Disclosure: The author has no relevant financial relationships to disclose.

doi: 10.3928/00904481-20130619-09



Influenza vaccines, commonly known as trivalent injectable influenza vaccine (TIV), are grown on embryonated chicken eggs. For several decades, there has been concern that residual egg protein (ovalbumin) may provoke an allergic reaction in an egg-allergic individual (EAI).¹ As recently as the 2009, the Centers for Disease Control and Prevention's (CDC) Advisory Committee on Immunization Practices (ACIP) and the American Academy of Pediatrics' (AAP) Committee on Infectious Diseases (*Red Book* committee) advised that "children with known severe allergic reactions (eg, hives, angioedema, allergic asthma, or systemic anaphylaxis) to chicken or egg proteins should not receive trivalent injectable influenza vaccine."² Thus, it was commonplace to withhold TIV in EAI, or only administer it in an allergist's office after a series of risk-reducing steps such as having negative vaccine skin test and using stepwise vaccine administration involving only low ovalbumin containing TIV.^{3,4}

With the outbreak of the 2009 H1N1 influenza pandemic, a flurry of new research has re-addressed the safety of TIV in EAI. The results strongly suggest that both the H1N1 and TIV vaccines are safe, and that the risk-reducing measures are unnecessary.⁵⁻¹² Based on these data, the 2011 guidelines from the CDC's Advisory Committee on Immunization Practices (ACIP) were updated and no longer recommended withholding TIV from EAI.¹³ EAI with "only hives" after egg ingestion were advised to receive TIV at their primary care physician, provided they could be observed for 30 minutes afterward. The more severe EAI could still receive TIV, but referral to an allergist was advised for administration.^{13,14}

To date, there is published data regarding 4,315 patients who have safely received 4,872 total doses of TIV, including 656 EAI with severe egg aller-

gy (including anaphylaxis to egg) who safely received 740 doses of TIV.^{12,15} Thus, ample data exist that support the safety of providing TIV to EAI in the primary care setting. This review article will trace the evolution of this practice.

INFLUENZA VACCINATION IN FOOD-ALLERGIC CHILDREN

Approximately 294,128 hospitalizations annually are attributable to influenza A, including 21,156 occurring in children 5 years of age or younger.¹⁶ Approximately 8% of US children are food allergic, including approximately 2% with egg allergy.¹⁷ As many as 33% of food-allergic children also have comorbid asthma.¹⁸ Withholding TIV in these EAI places these children at significant risk for influenza-related morbidity.^{14,19} The benefits of influenza vaccination in asthmatic patients are well-documented and strongly supported by a recent Cochrane review.²⁰ The CDC and World Health Organization (WHO) recommend all children younger than age 5 years receive annual TIV.^{13,19}

TIV Pre-1998

Since the 1940s, data suggested some risk to EAI posed by the ovalbumin contained in TIV.^{21,22} A small 1952 study documented two systemic reactions to TIV in five patients, all of whom had positive vaccine skin tests.²³ Nine studies conducted prior to 1998 demonstrated that a moderate percentage of EAI would have positive prick or intradermal skin tests to either full-strength or dilute TIV. However, in five small studies investigating vaccine tolerance in this population, only nine of 50 EAI vaccinated between 1952 and 1992 manifested symptoms (12%).¹² A 1976 CDC surveillance of TIV-related reaction noted 11 cases of anaphylaxis, of which none were in EAI populations.²⁴

Fatality attributed to the vaccine in EAI has been rarely reported, with one known case in 1969.²⁵ From 1990 to

2005, four deaths attributed to anaphylaxis from TIV were reported, though it is not known if these occurred in EAI.²⁶ During this time, there was wide variability in the known egg content of the vaccine, which ranged from undetectable to as high as 45 mcg/mL. The egg content depended both on the manufacturer and year.²⁷ Based on these data, the *Red Book* has always issued a contraindication to EAI receiving TIV.²

Cautious Approach

In 1988, James et al⁵ conducted a landmark study pertaining to TIV safety in EAI. In a 3-year, multicenter randomized controlled trial, 83 egg-allergic children (including 27 severely EAI), and 124 control patients were vaccinated to TIV. All patients, including controls, underwent prick skin testing to full strength vaccine and received TIV as a two-step graded challenge consisting of 10% of the age appropriate dose, followed by the residual 90% after 30 minutes of observation for symptom development. Skin testing was positive in four EAI and one control; eight of 83 EAI developed mild and localized symptoms (just two patients received treatment) versus four of 123 controls with similar symptoms (one patient was treated).

There were no reactions among those with positive skin tests. The TIV ovalbumin content was measured and ranged between 0.02 mcg/L and 1.2 mcg/mL. It was concluded that EAI could be safely by a two-step graded process, and that using vaccine with ovalbumin content of less than 1.2 mcg/mL was safe.⁵

This study provided a basis for a cautious approach for the allergist to vaccinate EAI, using a two-step graded process and a vaccine with less than 1.2 mcg/mL ovalbumin.³ However, through 2009, the *Red Book* on immunization practices still recommended that EAI generally should not receive TIV.² During this time, a handful of other studies in addition to James et al⁵ evaluated an

additional 618 patients in the US, Canada, and Europe, which noted 19 mild or local reactions in published data.¹²

Pandemic and Renewed Research Interest

The onset of the 2009 H1N1 pandemic spurred several groups to re-evaluate the safety of both the H1N1 and TIV vaccines in EAIs, given the well-established benefits and a strong desire from many of these patients to receive both vaccines.

The Risk of H1N1 Influenza Vaccine

Two 2009 studies directly addressed H1N1 influenza vaccine safety. Gagnon et al⁶ performed a prospective multicenter trial conducted in Canada using an adjuvanted H1N1 influenza A vaccine (pH1N1) containing approximately 0.3 mcg/mL ovalbumin, without vaccine skin testing. They successfully vaccinated 850 EAIs with physician confirmed allergy and 393 control patients. Among the 850 EAIs, 72 had either a history of severe cardiovascular/respiratory symptoms attributable to egg or poorly controlled asthma and were vaccinated with a two-step graded challenge.

The remaining 758 EAIs received a single dose. There were 3% who developed mild symptoms within a 1-hour observation period, and an additional 13.7% reporting mild gastrointestinal symptoms or rhinitis at 24 hours after vaccination, compared with 14.7% in the control group. Based on this success, a separate group of 3,640 patients with self-reported egg allergy were vaccinated using the same protocol, with 69 patients (2%) developing symptoms consistent with an allergic reaction, including two patients requiring epinephrine (without fulfilling criteria for anaphylaxis).

This was the first study to demonstrate the safety of a single-dose approach, and that vaccine skin testing was unnecessary.⁶ This group released safety data pertaining to specific allergic

symptoms provoked by the pH1N1 vaccine. Among 95 patients with a history of reactivity to the pH1N1 (including two EAIs), they noted that reactions to pH1N1 were rare and unlikely to be IgE-mediated.²⁸

In the US, a controlled prospective study was conducted of 105 egg-allergic children and 19 non-egg-allergic controls.²⁹ All patients, including controls,

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received skin testing. Control patients and EAIs with negative vaccine skin testing received a single-dose injection, and EAIs with positive skin testing ($n = 44$) received two-step graded challenge. Only minor symptoms were reported, and nobody with a positive H1N1 skin test developed symptoms.

Positive skin tests correlated with increasing vaccine ovalbumin content, suggesting an irritant effect. There were 25 EAIs with a history of anaphylaxis attributable to egg, all of whom were vaccinated without developing symptoms (including 13 with a positive skin test). Moreover, 94 EAIs tolerated a booster from a different vaccine lot. The vaccine ovalbumin level was less than 50 ng/mL.^{29,30}

The Risk of Injectable Trivalent Influenza Vaccine

In 2009 and 2010, five studies investigated the safety of TIV in EAIs. Chung et al⁷ performed a retrospective review of 171 egg-allergic children without a history of severe reaction, all receiving a two-step protocol (similar to James et al⁵) without vaccine skin testing and concluded that that TIV was safe for non-anaphylactic egg-allergic children

without vaccine skin testing. Ovalbumin content was not measured.

Webb et al¹⁰ conducted a retrospective study of 152 patients (34 with anaphylaxis to egg) receiving 292 vaccinations, in which all 95% of patients undergoing skin testing to undiluted vaccine tested negative, and tolerated a single-dose administration (5% underwent graded-dose challenge for a positive test and tolerated the vaccine). Owens and McGinnitie⁹ conducted a retrospective review of 64 EAIs receiving TIV containing up to 1.4 mcg/mL of ovalbumin, using a two-step graded challenge without vaccine skin testing, concluding that TIV with ovalbumin at less than 1.2 mcg/mL was well tolerated.

Howe et al⁸ conducted a 5-year retrospective review of 135 patients receiving TIV from 2004 to 2009, including 28 patients without vaccine skin testing and 14 with anaphylaxis to egg, noting that vaccine skin testing was not predictive of reactivity, and that single dose administration was well-tolerated.

Lastly, DesRoches et al¹² published a large 5-year (2007-2011) retrospective series from five Canadian hospitals, as well as a prospective study from 2010 to 2012, describing a total of 367 patients who safely received 457 doses of TIV, including 132 patients (153 doses) with severe egg allergy, noting the vaccine was safe to administer without skin testing and was safe in severely EAIs.

The Risk of TIV in Severely Egg-Allergic Individuals

Most recent studies deliberately evaluated a subgroup of severely egg-allergic patients and showed this was safe. However, only two studies have specifically focused on this population. Fung et al¹¹ described a case series of 56 children (119 vaccinations) children with a history of anaphylaxis to egg who received TIV. Vaccine skin testing was performed, and if positive, a stepwise

desensitization was used for administering TIV: three or four steps in 2007, and a two-step graded challenge in 2008 and 2009). There were 15 participants with positive TIV skin tests (wheal > 3 mm), but only three localized reactions were noted in the cohort (two had positive skin testing).¹¹

Greenhawt et al¹⁵ performed a 2-year, multicenter, double-blind, randomized, placebo-controlled trial (RCT) in severely EAIs, and compared the safety of a single dose versus a two-step graded challenge. These data were supplemented by a retrospective phase investigating the same outcome.

In the RCT, 31 patients were randomly assigned to receive either a two-step graded challenge ($n = 16$) or a sham “10%” dose of saline, followed by 100% of the full, age-appropriate dose to simulate the “90%” residual of a graded challenge ($n = 17$). The retrospective phase evaluated open-label vaccination of TIV as a single vs. split-dose across the same centers. Among 143 total participants, three of 31 RCT patients reported symptoms, none of which were vaccine-related allergic reactions. No reactions occurred among the 112 retrospective patients ($n = 25$, two-step protocol; $n = 87$, single dose). Seventeen patients received TIV at their primary care provider's office.¹⁵

ADVICE FOR THE PEDIATRICIAN

Although the research summarized herein strongly indicates that providing TIV to any EAI is safe, provider implementation and comfort with new policy is not immediate. Within the allergy literature, there was a stepwise change in policy.⁴ The CDC and ACIP revised its recommendation in the summer of 2011, formally removing any language recommending that TIV be contraindicated in egg-allergic or chicken-allergic individuals. These groups recommended that EAIs with a history of developing only hives after egg ingestion could receive

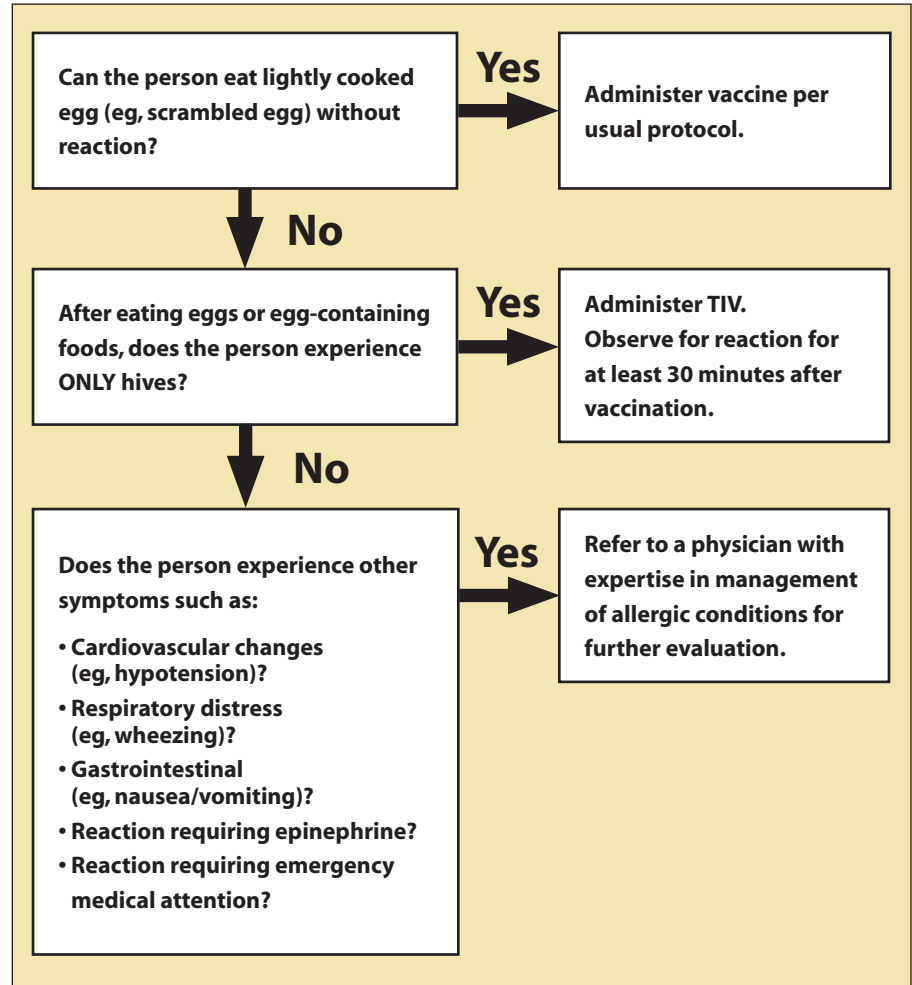


Figure 1. Recommendations regarding influenza vaccination for persons who report allergy to eggs from Advisory Committee on Immunization Practices, United States, 2012–13 influenza season. TIV = trivalent influenza vaccine. TIV = trivalent influenza vaccine. (Adapted from Grohskopf et al¹³)

TIV at their primary care provider's office if they so desired (see Figure 1).¹³ This guidance will have been re-visited at the June 2013 ACIP annual meeting and will likely change for the fall of 2013. (personal communication).

EVIDENCE-BASED GUIDE TO FLU VACCINATION AND EAI

The following summary points can help to serve as an evidence-based guide to the upcoming influenza vaccination season:

Vaccine Skin Testing

Vaccine skin testing in egg-allergic patients is a poor indicator for predict-

ing EAIs at risk for a reaction to TIV. Several studies have been safely conducted without the use of skin testing; thus, vaccine skin testing of EAIs is not recommended.^{10,14,29}

Low Ovalbumin-Containing Vaccine

There are no data suggesting that an ovalbumin content of greater than 1.2 mcg/mL is not well-tolerated. In the past, ovalbumin levels were not always disclosed, though more recently, US vaccine makers have disclosed their ovalbumin content the summer before each flu season starts. All brands of TIV available in the US now contain less than 1 mcg/mL of ovalbumin. Given that it is

unlikely future TIV will contain more than 1 mcg/mL ovalbumin, this issue is moot, and all available US TIV should be considered safe for EAI. Cell-cultured TIV is now available for EAI older than 18 years who desire this option; however, it is unnecessary.^{9,14,30,31}

Safety of Single Dose

Both single and divided dose strategies have been studied; there is no difference in outcome, irrespective of baseline severe reactivity to egg. Therefore, a single dose is sufficient.^{10,14}

TIV Safety for Severely Egg-Allergic Patients

In published studies dating back to 1998, 656 severely EAI have safely received 740 doses of TIV (one patient was noted to be included in a 1977 study). These data from both the US and Canada span open-label and controlled trials, including one double-blind, placebo-controlled, multicenter study.^{11,12,15}

Office-Based Vaccination and Observation of EAI:

Figure 1 details the decision-making process for office-based EAI vaccination and observation. These recommendations may change for the 2013 season, however. In the office setting, EAI should be observed for 30 minutes in a setting where a reaction could be assessed and treated (this is a *Red Book* recommendation for any vaccine).³² It is not recommended that EAI receive TIV at a pharmacy or other nonmedical settings, specifically because these sites cannot provide the observation.^{2,13,14}

EAI and Live-Attenuated Influenza Vaccine

There are no data evaluating the safety of this vaccine in EAI. Logically, this likely is safe, but again, until there are published studies evaluating this process, EAI should only be provided TIV.¹⁴

Non-Egg-Allergic TIV Reactions

Reactions to TIV in non-EAI are a distinct topic, and are well-described elsewhere. Patients with an apparent allergic reaction to any vaccine should be evaluated by an allergist.¹⁴

CONCLUSION

Providing TIV to an EAI is safe and no longer is contraindicated, according to the latest CDC/ACIP recommendations. This is backed by very convincing data from 10 recent studies that show significant allergic reactions to TIV are unlikely to occur in EAI, and that the risk of reaction to the vaccine is no greater when compared with the general population. Risk-reducing strategies such as low-ovalbumin containing vaccine, vaccine skin testing, and providing graded dosing do not mitigate risk and are unnecessary. EAI can safely enjoy the well-established benefits from annual TIV vaccination. ■

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