

Administering influenza vaccine to egg-allergic persons

Expert Rev. Vaccines 13(8), 1049–1057 (2014)

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The most serious form of type I or IgE-mediated hypersensitivity reaction is anaphylaxis. A standardized case definition of anaphylaxis as an adverse event after immunization has been developed. Such reactions to vaccines, including influenza vaccine, are rare but potentially life-threatening. Until recently, all influenza vaccines were manufactured in eggs. Residual egg protein in the vaccines was thought to pose a risk to egg-allergic vaccine recipients. However, a large number of recent studies have demonstrated that egg-allergic recipients are no more likely than those without egg allergy to suffer such reactions. Published guidelines have been updated to recommend that patients with egg allergy receive annual influenza vaccination. Any patient who has an anaphylactic reaction to influenza vaccine should be carefully evaluated by an allergist for guidance on subsequent immunization.

KEYWORDS: allergy • egg allergy • hypersensitivity • immunization • influenza • vaccination

Anaphylaxis

Immunologic hypersensitivity describes an inappropriate or exaggerated immune response to an antigen or allergen. Such reactions are divided into four types, with type I or IgE-mediated hypersensitivity being thought of most often as allergy. In this type of hypersensitivity, exposure to an antigen in an immunologically predisposed person results in the production of IgE antibody directed against that specific antigen, which, given such a response, would now be termed an allergen. This IgE antibody becomes bound to mast cells, such that subsequent exposure to the allergen can bind to the mast cell-bound IgE triggering mast cell degranulation with the release of histamine and other mediators, leading to a clinical allergic reaction. The most serious form of IgE-mediated hypersensitivity is anaphylaxis, a widely accepted definition of which is ‘a serious allergic reaction that is rapid in onset and may cause death’ [1]. The clinical syndrome of anaphylaxis can, however, be brought on by non-IgE-mediated mast cell degranulation as well.

Anaphylaxis after immunization

The Brighton Collaboration has developed standardized case definitions for various adverse

events following immunization [2], including anaphylaxis [3]. This definition includes the elements of sudden onset, rapid progression and the involvement of multiple organ systems typically affected by mast cell degranulation, specifically dermatologic/mucosal, cardiovascular, respiratory and gastrointestinal. The definition further distinguishes three levels of diagnostic certainty, level 1 being more specific but less sensitive and level 3 being less specific but more sensitive. Level 1 of diagnostic certainty requires dermatological and cardiovascular and/or respiratory symptoms. Level 2 requires cardiovascular and respiratory symptoms, or cardiovascular or respiratory symptoms and symptoms involving at least one other system. Level 3 requires less severe cardiovascular or respiratory symptoms and symptoms from different systems/categories.

Incidence of anaphylaxis after vaccination

There are several ways to estimate the incidence of various adverse events following immunization. The Vaccine Adverse Event Reporting System (VAERS) passively receives reports by providers or patients of such events. A review of reports to VAERS over a 10-year period from 1991 through 2001, during which

1,903,383,258 doses of vaccines were distributed, found 452 of 128,717 reports (0.4%) that described 'anaphylactoid' reactions [4]. Thus, 0.2 per million vaccine doses distributed resulted in a report of such a reaction. The Vaccine Safety Datalink (VSD) project actively monitors over 9 million members enrolled in several large managed care organizations for adverse events following immunization. A VSD evaluation of 7,644,049 vaccine doses administered to 2,226,907 children and adolescents from 1991 to 1997 revealed five cases of potential vaccine-associated anaphylaxis or 0.65 cases per million doses [5].

Incidence of anaphylaxis after influenza vaccination

A VSD report on the administration of 4,512,366 H1N1 and seasonal influenza vaccine doses during the 2009–2010 influenza season found four cases of anaphylaxis, or 0.9 per million doses [6]. The manufacturers of adjuvanted monovalent H1N1 influenza vaccines distributed in 42 countries (excluding the USA) in 2009 and 2010 reviewed a database of reactions reported by health care providers, regulatory agencies and consumers [7]. At least 30 million doses were administered. The Brighton Collaboration definitions of anaphylaxis were applied. The calculated rate of anaphylactic reactions was 1.9 per million doses. A review of VAERS reports after the distribution of 127,075,320 doses of monovalent H1N1 influenza vaccines in the USA in 2009 and 2010 using Brighton Collaboration criteria found an anaphylaxis rate of 0.8 per million doses [8].

Fatal anaphylaxis after influenza vaccination

A review of 18,245 reports to VAERS regarding adults over a 15-year period from 1990 through 2005, during which nearly 750 million doses of influenza vaccine were distributed, included 35 reports of death on the day of vaccination, four of which listed anaphylaxis as the cause, although no additional details were provided [9]. The Vaccine Injury Compensation Program receives claims of injury after vaccination. Over a 10-year period from 2000 through 2009, the Vaccine Injury Compensation Program received a single claim of anaphylaxis after influenza vaccine involving a geriatric female with hypertension who developed tongue swelling, hypotension and respiratory arrest 2 min after receiving an influenza vaccine who died despite receiving three doses of epinephrine and defibrillation [10]. This case was judged to meet level 2 of diagnostic certainty for anaphylaxis by Brighton Collaboration criteria.

Vaccine nomenclature

Injectable inactivated influenza vaccine has typically contained three strains of influenza virus, two influenza A strains and one influenza B strain, and thus termed trivalent influenza vaccine [11]. Some influenza vaccines now contain four strains of influenza virus, two A and two B, and are thus quadrivalent. The abbreviation TIV has been replaced with the new abbreviation IIV for inactivated influenza vaccine. The inactivated vaccines which contain three strains are termed IIV3 and those that contain four strains are termed IIV4. Intranasally

administered live attenuated influenza vaccine is a quadrivalent vaccine and termed LAIV4.

The majority of influenza vaccine viruses, including LAIV, are grown in eggs. However, two new non-egg-based methods of inactivated influenza vaccine production have been developed [11]. One (FLUCELVAX[®], Novartis, Cambridge, MA, USA) involves the production of influenza virus in cell culture and is available as a trivalent formulation termed ccIIV3. It is approved for recipients 18 years of age and older. The other (Flublok[®], Protein Sciences, Meriden, CT, USA) involves the production of recombinant hemagglutinin protein in an insect cell line and is available as a trivalent formulation termed RIV3. It is approved for patients aged 18–49 years.

Influenza vaccine & egg allergy

Studies on the administration of egg-based influenza vaccines to egg-allergic recipients

The overwhelming majority of attention regarding IgE-mediated reactions to influenza vaccines has focused on egg allergy. Until recently, all influenza vaccines were grown in eggs, and this continues to be the case for the majority [11]. This production technique leaves some amount of residual egg protein in the vaccines and raises the possibility that the administration of such a vaccine to a patient with egg allergy could result in an allergic reaction. However, many studies have been performed to determine whether or not egg-allergic patients can safely receive influenza vaccines containing egg protein, and the pace of such studies has accelerated dramatically in recent years. As with other IgE-mediated reactions to foods, diagnosis of egg allergy requires a clinical history of a recent reaction to the ingestion of egg, where the nature (e.g., hives, wheezing, lightheadedness) and timing (typically within minutes of exposure) suggest mast cell granulation, as well as evidence of IgE antibody to egg demonstrated by immediate-type skin testing or serum-specific IgE testing.

A study published in 1977 described 28 children aged 3–18 years who were allergic to eggs based on history and skin testing but who had negative prick (full-strength) and intradermal (diluted 1:100) skin tests with influenza vaccine who were administered the vaccine with no immediate allergic reactions [12].

A 1998 report describes 83 patients from 1 to 46 years of age (median age 3) with egg allergy by history confirmed with skin testing, as well as 124 control subjects aged 1–78 years (median age 37.5 years) without egg allergy, all of whom underwent prick skin testing with full-strength influenza vaccine [13]. Four (4.8%) of the egg-allergic subjects and one (0.8%) of the control subjects had a positive skin test to the vaccine. Irrespective of skin test results, all subjects received the vaccine; egg-allergic subjects received 1/10 of the dose followed 30 min later by the remaining 9/10, and control subjects received the vaccine as a single dose. All subjects, including 27 patients with a history of severe/anaphylactic reactions after the ingestion of egg as well as the subjects with positive vaccine skin tests, tolerated the vaccine without any significant allergic

reactions. Two of the egg-allergic subjects developed a single hive that resolved spontaneously and they tolerated booster doses uneventfully. One developed mild throat itching, cough and wheeze after the 1/10 dose which resolved spontaneously prior to the 9/10 dose which was tolerated without reaction. One had delayed emesis, mild cough and wheeze, which were treated with a nebulizer treatment who subsequently tolerated a booster dose uneventfully. One child developed delayed fussiness and another mild URI symptoms, both of which resolved spontaneously. Of note, one of the non-egg-allergic control subjects developed an urticarial reaction treated with diphenhydramine and another also had delayed emesis. Although the vaccine was administered to egg-allergic subjects in divided doses as above, the authors commented that 'administration of the vaccine in two doses may be no different than administration of a single dose.' The amount of egg protein measured as ovalbumin present in influenza vaccines was also reported in this study. The vaccines administered contained between 0.02 and 1.2 mcg/ml. The ovalbumin content of two other vaccines not used in the study contained between 1 and 42 mcg/ml.

A report in 2000 described 28 egg-allergic patients (mean age 7 years) who underwent prick skin testing with undiluted vaccine, with three positive results [14]. Eight of the subjects underwent intradermal skin testing with the vaccine diluted 1:100, all with positive results. The vaccine was given by a graded, multi-dose protocol. Two of the 28 (7%) were reported to have had cough, hoarseness, rhinitis and or urticaria reactions, 1 to 0.05 ml of 1:10 vaccine (had had a positive SPT result) and 1 to full-strength vaccine (had had positive intradermal skin test result). The vaccine used in the study was reported to have 6.5 mcg/ml of ovalbumin.

An abstract from 2005 describes 55 patients with egg allergy who underwent prick skin testing to influenza vaccine [15]. Thirty-two (58%) had negative vaccine skin prick tests and underwent vaccination, with one developing mild wheezing. Five patients with positive vaccine skin prick tests were vaccinated nonetheless, and none developed reactions. The vaccines used were reported to contain between 4.9 and 14.6 mcg/ml of ovalbumin.

An abstract from 2008 reported a 6-year experience describing 115 egg-allergic children who received a total of 173 doses of influenza vaccine [16]. Only 12% of the doses were preceded by intradermal vaccine skin testing, of which 29% were positive. Half the patients received the vaccine as a single dose and the others in two or more steps. Three of the doses led to the development of a single hive which resolved spontaneously. Otherwise, there were no allergic reactions including no reactions in the patients that have had positive skin tests.

A paper published in 2008 described the use of a virosomal adjuvanted influenza vaccine containing only 2 ng/ml of ovalbumin [17]. The vaccine was administered to 88 children with asthma, 44 with egg allergy and 44 without. Eleven of the children with egg allergy had a history of anaphylactic reactions to the ingestion of egg. Prick skin tests with undiluted vaccine

were negative in all subjects, who all subsequently received the vaccine as a single dose. Two patients, one with and one without egg allergy, had bronchospasm.

An abstract in 2008 reviewed the outcomes of 45 children with egg allergy who received influenza vaccine [18]. Patients underwent prick skin testing with undiluted vaccine and 12 (26%) had positive vaccine skin tests and received the vaccine in graded doses, leading to one episode of hives. The remainder had negative vaccine skin test results and received the vaccine uneventfully.

A 2009 abstract presented a retrospective study of 349 children with egg allergy confirmed by history and skin testing or oral challenge, who were skin tested to the full-strength influenza vaccine [19]. Fifty-eight (17%) patients had positive vaccine skin tests and received the vaccine in graded doses, while the remainder received the vaccine as a single dose. Twelve (3%) patients had had hives or redness, mostly at the injection site, and 2 (0.6%) had eczema flares. 335 patients (96%) had no reactions.

Another abstract from 2010 describes a protocol whereby egg-allergic children underwent prick skin testing with full-strength influenza vaccine, and if negative were given the vaccine in two doses (1/10, 9/10) [20]. Two hundred and fourteen doses were administered without serious adverse reactions. Five children (2.3%) developed some urticaria or erythema.

A 2010 publication describes the rate of reactions to influenza vaccine in egg-allergic children under two different protocols [21]. Initially, 146 children had been skin tested with full-strength vaccine prior to its administration; if positive, the vaccine was withheld and if negative, the vaccine was given in two doses (1/10, 9/10). Under this protocol, 56 (38%) children (mean age 6.2 years) received the vaccine, but it was withheld from 90 (62%) children. Subsequently, vaccine skin testing was removed from the protocol, and 115 egg-allergic children (mean age 3.9 years) received the vaccine in two doses. No vaccine recipient under either protocol developed anaphylaxis or multi-systemic allergic reactions. Seven children, including three who had negative skin tests and four who had not been skin tested, had mild systemic reactions including wheezing, eczema exacerbation or hives. The authors concluded that since the rate of reactions was no different whether or not vaccine skin testing was included in the protocol, such testing was unnecessary.

A 2010 publication describes the Canadian experience, with administration of a 2009 monovalent pandemic influenza H1N1 vaccine containing less than 0.015 mcg/ml of ovalbumin [22]. Eight hundred and thirty patients with histories of immediate-type allergic reactions after the ingestion of eggs, confirmed by positive skin test or egg specific IgE tests, were vaccinated. Seventy-two of the patients, whose reactions to the ingestion of egg included respiratory or cardiovascular symptoms, received the vaccine in divided doses (1/10, 9/10), while the remainder received the vaccine as a single dose. No vaccine recipient had an anaphylactic reaction. Thirteen patients (1.6%) had cutaneous symptoms (two with generalized hives),

three had respiratory symptoms (one each with hoarse voice, sensation of throat closure and wheezing) and one had mild abdominal pain. Importantly, 393 control subjects without egg allergy received the same vaccine with similar rates of reactions; 1.5% had cutaneous symptoms and six others had other symptoms including emesis and sensation of throat closure. Application of this same protocol to 3640 patients with self-reported egg allergy also caused no cases of anaphylaxis. 1.2% of these patients developed skin reactions and 0.7% developed other symptoms including throat tingling or tightening, cough or wheezing.

Another publication from 2010 describes the administration of a different monovalent H1N1 influenza vaccine to 105 patients, with egg allergy defined as a convincing history and positive egg skin test or specific IgE (mean age 5.5 years), including 25 with prior histories of anaphylactic reaction to egg ingestion as well as 19 control subjects (mean age 6.3 years) [23]. Skin tests with the vaccine (prick full-strength and if negative intradermal 1:100) were performed: If positive, the vaccine was administered in divided doses (1/10, 9/10) and if negative, the vaccine was administered as a single dose. Two of 105 egg-allergic subjects and 1 of 19 control subjects had positive prick vaccine skin tests. Forty of 105 egg-allergic subjects and 1 of 19 control subjects had positive intradermal vaccine skin tests. The maximum ovalbumin content among the various lots of H1N1 vaccine used was 0.05 mcg/ml. No reactions occurred in any of the vaccine recipients.

Another abstract from 2010 describes the administration of H1N1 influenza vaccine to 50 egg-allergic recipients and seasonal influenza vaccine to 31 egg-allergic recipients [24]. Twenty-one patients underwent prick and intradermal vaccine skin testing: three who had positive intradermal test results were given the vaccine in divided doses (1/10, 9/10) and those with negative vaccine skin tests or not tested received the vaccine as a single dose. No systemic reactions were seen in any subject.

A final publication from 2010 involved 62 egg-allergic children (defined as a clinical history of egg allergy and positive egg skin test, mean age 3.7 years) who underwent prick skin testing with full-strength H1N1 influenza vaccine [25]. All patients had negative vaccine skin tests and received the vaccine in three graded doses uneventfully.

A 2011 publication describes 53 children from age 2 through 7 years, with histories of reactions to the ingestion of egg and positive egg skin tests who underwent skin testing with H1N1 vaccines [26]. Two children had positive vaccine skin tests and were given the vaccine in two divided doses (1/5, 4/5), while the others received the vaccines as a single dose. No systemic reactions were observed.

An abstract from 2011 reports on 101 egg-allergic (positive history and positive skin test and/or specific IgE to egg) children aged 7 months to 18 years who underwent prick skin testing with either seasonal or H1N1 influenza vaccine [27]. No child had a positive vaccine skin test, and all received the vaccine as a single dose without systemic reactions.

Another abstract from 2011 describes 62 patients with confirmed egg allergy (egg-specific IgE range 8.31 to >100 kU/l, mean age 3.8 years), 20 of whom underwent vaccine skin testing with either seasonal or H1N1 influenza vaccine, seven of which were positive [28]. Including boosters, a total of 131 vaccinations (66 H1N1 and 65 seasonal) were administered to these children, only three in split doses (1/2, 1/2) and all were tolerated without systemic reaction.

A 2011 publication describes 64 patients with egg allergy (positive clinical history and positive skin test or egg-specific IgE) who were given a total of 96 either seasonal or H1N1 influenza vaccinations in divided doses (1/10, 9/10), four of whom had mild cutaneous reactions but no other systemic reactions [29]. The seasonal vaccines used in the study contained up to 1.4 mcg/ml of ovalbumin.

Another study from 2011 retrospectively reviewed 135 egg-allergic children, including 14 with a history of anaphylaxis to egg ingestion, under age 3 who had received seasonal influenza vaccine, with four children developing hives and one diarrhea [30]. The same authors prospectively evaluated 69 egg-allergic children and 14 non-egg-allergic controls. Half of the children underwent prick skin testing to full-strength vaccine: six had positive results and received the vaccine in two divided doses (1/10, 9/10). The other half of the children were not skin tested and received the vaccine as a single dose. All children received booster doses as a single dose. Two egg-allergic children developed hives as did two non-egg-allergic children. The ovalbumin content of the vaccines used was as high as 1.087 mcg/ml. The authors concurred that vaccine skin testing was unnecessary.

Another 2011 publication reported on 152 patients from age 7 months to 30 years (median 3 years) with egg allergy confirmed based on history and skin testing or specific IgE testing, including 34 with a history of anaphylaxis to egg ingestion, who received a total of 285 influenza vaccinations (containing as much as 1.4 mcg/ml of ovalbumin) as a single dose with no systemic reactions reported [31].

Another publication from 2011 reported on 59 patients (aged 1 through 27 years, mean 5.6 years) with egg allergy (clinical history and positive skin test or specific IgE) who underwent prick skin testing with full-strength vaccine [32]. Only one patient had a positive vaccine skin test and was administered the vaccine in a divided doses (1/10, 9/10) uneventfully. All other patients received the vaccine as a single dose uneventfully.

A final publication from 2011 describes 60 egg-allergic children (clinical history and positive skin test and/or specific IgE, mean age 4.5 years) who received adjuvanted H1N1 vaccine containing less than 0.165 mcg/ml of ovalbumin in divided doses (1/10, 9/10) [33]. Two children developed hives and one developed a hyporesponsive episode with uneventful recovery. There were no cases of anaphylaxis.

In 2012, a study from Norway evaluated 80 children with positive egg skin tests or specific IgE who were unable to tolerate even baked goods containing egg, indicating a more severe

egg allergy [34]. These children were administered an H1N1 vaccine containing less than 0.33 mcg/ml of ovalbumin, half by divided dose and half as a single dose. Two children developed mild swelling (eye, lip) and one each sneezing and abdominal pain. There were no serious reactions.

Another 2012 study reviewed children specifically with anaphylactic reactions to the ingestion of egg [35]. Fifty-six such patients underwent prick skin testing with full-strength vaccine. In eight children in whom the vaccine skin test was positive, the vaccine was administered in graded doses. However, in seven other children with positive vaccine skin tests, the vaccine was administered as a single dose. One hundred and nineteen total doses of influenza vaccine were given to the 56 children. One child had hives 30 min after the vaccine but received a single dose booster 1 month later uneventfully. The authors stated that 'our study adds to growing data that influenza skin tests and division of vaccination doses might be unneeded practices.'

An abstract from 2012 reported on 660 egg-allergic children (clinical history and positive egg skin test and/or serum specific IgE, aged 6 months to 13 years, mean age 5 years) given influenza vaccine either as a single dose or as a split dose [36]. There were no systemic reactions. The authors concluded that 'splitting the dose did not show any benefit'.

A report from 2012 described 77 egg-allergic patients, including 24 with anaphylactic reactions to egg ingestion, who were vaccinated with an adjuvanted H1N1 vaccine containing less than 0.165 mcg/ml of ovalbumin [37]. Only those with the most severe reactions to the ingestion of egg such as intensive care unit admission were skin tested to the vaccine and, if positive, administered the vaccine by graded doses. Most of the other children received the vaccine without prior vaccine skin testing in two doses (1/10, 9/10). There were no systemic reactions to vaccine administration in any of these children.

Also in 2012, a group of investigators reviewed all of the aforementioned studies on the administration of influenza vaccine and added their own experience regarding 367 patients who received a total of 457 doses of seasonal influenza vaccine as a single dose without prior vaccine skin testing [38]. Among these children were 132 patients (153 doses) who had a history of severe reactions to the ingestion of egg. There were no adverse reactions. The authors concluded that 'there is now robust evidence that egg-allergic patients, even those with severe allergy can be safely vaccinated against influenza'.

A final study from 2012 described 31 children with severe reactions to the ingestion of egg who are randomized to receive 0.1 ml of either influenza vaccine or saline followed 30 min later by 0.4 or 0.5 ml of influenza vaccine, respectively [39]. No allergic reactions were seen. These authors also retrospectively evaluated 112 children with severe egg allergy, 87 of whom received the vaccine as a single dose and 25 as a split dose, all uneventfully.

We clearly have a wealth of information regarding the safety of administration of egg-containing influenza vaccines to egg-allergic recipients. The 28 studies above collectively describe

the administration of influenza vaccine to 4315 egg-allergic recipients, including 656 with histories of anaphylactic reactions to the ingestion of eggs, with no serious reactions reported. Although many of the studies involved either prick or intradermal skin testing with the influenza vaccine prior to administration, results of these tests have not predicted reactions, and study authors have universally concluded that such testing is therefore unnecessary. Similarly, although many of the studies involved administration of the vaccine in divided doses (most often 1/10 dose followed 30 min later by the remaining 9/10), since the full dose was ultimately tolerated, most authors have concluded that dividing the dose in this fashion is also unnecessary. Also important to note is that in studies that included non-egg-allergic control subjects, the rate of minor reactions was approximately the same as in the egg-allergic recipients. Thus, patients may rarely develop hives after influenza vaccination whether or not they are egg allergic.

Quantity of egg protein in influenza vaccines

Influenza vaccine manufacturers used to not indicate the quantity of egg protein in their vaccines. All manufacturers currently indicate, either in the package inserts or by personal communication, that the vaccines contain less than 1 mcg of ovalbumin per dose. Assay of various lots of the vaccines in independent laboratories have typically demonstrated ovalbumin levels to be only a fraction of the claimed amounts [40–42]. Although reactions to injected egg protein may be different than ingested egg protein, the lowest dose of egg protein ever reported provoking an allergic reaction was 130 mcg [43], and an amount calculated to elicit no reaction in 99% of the egg-allergic population and only minor reactions in the remainder is 30 mcg [44]. Thus, it is likely that even in exquisitely egg-allergic children, the amount of egg protein in the influenza vaccine is not enough to provoke an allergic reaction.

Risks of not vaccinating

The overwhelmingly reassuring data regarding the safety of administering egg-based influenza vaccines to egg-allergic recipients is balanced against the very real risk of leaving such patients unvaccinated. The vast majority of egg-allergic patients are children. There are on average over 20,000 hospitalizations and over 100 deaths from influenza in children each year in the USA [45,46]. These hospitalizations and deaths occur primarily in children who are not vaccinated, some because they were egg allergic. Leaving children, including egg-allergic children, unvaccinated against influenza leaves them at risk for vaccine-preventable morbidity and mortality.

Published recommendations

As the reviewed studies have been published, official recommendations regarding the administration of influenza vaccine to egg-allergic recipients have changed. As recently as 2010, recommendations from the Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices (ACIP) stated that, 'Persons who have had symptoms such as

hives or swelling of the lips or tongue or who have experienced acute respiratory distress after eating eggs should consult a physician for appropriate evaluation to help determine if future influenza vaccine should be administered' [47]. However, beginning in 2011, based on a review of publications regarding the administration of influenza vaccine to egg-allergic recipients, the ACIP recommended that 'persons who have experienced only hives following exposure to egg should receive influenza vaccine...[and]... be observed for at least 30 min for signs of a reaction following administration of each vaccine dose' and that persons with more severe reactions to the ingestion of egg 'be referred to a physician with expertise in the management of allergic conditions' [48]. The American Academy of Pediatrics Committee on Infectious Diseases has published guidelines with the same recommendations [49]. Practice parameters for allergists published in 2012 stated that even patients with these more severe reactions to the ingestion of egg should receive influenza vaccination as a single dose without prior vaccine skin testing [50]. Importantly, since the implementation of these new guidelines, there has not been an increase in reports of allergic reactions after influenza vaccination [11].

Given the overwhelmingly reassuring safety data regarding the administration of egg-based influenza vaccines to egg-allergic recipients, a statement endorsed by the Joint Task Force on (Allergy) Practice Parameters concludes that, 'Special precautions regarding medical setting and waiting periods after administration of IIV to egg-allergic recipients beyond those recommended for any vaccine are not warranted' [51]. As above, recipients of influenza vaccine may rarely experience anaphylaxis, although this is no more likely if they are egg allergic. Despite the fact that influenza and other vaccines are increasingly being administered in non-medical settings such as pharmacies, per ACIP General Recommendations on Immunization, providers should be aware that 'Although anaphylactic reactions are rare after vaccination, their immediate onset and life-threatening nature require that all personnel and facilities providing vaccinations have procedures in place for anaphylaxis management' [52].

Use of LAIV in egg-allergic recipients

All of the studies published to date regarding the use of influenza vaccine in egg-allergic recipients have involved the injectable, inactivated influenza vaccine, and thus IIV is recommended for these patients [11,49,50]. However, the intranasally administered, LAIV also contains a very low amount of ovalbumin (<0.24 mcg per 0.2 ml dose) and would likely be equally well tolerated in egg-allergic recipients.

Use of non-egg-based influenza vaccines in egg-allergic recipients

As above, two new non-egg-based methods of inactivated influenza vaccine production have been developed, cell culture and recombinant. Because the cell culture-based vaccine uses seed virus grown in eggs, the vaccine in theory could contain 100 femtograms (1×10^{-7} µg/ml) of ovalbumin [11]. The

package insert does not mention egg allergy as a precaution or contraindication. The recombinant influenza vaccine is made using a process that does not involve eggs. Various influenza vaccines are approved for use in various age groups [11]. These age indications are not arbitrary, but rather based on data regarding safety and efficacy, and thus influenza vaccines should not be used 'off label' outside of the age ranges for which they are approved. For egg-allergic patients aged 18 years or older, egg-based or cell culture-based vaccine can be administered, and for those aged 18–49 years, recombinant vaccine could also be used. Most egg-allergic patients are children however, and the use of egg-based vaccines in these patients is safe as reviewed above. Also as noted above, the ACIP recommends that persons with more severe reactions to the ingestion of egg 'be referred to a physician with expertise in the management of allergic conditions'.

Expert commentary

It is clear that although IgE-mediated hypersensitivity reactions to influenza vaccine have historically been blamed on residual egg protein in the vaccine, the overwhelming majority (perhaps all) of egg-allergic recipients tolerate egg-based influenza vaccines uneventfully. Although anaphylactic reactions to influenza vaccination are rare, the majority occur in non-egg-allergic subjects. Occasionally, reactions have been found to be due to an IgE-mediated reaction to some other vaccine constituent. A case report from 2007 describes a 2–1/2-year-old boy who developed cough, wheeze and diffuse urticaria within 10 min of an influenza booster vaccine [53]. He had had previous episodes of hives after eating gelatin-containing candies, but consumed eggs and all other foods uneventfully. The particular brand of influenza vaccine he had received contained gelatin and both skin testing and serum-specific IgE antibody testing were positive for gelatin.

When a patient suffers one of these rare, potentially anaphylactic adverse events after influenza immunization, an investigation to try to determine the cause is appropriate.

Such investigation would typically be performed by an allergist and include a careful history of the nature of the reaction and its timing relative to immunization to assess the likelihood that the event represented an allergic reaction and the likelihood that it was in fact due to the vaccine. The Brighton Collaboration standardized case definition for anaphylaxis as an adverse event following immunization describes the various dermatologic, respiratory, cardiovascular, gastrointestinal and other symptoms that would be typical of an anaphylactic reaction [3]. This definition does not include timing relative to vaccination, so as not to exclude rare events with a late onset, but nonetheless acknowledges that 'clinical manifestations of anaphylaxis are typically described as starting within seconds to minutes of exposure to a given substance. Most cases start within 1 h of exposure.' Should the history of a patient's adverse event after immunization potentially be consistent with an anaphylactic reaction so defined, it would be appropriate to determine whether or not the patient has evidence of specific IgE

antibody to the vaccine or a constituent [50]. Vaccine skin tests would be performed with the same brand, and ideally the same lot, of influenza vaccine suspected of causing the reaction, first by the prick method with undiluted vaccine and, if negative, by the intradermal method with the vaccine diluted 1:100, a concentration which has been determined to be nonirritating [54]. If such tests are negative, the likelihood that the vaccine caused the reaction by an IgE-mediated mechanism is quite small. Although anaphylaxis can be induced by non-IgE-mediated mechanisms [1], the inability to demonstrate IgE antibody to the suspect vaccine makes such a mechanism unlikely and suggests that the event was not anaphylactic but perhaps some other event such as vasovagal syncope [55]. If vaccine skin testing gives positive results, further attempts should be made to determine the culprit allergen so that vaccines containing the allergen can be avoided in the future if possible or administered in graded doses under observation [50].

Five-year view

Given that anaphylactic reactions to influenza vaccine are exceedingly rare, and that culprit allergens or other mechanisms

for these reactions have not been elucidated, attempts should be made to thoroughly investigate these events as outlined above, and for the results to be published.

It is important for egg-allergic persons to receive annual influenza vaccination according to current guidelines and for monitoring systems to continue to evaluate any possible increase in allergic reactions as the guidelines are more widely appreciated and adopted. Although such reactions appear to be no more common in egg-allergic than non-egg-allergic recipients, it is appropriate for vaccine manufacturers to continue to minimize the amount of ovalbumin present in the vaccine to minimize the risk to those with egg allergy.

Financial & competing interests disclosure

The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Key issues

- Anaphylactic reactions after influenza vaccination are rare, less than one per million doses.
- Such reactions are no more common in egg-allergic recipients, and patients with egg allergy should receive annual influenza vaccination to protect them from the morbidity and mortality associated with the disease.
- Careful evaluation of allergic reactions to influenza vaccine in individual recipients may identify culprit allergens to inform more cautious subsequent vaccination.

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