

Rostrums

Current issues with influenza
vaccination in egg allergyRobert S. Zeiger, MD, PhD *San Diego, Calif*

Influenza infection, with its accompanying morbidity and mortality, represents a major public health concern yearly to the elderly and high-risk groups, including asthmatic patients. Active prevention with vaccination consistently falls short of reaching optimal immunization rates in all risk groups. Asthmatic patients and others with concomitant egg allergy might be denied active immunization because of the risk of inducing adverse reactions with a vaccine derived from egg embryo tissue. Evidence supports the relatively safe administration of influenza vaccine to individuals with egg allergy in whom vaccination is indicated when specific protocols are followed under the supervision of experienced physicians. A practical protocol that includes incremental dosing of influenza vaccine is presented to guide clinicians in influenza vaccination in this high-risk group. (*J Allergy Clin Immunol* 2002;110:834-40.)

Key words: Influenza vaccination, egg allergy, asthma

Controversy and ambiguity exist concerning influenza vaccination in high-risk groups with egg allergy. Recent studies have led to endorsement of influenza vaccination in a broader group of patients, including healthy children aged 6 to 23 months.¹ These young children are at increased risk for influenza-related hospitalization, and such vaccinations might both reduce their risk and also provide protection and reduce mortality from influenza among older patients.² Implementation of these recommendations will increase the potential exposure of individuals with egg allergy to influenza vaccination because egg allergy peaks in infancy and early childhood. Only a few publications have dealt with immunization with inactivated parenteral influenza vaccine in egg allergy.³⁻⁷ The following rostrum will present the issues leading to these uncertainties and propose a practical approach to individuals with egg allergy in whom influenza vaccination is indicated.

INFLUENZA AND INFLUENZA VACCINATION
RATES IN PATIENTS WITH ASTHMA

Asthmatic children with influenza infection exhibit increased wheezing and hospitalizations for asthma exacer-

Abbreviations used

AAP: American Academy of Pediatrics
ACIP: Advisory Committee for Immunization Practices
HMO: Health maintenance organization
SPT: Skin prick test

erbations.^{8,9} Additional influenza-associated hospitalization rates of 5.6 per 1000 children have been reported in asthmatic patients 1 to 3 years of age.¹⁰ In addition, asthmatic children younger than 15 years of age experience increases in outpatient visits and antibiotic prescriptions during the influenza season. In children influenza virus increases asthma exacerbations, susceptibility to bronchospasm, and protracted decreases in lung function.¹¹

Annual influenza vaccination is recommended by the Advisory Committee for Immunization Practices (ACIP),¹ the American Academy of Pediatrics (AAP),¹² and the Second Expert Panel for the Diagnosis and Management of Asthma¹³ to protect asthmatic patients from this increased burden. Notwithstanding these recommendations, only a minority of asthmatic children receives influenza vaccination, reaching only 25%¹⁴ of children with moderate-to-severe asthma and 9% with asthma between 1 and 6 years of age.¹⁵ This rate is certainly much lower in asthmatic patients with concomitant egg allergy.

SAFETY OF INFLUENZA VACCINATION IN
PATIENTS WITH ASTHMA

Data on the safety of influenza vaccination in patients with asthma are shown in Table I.¹⁶⁻²⁰ A Cochrane systematic review of the literature in 2000 on the basis of controlled clinical trials through 1998 reported that the safety of influenza vaccination in patients with asthma remains inconclusive.²¹ This uncertainty was driven by a double-blind placebo-controlled crossover trial that reported a trend ($P = .06$) toward a higher incidence of patients with a greater than 20% decrease in peak expiratory flow 72 hours after influenza vaccination compared with that after placebo injections. This difference, however, disappeared after excluding patients with obvious upper respiratory tract infections.¹⁶ Additionally, no adverse effects were observed for asthma medication use within 72 hours after injection or for hospital admissions, medical consultations, antibiotic use, rescue medication, or oral steroid use during the 7 days after vaccination.

A very recent, high-quality, double-blind, placebo-controlled crossover study of a large cohort of nearly

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TABLE I. Safety of influenza vaccination with inactivated parenteral vaccine in asthmatic patients in controlled clinical trials

Study (y)	Cohort size	Age (y)	Design	Parameter measured	Adverse effects
Stenius-Aarniala et al, 1986 ²⁰	318	17-73	Randomized DBPC	Sx, PEF, Meds	None
Nicholson et al, 1998 ¹⁶	262	18-75	Multicenter DBPC, randomized, crossover	20% PEF decrease in 72 h	Marginal % of patients with decline
Reid et al, 1998 ¹⁸	22	19-71	Randomized DBPC	BHR	None
Sener et al, 1999 ¹⁹	24	18-64	Prospective single-blind, placebo-controlled	BHR, PEF, Sx, Meds	None
ALA, 2001 ¹⁷	1952	3-64	Multicenter DBPC, randomized, crossover	Exacerbation, PEF, Meds	None

DBPC, Double-blind, placebo-controlled; Sx, asthma symptoms; PEF, peak expiratory flow; Meds, rescue medications; BHR, bronchial hyperresponsiveness (PC₂₀ methacholine).

2000 children and adults with asthma published after completion of the above systematic review convincingly documents the safety of influenza vaccination among asthmatic patients.¹⁷ Taken together, these studies present strong evidence that influenza vaccination does not alter bronchial reactivity^{18,19,22} or lung function, asthma symptoms, exacerbations, or increased use of rescue medications.^{17,20,21} The American Lung Association study¹⁷ should provide adequate robustness to drive future systematic reviews to conclude that influenza vaccination is safe for children and adults with asthma, regardless of disease severity. In addition, influenza antibody responses are not reduced in asthmatic children during short courses of oral corticosteroids.^{23,24} These findings should reassure both physicians and patients about the safety of influenza vaccination in asthma and encourage vaccination of asthmatic patients, even during asthma exacerbations requiring emergency care and oral corticosteroid bursts.

BENEFIT OF INFLUENZA VACCINATION IN PATIENTS WITH ASTHMA

Although inactivated parenteral influenza vaccination has an efficacy of 68% (95% CI, 49%-79%) in preventing influenza,²⁵ vaccination remains to be proved beneficial for asthma control in controlled clinical trials, as documented for chronic obstructive lung disease.²⁶ However, there is epidemiologic evidence to support a beneficial effect in patients with asthma. Hospitalization rates for influenza-like illnesses are reduced in asthmatic children after influenza vaccination.²⁷ More recently, influenza vaccination was shown to protect against acute asthma exacerbations, controlling for asthma severity in children 1 to 6 years of age in a population-based retrospective cohort study from 4 large health maintenance organizations in the United States during the 3 influenza seasons from 1993 to 1996.¹⁵ A retrospective study of 349 asthmatic children during 2 influenza seasons from 1995 to 1997 noted a 55% (95% CI, 20%-75%; $P = .01$) reduction in acute respiratory disease among the subgroup younger than 6 years of age.²⁸ Although definitive

clinical trials are needed, these findings support the recommendation to vaccinate asthmatic children and adults against influenza.²⁹

CONTROVERSIES IN INFLUENZA VACCINATION IN EGG ALLERGY

Egg allergy poses an additional challenge in influenza vaccination programs. Influenza vaccines are derived from the extra embryonic fluid of chicken embryos inoculated with specific types of influenzavirus. The vaccines typically contain measurable quantities of egg protein allergens, such as ovomucoid-ovalbumin.³⁰ Adverse allergic reactions have been seen in patients with egg allergy injected with inactivated influenza vaccines (Table II).^{3-7,31-33} The AAP 2000 Red Book Report of the Committee on Infectious Diseases acknowledges that children with "severe anaphylactic reactions (generalized urticaria, hypotension, or manifestations of upper or lower airway obstruction) to chicken or egg protein can experience, on rare occasions, a similar type of reaction to killed influenza vaccines."¹² The AAP adds that "skin testing has been used for children with severe anaphylactic reactions to eggs who are to receive influenza vaccine." Additionally, the AAP recommends that "although influenza vaccine has been administered safely to such children after skin testing and even desensitization; these children *generally* [author's italics] should not receive influenza vaccine because of their risk of reactions, the likely need for yearly vaccination, and the availability of chemoprophylaxis against influenza infection."¹²

The ACIP recognizes the potential for experienced allergists to vaccinate individuals with egg allergy with influenza vaccine after evaluation and a desensitization protocol, if necessary. Their recommendation states that "inactivated influenza vaccine should not be administered to persons known to have anaphylactic hypersensitivity to eggs or to other components of the influenza vaccine without first consulting a physician. Prophylactic use of antiviral agents is an option for preventing influenza among such persons. However, persons who have a history of anaphylactic hypersensitivity to vaccine com-

TABLE II. Skin test sensitization and systemic allergic reactions to influenza vaccination in patients with egg allergy

Study (y)	N	Age (y)	Vaccine route	Skin dose	Positive test result (%)	Systemic reactions to vaccine (% of patients)	Symptoms
Ratner and Untraucht, 1952 ³²	5	4-15	Intradermal	Neat	100	40	Urticaria, wheeze
Davies and Pepys, 1976 ³¹	22	11-66	SPT	Neat	32	Vaccination not done	Not applicable
Miller et al, 1983 ⁵	3	17-19	Intradermal	1:100	67	33	Pruritus, throat symptoms
Murphy and Strunk, 1985 ⁶	6	4-7	SPT	1:10	17	17*	Wheeze
			Intradermal	1:100	100		
Anolik et al, 1992 ³³	8	Children	SPT	Neat	13	0*	None
			Intradermal	1:100	100		
James et al, 1998 ⁷	83	Median 3	SPT	Neat	5	0 after 2-dose protocol	None
Zeiger†	28	Mean 7	SPT	Neat	11	7*	Cough, hoarseness, rhinitis, urticaria‡
			Intradermal (n = 8)	1:100	100		

*Graded multidose protocol.⁶

†1997-1998 FluShield vaccine: ovomucoid-ovalbumin content = 6.5 µg/mL.

‡Reactions to 0.05 mL of 1:10 vaccine (had positive SPT result) and full-strength vaccine (had positive intradermal skin test result).

TABLE III. Studies evaluating the prevalence of egg sensitization and egg allergy in asthmatic patients

Study (y)	N	Age (y)	Asthma selection	Positive egg SPT result (%)	Egg allergy (%; DBPCFC)
Ratner and Untracht, 1946 ³	143	≤18	None	20.3	NR
Onorato et al, 1986 ⁴³	300	28.2 ± 21.6	Consecutive and chronic	NR	2.3 (6 children, 1 adult)
Novembre et al, 1988 ⁴⁴	140	Children	≥3 episodes	NR	3.6
Yazicioglu et al, 1999 ⁴⁵	50	1.5-6	Positive IgE food panel	36	2

DBPCFC, Double-blind, placebo-controlled food challenge; NR, not reported.

ponents, but who are also at high risk for complications of influenza can benefit from vaccine after appropriate allergy evaluation and desensitization. Protocols have been published for safely administering influenza vaccine to people with egg allergies".^{1,6,7,12}

SIZE OF THE HIGH-RISK ALLERGIC POPULATION

Can we estimate the number of individuals in the United States with egg allergy? In a random-sample, population-based, questionnaire-driven study from France, 3.24% (range, 3.04%-3.44%) of 16,174 children and adults 60 years of age or younger evidenced a convincing history of food allergy, with 4% attributable to egg, resulting in an overall prevalence of egg allergy of 0.13%.³⁴ In young children the prevalence of egg allergy is considerably higher, reaching a point prevalence of documented egg allergy at 2½ years of age of 1.6% (95% CI, 1.3%-2.0%) in a population-based birth cohort study of 2721 Norwegians.³⁵ The prevalence of egg allergy is higher in allergic children in general, reaching 5.6% in 500 consecutive allergic patients followed in a specialty clinic.³² Among children and adolescents with moderate-to-severe atopic dermatitis, egg allergy occurs in approximately 40%.³⁶⁻⁴⁰ In addition, egg sensitization and allergy in early infancy predicts later aeroallergen sensitization and respiratory disorders, including asthma and allergic rhinitis.^{41,42}

Although the exact prevalence of egg allergy in asthmatic children is unknown because pertinent large-scale epidemiologic studies have yet to be done, some evidence exists that might be helpful in generating an approximation. In selected subgroups of asthmatic patients, egg allergy was documented in 2.0% to 3.6% of the cohorts (Table III).^{3,43-45} Onorato et al⁴³ evaluated 300 consecutive chronic asthmatic patients of all ages and found 2.3% with egg allergy by means of double-blind, placebo-controlled food challenge. Six of the 7 asthmatic patients with egg allergy were children. Of 140 children with at least 3 episodes of asthma reported by Novembre et al,⁴⁴ 3.6% exhibited egg allergy on double-blind, placebo-controlled food challenges. Evidence suggests that more severe asthma is found in patients with egg allergy and asthma. Severe bronchial asthma was noted with twice the frequency (41%) in 84 children with egg allergy 1 to 15 years of age compared with 72 age- and sex-matched egg-tolerant allergic children (23%).⁴⁶ From these data, one would expect concomitant egg allergy and asthma in children seen by specialists to be between 2% and 3.6%⁴³⁻⁴⁵ but considerably lower among asthmatic patients in the general population. In the United States asthma has been estimated in 5% of the general population,⁴⁷ with 25% being managed at least in part by asthma specialists from representative individual provider associations.⁴⁸

Children, particularly the young, are the group of asthmatic patients with the highest frequency of concomitant

TABLE IV. Egg protein content in various lots of influenza vaccines

Year	Egg protein (ovomucoid-ovalbumin) content ($\mu\text{g/mL}$)*		
	Fluvirin (Evans)	Fluogen (Parke Davis)	FluShield (Wyeth)
2001-2002	0.06	Not done	29.5, 33.1
2000-2001	Not done	Not done	38.4, 42.4
1999-2000	Undetectable	Not done	Not done
1998-1999	0.8, 0.05	Not done	10.9
1997-1998	Not done	Not done	6.5, 8.3
1996-1997	Not done	0.02	1.0
1995-1996	Not done	1.2	Not done
1994-1995	0.01	0.1	27.2

*Determined by means of ELISA inhibition by Sampson, except 1994 to 1995 Fluvirin.⁶¹ Two values represent analyses from different lots. Connaught's Flu-zone contained 42.0 $\mu\text{g/mL}$ in 1994 to 1995.

egg allergy. Egg allergy, although present, is extremely uncommon in adults.⁴⁹⁻⁵¹ Jansen et al⁵¹ failed to identify a single patient with egg allergy from a random sample of 1483 Dutch adults. In asthmatic adults attending a specialty clinic, only 1 patient was identified with egg allergy by means of confirmed challenge.⁴³ These findings are consistent with the decrease in the prevalence of egg allergy that occurs with age.⁵²⁻⁵⁴ As such, the number of adults with egg allergy requiring influenza vaccination will be quite small.

DIAGNOSIS OF EGG ALLERGY

The diagnosis of egg allergy is based on determination of clinical history, determination of egg sensitization by means of skin prick tests (SPTs) or in vitro RASTs (particularly CAP fluorescent enzyme immunoassay), and supervised egg challenge, as discussed in detail elsewhere.^{40,55-58} Definitive diagnosis of egg allergy generally requires documentation by food challenge under physician observation unless the egg CAP RAST result is equal to or greater than the 95% positive predictive level or there is a clear recent history of anaphylaxis associated with egg ingestion.⁴⁰

SAFETY OF INFLUENZA VACCINATION IN PATIENTS WITH EGG ALLERGY

Can influenza vaccination be administered with acceptable safety in individuals with egg allergy? A Centers for Disease Control and Prevention-coordinated nationwide surveillance for adverse reactions after influenza vaccination in 1976 of greater than 48 million Americans revealed 11 cases of anaphylaxis, none of which included a known prior history of egg allergy.⁵⁹ Despite this observation, an anaphylactic death after influenza vaccination has been reported in a child known to be allergic to egg.⁴ A few earlier studies on a small number of patients with egg allergy provide some evidence that individuals with egg allergy can be immunized with influenza vaccine when certain precautionary steps are taken.^{6,33}

A recent large-cohort multicenter study extended on these observations in a prospective controlled clinical trial.⁷ This study was conducted in 83 subjects at least 6 months of age and older (median age, 3 years) with egg allergy, nearly all of whom had asthma. All patients had documented IgE reactivity to egg, as determined by means of SPT or RAST testing, and either positive blinded oral egg challenge results ($n = 25$), histories of anaphylaxis ($n = 27$), or convincing recent histories of objective reactions ($n = 31$) to egg on ingestion. A control group of 124 patients was comprised of those with either negative histories of egg allergy ($n = 109$), positive histories and negative egg SPT results ($n = 13$), or equivocal histories, positive egg SPT results, and negative blinded challenge results ($n = 2$). The study showed that influenza vaccination could be administered safely, without systemic reactions, to the 83 subjects in a 2-dose injection protocol (one-tenth dose followed in 30 minutes with nine-tenth dose) with vaccines containing no more than 1.2 $\mu\text{g/mL}$ egg protein (range, 0.02-1.2 $\mu\text{g/mL}$ from 1994-1997). The absence of a significant immediate or delayed reaction to the 2-dose protocol in the 83 patients resulted in an exact 95% CI of 95.7% to 100%. A single booster injection 1 month after initial vaccination was tolerated by all 34 patients who needed a second dose. All control patients tolerated a single full dose of the vaccine without a systemic reaction.⁷

EGG PROTEIN CONTENT IN INFLUENZA VACCINES

Stull,⁶⁰ in 1946, first documented by means of Prausnitz-Kustner testing that vaccines grown on chick egg yolk contain sufficient egg protein (about 2000-fold the amount considered safe for skin testing) to elicit severe systemic allergic reactions in egg-sensitive individuals. Egg protein content in influenza vaccine was first estimated by means of PAGE at 20 to 45 $\mu\text{g/mL}$.³¹ Egg protein (ovomucoid-ovalbumin) levels in influenza vaccines from various manufacturers determined by means of ELISA inhibition vary by greater than 3 logs (1994-2002), being as low as nondetectable to as high as 42

µg/mL (Table IV).^{7,61} Variation in egg protein content in influenza vaccines has been reported among European influenza vaccines.⁶¹ Influenza vaccines are manufactured by only 3 companies for distribution in the United States: Aventis Pasteur SA (Fluzone, previously manufactured by Connaught), Evans Vaccines Limited (Fluvirin), and Wyeth-Ayerst Laboratories (FluShield). All package inserts for influenza vaccines note that their use is contraindicated in "anyone with a history of hypersensitivity (allergy) to chicken eggs, chicken, chicken feathers, or chicken dander."

Egg protein content in FluShield has varied from as low as 1 µg/mL to as high as 42.4 µg/mL, with only 1 of 6 years exhibiting levels of less than 1.2 µg/mL (Table IV). Fluzone had an egg protein level of 42.4 µg/mL on the one occasion it was analyzed. Parke-Davis, the manufacturer that provided the influenza vaccines for our controlled clinical trial, no longer produces it. Egg protein content in Fluvirin in the years 1994 to 2002 was consistently less than 1 µg/mL, ranging from undetectable to 0.8 µg/mL (Table IV). Fluvirin is a purified subunit surface antigen vaccine of a trivalent Type A and Type B split-virus preparation indicated for use in patients 4 years of age and older. Studies of the effectiveness of Fluvirin have been inconsistent in children less than 4 years of age.

A live, attenuated, cold-adapted, trivalent, intranasal influenza virus vaccine, FluMist, developed by Aviron and now owned by MedImmune, has been shown to be safe, immunogenic, efficacious in adults and children,⁶² and cost effective⁶³ against influenza in children but is awaiting Food and Drug Administration approval for safety. This intranasal influenza vaccine contains egg protein and, until further study, is not recommended in patients with egg allergy.

AAP RECOMMENDATIONS FOR CHILDREN WITH EGG ALLERGY

The AAP recommends that reactions to egg less severe than anaphylaxis (as noted above) or local manifestations of allergy to egg or to feathers do not contraindicate influenza vaccination and do not warrant vaccine skin testing.¹² A child with egg allergy, according to the AAP, should be skin tested before receiving any egg-containing vaccine. If either an SPT or intradermal skin test reveals a positive result to the vaccine preparation, the influenza vaccine should not be administered in the usual fashion but, if indicated, by means of a graded multidose protocol.¹²

AMBIGUITIES IN INFLUENZA VACCINATION IN EGG ALLERGY

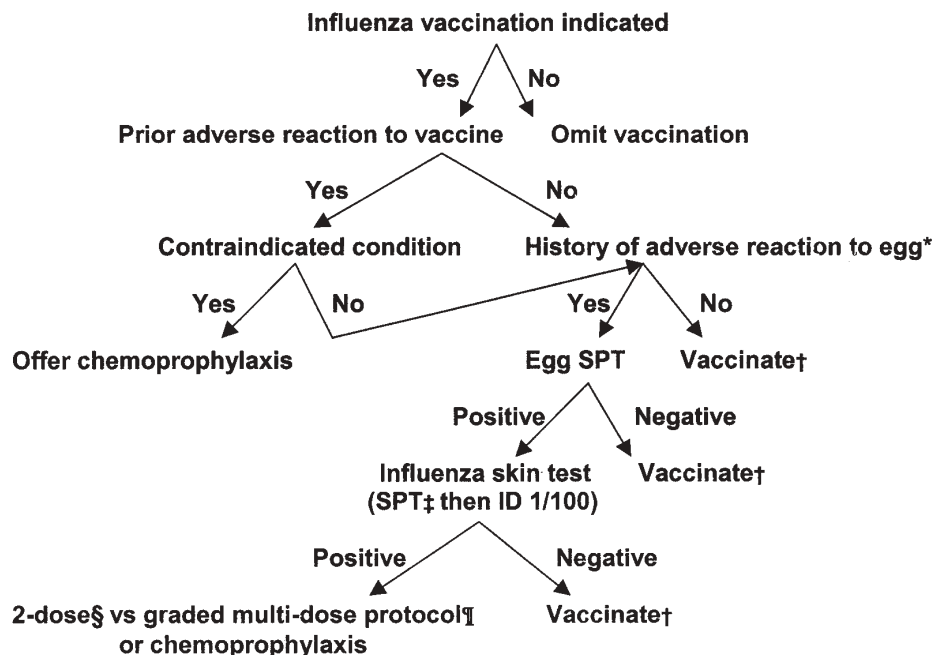
Many conflicting and challenging issues are apparent from the above discussion: (1) the AAP does not generally recommend influenza vaccination in children with egg allergy and a history of anaphylaxis, but in its guidance acknowledges, indirectly, that vaccination might be

pursued in some cases,¹² and the ACIP recommends that individuals with a history of anaphylactic hypersensitivity to vaccine components and are also at high risk for complications of influenza might benefit from vaccine after appropriate allergy evaluation and desensitization¹; (2) package product inserts for influenza vaccines state that influenza vaccination is contraindicated in patients with allergy to eggs and chickens; (3) influenza vaccination in individuals with egg allergy appears to be generally safe when vaccines with no more than 1.2 µg/mL egg protein are used in a 2-dose protocol⁷; (4) egg protein in influenza vaccine vary several logs from manufacturer to manufacturer and from year to year (Table IV)^{7,61}; and (5) no company analyzes or reports the egg content of their influenza vaccines.

PROPOSED PRACTICAL GUIDELINES FOR INFLUENZA VACCINATION IN PATIENTS WITH EGG ALLERGY

A practical approach is presented to facilitate influenza vaccination in individuals with histories of or confirmed egg allergy when vaccination is indicated (Fig 1). In all patients one should inquire about a history of adverse reactions to egg or influenza vaccines before vaccination. Certain diseases, such as the Guillain-Barre syndrome, are contraindications for influenza vaccination. Egg allergy can be ruled out if an individual presently ingests eggs or egg-containing products in a full portion without any reaction. In those with a history of an adverse reaction to egg who might also benefit from influenza vaccination, referral to an allergist should be recommended. An SPT to egg (1:20) should be performed, with appropriate histamine and saline controls. A negative SPT result to egg with positive histamine control virtually rules out egg allergy and permits influenza vaccination in full dose, unless a non-IgE-mediated reaction, such as thimerosal sensitivity, is suspected.

Patients with a positive egg SPT result and documented egg allergy or historical reactions to egg ingestion (confirm the diagnosis at a later evaluation, as described above) are next skin tested to influenza vaccine first by means of SPT and then by means of intradermal testing, as shown in Fig 1. Negative saline and positive histamine controls should be used. If the skin test results are negative, the vaccine might be given in the usual single intramuscular dose adjusted to age. If the skin test results are positive (SPT wheal ≥ 3 mm or intradermal wheal ≥ 5 mm compared with that elicited by saline control), an individual risk-benefit assessment, including the severity of asthma and egg allergy, should be made to determine whether influenza vaccination is warranted. Options and alternatives need to be discussed. Asthmatic patients with egg allergy and others with egg allergy could be offered chemoprophylaxis, as recommended by the AAP.¹² If influenza vaccination is selected, the vaccine should be administered to subjects with egg allergy by allergists experienced in and equipped for treating anaphylaxis. Proper informed consent must be obtained before



* If egg allergy has not already been definitively diagnosed, do so at a later evaluation.

† Single IM dose appropriate for age.

‡ Start with 1/10 dilution if egg content unknown or > 1.2 ug/ml, otherwise full strength.

§ Egg content ≤ 1.2 ug/ml.

¶ Egg content unknown or > 1.2 ug/ml.

FIG 1. Algorithm for administering influenza vaccination in patients with egg allergy.

influenza vaccination is given. One could follow the 2-dose protocol reported above⁷ or follow a multiple graded-dose desensitization protocol,^{6,12} depending on the egg protein content in the vaccine (Fig 1).

FUTURE PROSPECTS

Expanding therapeutic options are becoming available to reduce influenza epidemics and the adverse public health effects of influenza infection.^{1,64} Influenza vaccination in asthmatic patients with egg allergy and toddlers raises important and ambiguous issues. Several management options exist that need to be resolved individually with physician guidance. It would be helpful for companies that manufacture influenza vaccines to determine the egg content of their vaccines. Perhaps the Food and Drug Administration could exert their influence, but it is not currently pursuing or requiring companies to test for egg content or requesting a low-egg-content influenza vaccine. It could be cost-effective for large medical organizations to implement proactive screening and vaccination programs for those with egg allergy needing influenza vaccination, as implemented for years in our center. Further research in this area will probably help develop more evidenced-based guidelines for influenza vaccination when indicated in individuals with egg allergy.

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