

An update on influenza vaccination in patients with egg allergy

David A. Gruenberg and Marcus S. Shaker

Dartmouth Hitchcock Medical Center, Lebanon,
New Hampshire, USA

Correspondence to David A. Gruenberg, MD, Assistant
Professor of Medicine and Pediatrics, Dartmouth
Hitchcock Medical Center, 1 Medical Center Drive,
Lebanon, NH 03766, USA
Tel: +1 603 653 3827;
e-mail: David.A.Gruenberg@hitchcock.org

Current Opinion in Pediatrics 2011, 23:566–572

Purpose of review

Egg allergy is a common problem affecting young children especially. There has been much debate over the past several decades on how to approach the subject of influenza vaccination in children with egg allergy.

Recent findings

Because of concern regarding the egg protein content in the influenza virus vaccine, pediatricians have in the past typically taken a conservative approach of avoiding influenza vaccination in egg-allergic patients. Subsequently, it was shown that the influenza vaccine could be safely administered to patients who had negative skin testing to the vaccine. Most recently, studies have demonstrated a low risk of giving the vaccine either in divided doses or as a single dose in a controlled setting without the need for skin testing.

Summary

In considering vaccination in a patient with a history of egg allergy, several factors should be weighed, including the severity of the egg allergy, the egg content of vaccines, and the setting of vaccine administration. However, it appears that the risk of anaphylaxis to the influenza vaccine in patients with egg allergy may be much lower than previously thought, suggesting that in many cases skin testing may not be necessary.

Keywords

egg allergy, influenza, vaccine reactions

Curr Opin Pediatr 23:566–572
© 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins
1040-8703

Introduction

Influenza is a common cause of vaccine-preventable morbidity and mortality. Because of annual drifts in antigenic immunogenicity, effective public health policy requires annual vaccination. Children with asthma represent one particular at-risk population that can benefit from influenza vaccination. Food allergy affects 4–6% of US children [1,2], and egg allergy is reported in 1–2% of children [3]. Association of atopic conditions including food allergy, eczema, rhinitis, and asthma defines the allergic march of childhood, and as such a significant proportion of children with asthma carry a diagnosis of egg allergy. The influenza virus vaccine contains small but variable amounts of egg protein. For this reason, severe egg allergy has been long considered a contraindication to administration of the influenza vaccine.

The 2009–2010 influenza season presented significant vaccination challenges because of the recognition of novel H1N1 influenza disease. However, with great challenges come great opportunities, and over the past 2 years renewed interest in egg allergy and influenza has

generated new data that suggest the influenza vaccine may be administered safely to patients with egg allergy in controlled settings.

Recent trends in egg allergy

Egg allergy represents one of the most common food allergies affecting very young children [4]. However, it is often self-limited, with the majority of children with egg allergy developing tolerance by late childhood [3]. Risk factors for persistence of egg allergy beyond this time point include a high initial level of egg-specific IgE, a coexisting allergy to another food, and the presence of other atopic diseases [5•]. Symptoms of egg allergy may vary significantly in their presentation and severity, ranging from life-threatening anaphylaxis to localized skin reactions including exacerbations of atopic dermatitis. However, some children who are unable to tolerate raw, scrambled, or hard-boiled eggs may sometimes be able to tolerate eggs present in baked goods that have been cooked at very high temperatures, such as muffins, cakes, and pasta containing egg. Tolerance of baked egg tended to be associated with lower skin prick test sensitivity [6]. However, it has been noted as well that

tolerance to ingestion of cooked egg may not correlate with tolerance to the egg protein present in the influenza vaccine [7[•]].

Egg content of vaccines

The intramuscular inactivated and live attenuated intranasal influenza vaccines contain micrograms of egg protein from chicken embryos. The vaccines for measles, mumps, and rubella also contain even smaller amounts of egg protein (picograms to nanograms). In addition to reactions to the egg content of vaccines, susceptible individuals may also develop IgE-mediated reactions to other components of these vaccines, such as gelatin [8[•]]. Efforts to determine the relative risk of the influenza vaccine in patients with egg allergy compared with non-allergic patients have been hampered by the fact that this vaccine has been avoided in allergic patients because of concern regarding possible reactions. To further complicate matters, different preparations of the influenza vaccine can vary widely in their egg content [9[•]]. Egg content is usually reported in micrograms of ovalbumin per dose (or per ml). The amount of ovalbumin contained in a specific influenza vaccine product is important, because the risk of an egg-allergic reaction falls when the egg vaccine content is negligible. Indeed, this was demonstrated in a 1998 multicenter clinical trial by James *et al.* [10] that suggested that patients with egg allergy can safely receive an influenza vaccine in a two-dose protocol when the vaccine preparation contains less than or equal to 1.2 µg/ml egg protein. In this study, 83 patients with egg allergy and 124 controls underwent vaccine skin prick tests and vaccination. All patients with egg allergy tolerated vaccination using a two-dose protocol. In the study, eight egg-allergic patients experienced mild adverse reactions (with symptoms including mild throat itching, cough, wheeze, small hives, and delayed local reaction) compared with four controls (with symptoms including local erythema, emesis, and urticaria). After 1 month, 34 egg-allergic patients subsequently received a single, full-booster dose without any adverse reactions.

Unfortunately, for many years, vaccine manufacturers did not state the egg protein content of vaccines, but more recently most manufacturers now provide maximum ovalbumin content information on package inserts. Although, prior to 1994, independent evaluation of ovalbumin content was quite variable and as high as 42.4 µg/ml [11], more recent studies have demonstrated much lower ovalbumin content in influenza vaccines. The stated ovalbumin content in Food and Drug Administration-approved 2009–2010 seasonal influenza vaccines has varied depending on the manufacturer [12^{••},13[•]]. However, Waibel and Gomez [13[•]] evaluated actual ovalbumin content of 2009–2010 influenza vaccines and demonstrated that actual ovalbumin content

Key points

- Many patients with egg allergy would benefit from receiving the influenza vaccine, especially if asthma or other comorbid illnesses are present.
- Although children with egg allergy are at risk for allergic reactions to the influenza vaccine, as it contains small amounts of egg protein, the incidence of allergic reactions to the vaccine in these patients may be much smaller than previously thought.
- The benefits of vaccination should be weighed against the risks, which include potential allergic reactions in patients with egg allergy. Patients may be at increased risk of reactions to brands that contain higher ovalbumin content.
- Skin testing to the influenza vaccine is limited by time, patient discomfort, and false-positive reactions, which are particularly common with intradermal testing.
- Patients who have a history of egg allergy but no history of allergic reactions to the influenza vaccine can receive the vaccine in an allergy clinic as either a single dose or in divided doses without the need for prior skin testing.

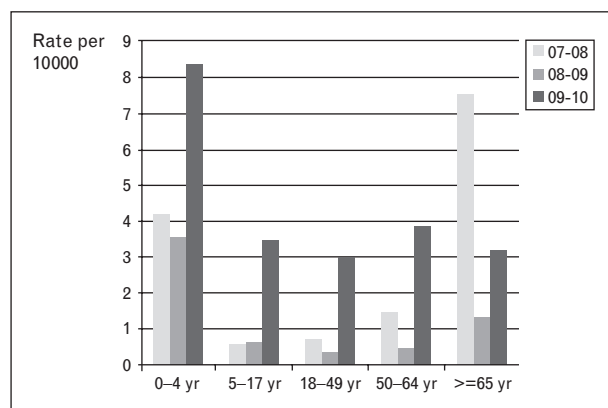
of specific lots tested was much lower than levels stated on package inserts. In early 2010, these investigators demonstrated that the actual ovalbumin content of brands and lots of vaccines tested from manufacturers claiming a maximum ovalbumin content of 2 µg/ml ranged from 0.018 to 0.41 µg/ml for injectable vaccines. The ovalbumin content from the manufacturer claiming a maximal ovalbumin content of 10 µg/ml (Fluzone, Sanofi Pasteur, Swiftwater, Pennsylvania, USA) ranged from 0.064 to 1.411 µg/ml. There have been no studies to date comparing the risk of anaphylaxis to the intramuscular versus the intranasal vaccines; however, measured levels of ovalbumin in nasal influenza vaccines were found to be lower than in injectable vaccines, ranging from 0.001 to 0.007 µg/ml. Data reported by Waibel and Gomez were subsequently confirmed in a similar study by Li *et al.* published in June 2010. In this subsequent report, median ovalbumin concentration of seasonal vaccine was 350 ng/ml (range 0.5–1002). The Fluzone vaccine (Sanofi Pasteur) demonstrated higher ovalbumin levels than other brands [9[•]]. These are important reports, because, although specific lots may still have higher ovalbumin content, this study suggests that ovalbumin content is likely below the 1.2 µg/ml level associated with tolerance in the study by James *et al.* [10]. These studies also highlight the need for more accurate labeling of vaccine ovalbumin content.

Risks associated with influenza infection

According to the most recent estimates, 15 and 40% of preschool and school aged children become infected with

the influenza virus each year, although not all seek medical care. The risk of serious complications is increased in children under the age of 4 years and in children who have asthma [14^{••}]. These include asthma exacerbations, pneumonia, and, rarely, death [15]. During the 2009–2010 influenza season, the rate of hospitalization for influenza infection in children under age 5 was greater than twice that of other age groups surveyed (Fig. 1) [16[•],17[•]]. Moreover, the 2009 pandemic influenza virus was associated with a higher morbidity and mortality among children than the usual seasonal influenza virus, as well as a substantial healthcare and economic burden [18[•]]. In contrast to seasonal influenza, most severe illness attributed to the H1N1 pandemic occurred in children and adults under the age of 65 [19^{••}]. Vaccination against the H1N1 and seasonal influenza virus is therefore crucial in preventing many of the complications associated with influenza infection. The Advisory Committee on Immunization Practices (ACIP) published 2010 recommendations for prevention and control of influenza with vaccines in August 2010 [14^{••}]. This report provided an excellent summary of annual influenza epidemics and specific recommendations on vaccinations. The American Academy of Pediatrics (AAP) policy statement on recommendations for prevention and control of influenza in children for the 2010–2011 influenza season was also published online in August [16[•]]. The AAP and ACIP recommended annual vaccination for persons aged 6 months and older for the 2010–2011 influenza season.

Figure 1 Cumulative rates of hospitalization associated with laboratory-confirmed influenza virus infections compared over 3 years



During the 2007–2008 influenza season, the highest rates of hospitalization occurred in the elderly. Subsequent seasons saw a decrease in hospitalizations in the elderly and a sharp increase in hospitalizations in infants and young children during the 2009–2010 season. ■, 2007–2008; ■, 2008–2009; ■, 2009–2010. Reproduced with permission from [16[•]].

Risks of vaccination in egg-allergic patients

Anaphylaxis to the influenza vaccine is rare, occurring in approximately one in a million persons receiving the vaccine [14^{••}]. Non-IgE-mediated reactions such as febrile seizures, myalgias, and local swelling occur with much greater frequency. A nationwide survey of 48 million individuals residing in the USA during the 1976–1977 influenza epidemic identified only 11 cases of anaphylaxis. However, the authors thought that under-reporting of reactions following vaccination may have made this data less reliable [20]. From 1990 to 2005, during which 747 million doses of influenza vaccine were administered, only four reports of death from anaphylaxis to the influenza vaccine were reported that identified the influenza vaccine as the cause. It is unclear whether these may have been due to egg allergy, as no information on a history of egg allergy was provided [21]. There is a single case report from 1969 of fatal anaphylaxis in a child with egg allergy following administration of the influenza vaccine [22].

History of the controversy

Concern for influenza vaccination in egg-allergic children increased following the anaphylactic death after influenza immunization of a child known to be allergic to egg in a Seattle physician's office in 1969 [22]. However, as far back as the 1970s small studies had suggested that patients with a history of systemic reactions to eggs could safely receive the influenza vaccine after appropriate evaluation, particularly if intradermal skin tests to the vaccine were negative. Bierman *et al.* [22] studied 142 children aged 3–18 years with allergies to chickens, eggs, or feathers and found that children with negative influenza vaccine prick (full strength) and intradermal (with a 1:100 dilution) skin test results appeared to tolerate vaccination without any immediate reaction. Of 130 children immunized, three developed delayed reactions to the vaccine. As mentioned previously, influenza vaccines studied before 1994 likely contained higher amounts of ovalbumin [11].

Murphy and Strunk [23] evaluated a small cohort of six children with documented egg allergy and negative skin prick (1:10 dilution) but positive intradermal (1:100 dilution) skin tests to the influenza vaccine in 1985. Patients were immunized with a multidose (six intramuscular injections) approach. Most patients tolerated the procedure without reaction. One patient developed wheezing after the first administration but tolerated a second immunization with the same protocol without difficulty. In 1998, the study by James referenced above suggested that egg-allergic patients could receive influenza vaccine containing less than or equal to 1.2 µg/ml in a two-step protocol; still, concern existed that available

vaccine ovalbumin content was either unknown or above this threshold. A practice parameter from 2002 suggested an algorithm performing skin prick tests (full strength) followed by intradermal skin tests diluted 1:100 volume/volume to the influenza vaccine in patients with a history of egg allergy and proceeding with vaccination if these were negative. If skin testing was positive, there was an option to give the vaccine in divided dose (either a two-step approach if the vaccine content was known to be less than or equal to 1.2 µg/ml or a multidose protocol if the ovalbumin content was unknown or was above this threshold) [11]. This continued to be the prevailing recommendation for children with strongly suspected egg allergy through the end of 2009 [24]. However, a 2007 investigation by Wood *et al.* [25] concluded that, while false-positive reactions to skin prick testing were rare, intradermal testing with 1:10 dilutions of influenza vaccine would be of limited value because of high rates of false-positive reactions. The authors evaluated 20 healthy adult volunteers with no history of food, drug, or vaccine allergy. Volunteers underwent prick and intradermal skin testing to vaccine dilutions. Influenza vaccine intradermal testing at 1:100 dilutions was associated with a significant rate of false-positive reactions (15% false-positive rate).

Recent developments

Because of concern about false-positive reactions with intradermal skin testing to the influenza vaccine, investigators evaluated whether epicutaneous skin testing alone might be adequate. In 2008, 88 asthmatic children (44 with a history of egg allergy and 44 without) with negative influenza skin prick tests received the virosomal adjuvanted influenza vaccine as a single dose. No immediate or delayed adverse events were observed [26].

In 2009, the demand for influenza vaccine testing increased with the onset of the 2009 H1N1 pandemic. Increased interest in providing influenza vaccine to children with egg allergy prompted the investigation of alternative testing methods. Evidence of irritant skin test vaccine responses, combined with data suggesting actual ovalbumin content may be much lower than stated content in vaccines, led to revised recommendations for vaccinating egg-allergic patients. Kelso [27[•]] argued for a less conservative approach in an editorial appearing in the *Journal of Allergy and Clinical Immunology* in April 2010, suggesting that patients with less severe egg allergy could receive a vaccine with a stated ovalbumin content of less than 2 µg/ml as a single dose without prior vaccine testing. Greater caution was recommended if ovalbumin content was above this threshold. Questions remained regarding the safety of the intranasal influenza vaccines, as exposure is through the nasal mucosa rather than intramuscular injection. It was emphasized that immu-

nization in this group of patients should take place in a setting in which personnel and equipment are available to recognize and treat anaphylaxis.

Several studies published during the previous year suggest that influenza vaccination may be well tolerated in selected patients with a history of egg allergy. In May 2010, Chung *et al.* [28^{••}] published a retrospective chart review of 171 children which suggested that egg-allergic children could receive influenza vaccine without skin testing. Patients were 6 months to 18 years old with documented egg allergy. Ninety-seven percent [95% confidence interval (CI) 91.3–99.0] of patients were able to tolerate the influenza vaccine in two graded doses (10 and 90%) without serious adverse reactions. This number did not differ significantly among children who had skin testing prior to vaccine administration and those who did not undergo skin testing. Thirty-six patients experienced adverse reaction (seven systemic reactions including wheezing, eczema exacerbation, or hives on the face or chest). Selection bias could not be excluded because of the retrospective nature of the study, and patients with histories of recent egg-induced anaphylaxis were not included in the study. Despite these limitations, a 3–5% reaction rate was reported.

In August 2010, Gagnon *et al.* [29^{••}] published the experience of the Quebec Ministry of Health and Social Services during the 2009–2010 H1N1 pandemic. A prospective observational study was conducted in patients with confirmed egg allergy. Patients were enrolled at five Canadian sites and reaction rates to H1N1 vaccination were compared with controls. Patients with egg allergy with a history of respiratory or cardiovascular reactions after egg ingestion were vaccinated in two divided doses (10 and 90%), but other patients received a single dose. Among 830 patients with egg allergy, 9% received the two-step method. No anaphylactic reactions were reported. Nine patients experienced allergic reactions (symptoms included hives, abdominal pain, hoarse voice, sensation of throat closure, and wheezing). Subsequently, more than 3600 children with egg allergy were vaccinated (two patients received epinephrine for symptoms compatible with allergy following vaccination).

A study published by Greenhawt *et al.* [30[•]] in November 2010 demonstrated that skin testing was unnecessary prior to vaccination and that lot-to-lot variation was unlikely to be a significant concern. The authors conducted a prospective controlled trial of H1N1 vaccination between 105 egg-allergic patients and 19 controls. Prick and intradermal skin testing was positive in 2.4 and 33.1% of 124 patients, respectively. Patients with negative skin tests received a single dose of H1N1 vaccination, whereas those with positive skin tests received vaccination in a two-step protocol (10 and 90%). Booster vaccine, if

required, was given as a single dose from a different lot (but same manufacturer) without prior testing. No significant reactions resulted from either method of vaccination or subsequent booster doses. The authors concluded that H1N1 vaccine could be administered to egg-allergic children without prior skin testing or graded challenge.

In January 2011, Owens and MacGinnitie [31[•]] published the results of a retrospective chart review of 64 egg-allergic patients who received higher ovalbumin content vaccines. The Sanofi Pasteur seasonal (Fluzone) and H1N1 influenza vaccines were given to egg-allergic children using a two-step protocol (10 and 90%). Four mild allergic reactions occurred among 64 patients who received 96 total vaccinations, resulting in a reaction rate of 6.2% of patients (95% CI: 4.4–7.8) and 4.2% of vaccinations (95% CI 3.4–5.0). No patients had anaphylaxis and all reactions were limited to cutaneous symptoms of urticaria or erythema. Three of sixty-four patients reacted to the 10% dose and did not receive the subsequent 90% vaccine dose. Although the ovalbumin vaccine content of the product used in this study is higher than other brands, it should be noted that it was still likely lower than 1.2 µg/ml [9[•],13[•]].

In summary, this constellation of studies suggests that serious allergic reactions to the influenza vaccine are uncommon even in patients with documented egg allergy. Skin testing was likely to lead to false-positive reactions, especially when intradermal skin testing was used. Vaccination may be administered in one-step or two-step protocols in a closely monitored setting without the need for prior skin testing, and severe adverse reactions were rare.

Most recent recommendations

With the intensity of investigations over the last year, several themes have emerged. It appears skin testing to influenza vaccine is associated with a significant rate of irritant reactions. Furthermore, influenza vaccine skin testing does not appear to predict tolerance to the influenza vaccine. In October 2010, the American Academy of Allergy, Asthma, and Immunology (AAAAI) published an open letter regarding the administration of influenza vaccine to egg-allergic recipients on the society internet site (www.aaaai.org). The AAAAI recommended that influenza vaccine could be successfully administered to egg-allergic individuals via a number of approaches. Use of the lowest ovalbumin containing vaccine was recommended. The routine practice of skin testing to influenza vaccine was no longer recommended; however, it may be used in 'special cases ... as an extra level of caution, though there is no current evidence that has shown skin testing under such settings is necessary or predictive of outcome'. The option of either a single dose or a 10 and

90% two-step dose challenge (second dose after 30 min if first dose is tolerated) was recommended with equipoise noted between each (unless the patient has a history of anaphylaxis to egg, in which case a two-step approach was favored over a five or six multistep protocol). Patients should be observed 30 min after the last dose. For any provider administering vaccinations, it was stressed that proper resuscitative equipment needs to be available in the office to manage potential anaphylaxis [32].

It should be noted that current influenza vaccine recommendations in egg-allergic patients apply only to this particular clinical situation. These recommendations do not apply to patients with a history of allergic reactions to the influenza vaccine itself or to another ingredient of the vaccine besides egg and patients with allergic reactions to other vaccines or their ingredients. The reader is referred to the Adverse Reactions to Vaccines Practice Parameter published by the American College of Allergy, Asthma, and Immunology and the AAAAI for additional information regarding such situations [33].

In January 2011, a focused practice parameter update was published regarding the administration of influenza vaccine to egg-allergic recipients. The routine practice of skin testing was no longer recommended. Both the two-dose (10 and 90%) and single-dose methods were recommended as appropriate for providing influenza vaccine to egg-allergic individuals. Caution was recommended when vaccinating patients with a history of anaphylaxis or where the severity of their clinical reaction was uncertain, particularly when the ovalbumin content of the vaccine is unknown. Consultation with an allergist experienced in food allergy and anaphylaxis was strongly recommended in such situations. For patients requiring a booster dose, it was recommended the same manufacturer be used but the same vaccine lot is not required. If a product from the same manufacturer is not available, it may be prudent to take the same precautions as with an initial dose. A monitoring period of 30 min following vaccination was recommended. Which approach is chosen (two vs. single dose) is left to the discretion of the healthcare provider in circumstances in which previous egg-allergic reactions have not involved anaphylaxis. Again, appropriate preparedness to treat an anaphylactic reaction was recommended [34^{••}].

Although it is intuitive to choose an influenza vaccine with the lowest stated ovalbumin content, this decision may be made more difficult by age-specific label limitation on specific vaccine brand indications. For instance, in the 2010–2011 season, Fluzone (Sanofi Pasteur) was the only product approved in children 6 months to 3 years of age. At 3 years of age, Fluarix (GlaxoSmithKline, Brentford, UK) is approved for use, whereas the Novartis product Fluvirin was approved for patients 4 years of

Table 1 Comparison of available influenza vaccines for the 2010–2011 season

Manufacturer	CSL Behring	GlaxoSmithKline	MedImmune	Novartis		Sanofi Pasteur		
Brand	Afluria	Fluarix	FluLaval	FluMist	Fluvirin	Agriflu	Fluzone	Fluzone high dose
Ovalbumin content (μg/dose) ^a	Low	Low	Low	Low	Low	Low	Higher	Higher
Manufacturer's claims ^b	≤1	≤0.05	≤1	<0.24	≤1	<0.4	<5	<1.6
Independent assays ^c	0.009–0.011	<0.025	<0.05	<0.001–0.004	<0.025		<0.1–0.711	

With the exception of Fluzone, available vaccines contained low amounts of ovalbumin (less than or equal to 1 $\mu\text{g}/\text{dose}$). However, Fluzone was the only vaccine approved for children under 2 years of age and for children less than 3 years of age with asthma. This presented a particular challenge for young children with egg allergy, particularly when symptoms of asthma were also present. Reproduced with permission from [36*].

^aPer 0.5-ml dose, except FluMist per 0.2-ml dose.

^bPer package inserts, except FluMist and Fluzone and Fluzone High-Dose by personal communication.

^cOf 2009–2010 formulations.

age and older. Afluria (CSL, Parkville, Victoria, Australia) had a lower ovalbumin content (labeled ovalbumin content $< 1 \mu\text{g}/\text{ml}$) and was initially approved for persons aged 6 months and older; however, the vaccine was subsequently recommended for individuals 9 years and older because of an increased risk of febrile seizures [35*]. Fluvirin (labeled ovalbumin content $< 1 \mu\text{g}/\text{ml}$) also had lower ovalbumin content and Fluarix had ultra-low ovalbumin content (labeled ovalbumin content $< 0.05 \mu\text{g}/\text{ml}$), but concern existed for an attenuated immune response to Fluarix and Fluvirin in children younger than 3 and 4 years of age, respectively. But, while Fluzone may have provided a greater antibody response in children under 3 years of age, it remained the vaccine with the highest ovalbumin content [36*]. Still, independent assays indicated that actual Fluzone content may have been less than 1.4 $\mu\text{g}/\text{ml}$, and the study by Owens and MacGinnitie [31*] discussed earlier provided some level of reassurance in using this product. A summary of 2010–2011 influenza vaccine age-specific indications and ovalbumin content is provided in Table 1.

Conclusion

Recent studies and protocols have allowed us several options for administration of the influenza vaccine in egg-allergic patients. The option of forgoing skin testing in favor of a two-step or single-dose protocol may save significant time and discomfort for children requiring the vaccination and may avoid some of the false-positive reactions that may occur especially with intradermal skin testing. It has been suggested that influenza vaccine in egg-allergic patients be administered in an allergy/immunology clinic or other specialty care clinic [37]. In the case of a child who has documented egg allergy but no history of systemic symptoms or anaphylaxis, vaccination in a primary care setting may be feasible in the future if the clinic is equipped to properly monitor and treat reactions if they occur. However, in the setting of more severe egg allergy, vaccination in the allergy/immunology clinic is indicated. Further studies are needed to address these issues as well as to provide further evidence regarding the risks and benefits of influenza vaccination in patients with egg allergy.

Acknowledgements

Conflicts of interest

There are no conflicts of interest

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

- 1 Ostblom E, Wickman M, van Hage M, Lilja G. Reported symptoms of food hypersensitivity and sensitization to common foods in 4-year-old children. *Acta Paediatr* 2008; 97:85–90.
- 2 Sampson HA, Mendelson L, Rosen JP. Fatal and near-fatal anaphylactic reactions to food in children and adolescents. *N Engl J Med* 1992; 327: 380–384.
- 3 Savage JH, Matsui EC, Skripak JM, Wood RA. The natural history of egg allergy. *J Allergy Clin Immunol* 2007; 120:1413–1417.
- 4 Osterballe M, Hansen TK, Mortz CG, *et al*. The prevalence of food hypersensitivity in an unselected population of children and adults. *Pediatr Allergy Immunol* 2005; 16:567–573.
- 5 Boyce JA, Assa'ad A, Burks AW, *et al*. Guidelines for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel. *J Allergy Clin Immunol* 2010; 126 (6 Suppl):S1–S58.
- This is a thorough review of multiple topics pertaining to food allergies as well as related syndromes such as eosinophilic gastrointestinal diseases, atopic dermatitis, and food protein induced enterocolitis syndrome.
- 6 Lemon-Mule H, Sampson HA, Sicherer SH, *et al*. Immunologic changes in children with egg allergy ingesting extensively heated egg. *J Allergy Clin Immunol* 2008; 122:977 e1–983 e1.
- 7 Settipane RA. Management of influenza vaccination in patients with suspected egg allergy. *Med Health R I* 2010; 93:57–59.
- This is a brief but informative review of current recommendations for influenza vaccination, including a protocol for graded challenges.
- 8 Kelso J. Allergic reactions to vaccines. In: Adkinson N, editor. *UpToDate*. Waltham, MA: UpToDate; 2011.
- This is a thorough overview of potential side-effects of vaccines, both allergic and nonallergic.
- 9 Li JT, Rank MA, Squillace DL, Kita H. Ovalbumin content of influenza vaccines. *J Allergy Clin Immunol* 2010; 125:1412–1413; author reply 1413–1414.
- This letter to the editor compares egg protein content of several vaccines from different companies, noting the highest content in the Sanofi Pasteur product Fluzone.
- 10 James JM, Zeiger RS, Lester MR, *et al*. Safe administration of influenza vaccine to patients with egg allergy. *J Pediatr* 1998; 133:624–628.
- 11 Zeiger RS. Current issues with influenza vaccination in egg allergy. *J Allergy Clin Immunol* 2002; 110:834–840.
- 12 Kelso J. Influenza vaccination in individuals with egg allergy. In: Sicherer SH, editor. *UpToDate*. Waltham, MA: UpToDate; 2011.
- This article contains an excellent summary of the various approaches that have been used regarding vaccination in the egg-allergic population.
- 13 Waibel KH, Gomez R. Ovalbumin content in 2009 to 2010 seasonal and H1N1 monovalent influenza vaccines. *J Allergy Clin Immunol* 2010; 125:749–751; 751.e1.
- This is a nice review of egg content in vaccines and its potential clinical significance.

- 14 Fiore AE, Uyeki TM, Broder K, *et al.* Prevention and control of influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* 2010; 59:1–62.
This article summarizes the CDC's recommendations regarding the use of the influenza vaccine, including updated information on specific populations, such as young children and the elderly, who may benefit from vaccination.
- 15 Silvennoinen H, Peltola V, Lehtinen P, *et al.* Clinical presentation of influenza in unselected children treated as outpatients. *Pediatr Infect Dis J* 2009; 28:372–375.
- 16 Diseases COI. Policy statement recommendations for prevention and control of influenza in children, 2010–2011. *Pediatrics* 2010; 126:1–11.
This is an excellent overview of issues pertaining to use of the influenza vaccine. The first figure highlights a sharp increase in hospitalizations for influenza infection in children in contrast to the elderly.
- 17 CDC. Update: influenza activity – United States, 2009–10 season. *MMWR Morb Mortal Wkly Rep* 2010; 59:901–908.
This article contains an excellent summary of epidemiological data pertaining to influenza virus infection.
- 18 Kumar S, Havens PL, Chusid MJ, *et al.* Clinical and epidemiologic characteristics of children hospitalized with 2009 pandemic H1N1 influenza A infection. *Pediatr Infect Dis J* 2010; 29:591–594.
This is a retrospective chart review of hospitalized patients with laboratory-confirmed 2009 H1N1 infections.
- 19 Bautista E, Chotpitayasunondh T, Gao Z, *et al.* Clinical aspects of pandemic 2009 influenza A (H1N1) virus infection. *N Engl J Med* 2010; 362:1708–1719.
This review raises several interesting points regarding the differences in persons affected by the H1N1 pandemic in contrast to seasonal influenza, perhaps most importantly the increase in serious illness among children and nonelderly adults infected with the H1N1 virus.
- 20 Retalliau HF, Curtis AC, Storr G, *et al.* Illness after influenza vaccination reported through a nationwide surveillance system, 1976–1977. *Am J Epidemiol* 1980; 111:270–278.
- 21 Vellozzi C, Burwen DR, Dobardic A, *et al.* Safety of trivalent inactivated influenza vaccines in adults: background for pandemic influenza vaccine safety monitoring. *Vaccine* 2009; 27:2114–2120.
- 22 Bierman CW, Shapiro GG, Pierson WE, *et al.* Safety of influenza vaccination in allergic children. *J Infect Dis* 1977; 136 (Suppl):S652–S655.
- 23 Murphy KR, Strunk RC. Safe administration of influenza vaccine in asthmatic children hypersensitive to egg proteins. *J Pediatr* 1985; 106:931–933.
- 24 Rank MA, Li JT. Clinical pearls for preventing, diagnosing, and treating seasonal and 2009 H1N1 influenza infection in patients with asthma. *J Allergy Clin Immunol* 2009; 124:1123–1126.
- 25 Wood RA, Setse R, Halsey N. Irritant skin test reactions to common vaccines. *J Allergy Clin Immunol* 2007; 120:478–481.
- 26 Esposito S, Gasparini C, Martelli A, *et al.* Safe administration of an inactivated virosomal adjuvanted influenza vaccine in asthmatic children with egg allergy. *Vaccine* 2008; 26:4664–4668.
- 27 Kelso J. Administration of influenza vaccines to patients with egg allergy. *J Allergy Clin Immunol* 2010; 125:800–802.
This editorial contains an excellent summary of approved influenza vaccines, including their stated ovalbumin content.
- 28 Chung EY, Huang L, Schneider L. Safety of influenza vaccine administration in egg-allergic patients. *Pediatrics* 2010; 125:e1024–e1030.
This is a retrospective chart review of pediatric patients with egg allergy who had received the influenza vaccine and/or had skin testing performed to the vaccine.
- 29 Gagnon R, Primeau MN, Des Roches A, *et al.* Safe vaccination of patients with egg allergy with an adjuvanted pandemic H1N1 vaccine. *J Allergy Clin Immunol* 2010; 126:317–323.
This study investigated 830 patients with confirmed egg allergy who were vaccinated using either a single dose or divided dose (10% followed by 90%) protocol.
- 30 Greenhawt MJ, Chernin AS, Howe L, *et al.* The safety of the H1N1 influenza A vaccine in egg allergic individuals. *Ann Allergy Asthma Immunol* 2010; 105:387–393.
This prospective trial suggests that the H1N1 vaccine can be administered to egg-allergic children without prior skin testing or graded challenge dosing.
- 31 Owens G, MacGinnitie A. Higher-ovalbumin-content influenza vaccines are well tolerated in children with egg allergy. *J Allergy Clin Immunol* 2011; 127:264–265.
This study suggests that, even when patients with egg allergy are given vaccines containing higher amounts of egg protein, the rates of severe allergic reactions tend to be low, implying that the benefits of vaccination may outweigh the risk.
- 32 Greenhawt MJ, Li JT. Administering influenza vaccine to egg allergic recipients. 2010. www.aaaai.org. [Accessed October 2010]
- 33 Kelso J, Li JT. Adverse reactions to vaccines. *Ann Allergy Asthma Immunol* 2009; 103:S1–S14.
- 34 Greenhawt MJ, Li JT. Administering influenza vaccine to egg allergic recipients: a focused practice parameter update. *Ann Allergy Asthma Immunol* 2011; 106:11–16.
This important practice parameter suggests that even patients with severe egg allergy may be challenged with the vaccine without the need for skin testing.
- 35 CDC. Update: recommendations of the Advisory Committee on Immunization Practices (ACIP) regarding use of CSL seasonal influenza vaccine (Afluria) in the United States during 2010–11. *MMWR Morb Mortal Wkly Rep* 2010; 59:989–992.
In addition to reviewing Afluria specifically, this article contains a useful chart comparing different vaccine preparations in terms of their methods of administration.
- 36 Kelso JM. Administration of influenza vaccines to patients with egg allergy: update for the 2010–2011 season. *J Allergy Clin Immunol* 2010; 126:1302–1304.
This thoughtful editorial includes a useful table with information on the ovalbumin content and potential side-effects of different brands of influenza vaccines.
- 37 Erlewyn-Lajeunesse M, Brathwaite N, Lucas JS, Warner JO. Recommendations for the administration of influenza vaccine in children allergic to egg. *BMJ* 2009; 339:912–915.