Original article

Safe vaccination of patients with egg allergy with an adjuvanted pandemic H1N1 vaccine

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Background: Because influenza vaccine contains some residual egg protein, there is a theoretic risk of anaphylaxis when vaccinating patients with egg allergy. The objective of this study was to estimate the risk of anaphylaxis in children with egg allergy administered an adjuvanted monovalent 2009 pandemic influenza A/H1N1 influenza vaccine (Arepanrix; GlaxoSmithKline, Mississauga, Ontario, Canada).

Methods: Patients with confirmed egg allergy with a history of respiratory or cardiovascular reactions after egg ingestion were vaccinated in 2 divided doses (10% and 90%) administered at a 30-minute interval, whereas children with other types of egg-induced allergic reactions were vaccinated with a single dose. All patients remained under observation for 60 minutes after vaccination. A 24-hour follow-up telephone call was made to detect any delayed reaction. The main outcome was the occurrence of an anaphylactic reaction according to criteria specified by the Brighton Collaboration.

Results: Among the 830 patients with confirmed egg allergy, only 9% required the vaccine to be administered in divided doses. No patient had an anaphylactic reaction. Nine patients had minor allergic symptoms treated with an antihistamine (1 in the 60 minutes after vaccination and 8 in the following 23 hours), and 3 others received salbutamol (1 in the first 60 minutes after vaccination). Further vaccination of more than 3,600 other children with reported egg allergy caused no anaphylaxis based on the criteria of the Brighton Collaboration, although 2 patients received epinephrine for symptoms compatible with allergy.

Conclusion: Although anaphylaxis after influenza immunization is a theoretic risk, vaccination of patients with egg allergy with an adjuvanted monovalent pH1N1 influenza vaccine resulted in no cases of anaphylaxis and on that basis appears safe. (J Allergy Clin Immunol 2010;■■■:■■■-■■■.)

Key words: *Vaccination, egg allergy, influenza vaccine, 2009 pandemic influenza A/H1N1 vaccine, Arepanrix*

With the onset of the 2009 pandemic influenza A/H1N1 (pH1N1), vaccination was recommended by the World Health Organization and national public health authorities. Children were the age group most at risk of the severe complications of pH1N1, and their vaccination was a priority. This group includes a substantial number of children allergic to eggs. Because influenza vaccines are produced from embryonated hens' eggs and contain measurable quantities of egg protein allergens, there is concern about the risk of anaphylaxis in patients with egg allergy.[1,2]

The vaccination of patients with egg allergy against influenza has been discussed frequently in the past, and different vaccination approaches have been proposed. In 2002, Zeiger[2] recommended 2 doses or a multidose graded vaccination protocol depending on results of skin testing and the egg content of vaccine. For the 2009 pH1N1, the American Academy of Allergy, Asthma & Immunology recommended that each patient with egg allergy be evaluated by an allergist with pH1N1 vaccine skin prick tests (SPTs) and intradermal tests. If the response to either test was positive, patients were to be vaccinated according to a multidose graded protocol.[3] However, skin testing of patients with vaccine is considered potentially unreliable, with frequent false-positive results.[4,5] For the 2009 pH1N1 vaccine, a group of British allergists proposed to vaccinate without prior testing of the patients if the egg protein content in the vaccine was less than 1.2 μg/mL. For high-risk patients (cardiovascular symptoms, respiratory symptoms, or both after egg ingestion), vaccination would be administered in 2 doses, the first with 10% of the total dose required for age followed by 30 minutes of observation, after which the remaining 90% would receive vaccine assuming no concerning symptoms had developed.[6] The Canadian Society of Allergy and Clinical Immunology (CSACI) suggested a protocol similar to that of the British group but also included patients with a history of generalized hives in the high-risk group.[7]

Several studies have looked at the risk of anaphylactic reactions after vaccination against influenza in patients with egg allergy.[8-15] The summary of studies including 30 or more patients with egg allergy showed that a few had mild and limited allergic

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Supported by the Canadian Institutes for Health Research (CIHR), the Public Health Agency of Canada (PHAC) Influenza Research Network (PCIRN), and the Ministère de la santé et des services sociaux du Québec.

Disclosure of potential conflict of interest: M. N. Primeau has received research support from the Canadian Institutes for Health Research (CIHR). G. De Serres has received research support from GlaxoSmithKline and Sanofi Pasteur. The rest of the authors have declared that they have no conflict of interest.

Received for publication April 10, 2010; revised May 27, 2010; accepted for publication May 28, 2010.

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0091-6749/$36.00

doi:10.1016/j.jaci.2010.05.037

Abbreviations used
CSACI: Canadian Society of Allergy and Clinical Immunology
pH1N1: 2009 Pandemic influenza A/H1N1
SPT: Skin prick test

symptoms, but none of nearly 1,000 vaccinated patients experienced anaphylaxis (Table I).[8-15] Unfortunately, some patients perceived to be at greater risk of anaphylaxis were excluded in some of these studies or vaccinated in a graded approach, limiting the ability to confirm the safety of vaccination.

During the fall of 2009, the Quebec Ministry of Health and Social Services requested that the Association of Allergists and Immunologists of Quebec develop a strategy to ensure rapid but safe access to pH1N1 vaccination for patients with egg allergy. Given the limited number of allergists, it would not have been possible for all patients with egg allergy to be vaccinated if they required individual clinical investigation. A 2-stage approach was developed: an initial study would be conducted urgently by allergists from university hospitals with 900 patients with egg allergy receiving an adjuvanted pH1N1 influenza vaccine, and if results confirmed limited risk, this would be followed by the expanded vaccination of all other patients with egg allergy in hospitals by nurses supervised by either allergists or nonallergist physicians. We report the results of the initial study and those from the expanded vaccination of patients with egg allergy.

METHODS

This prospective observational study included patients with confirmed egg allergy and a group of control subjects without egg allergy of the same age. Patients with egg allergy were recruited in 5 Canadian sites (Quebec City, Montreal [2 sites], Sherbrooke, Toronto, and Edmonton) among patients consulting allergists to be vaccinated against pH1N1 between October 28 and December 15, 2009. These patients were vaccinated according to an approach recommended by a group of British allergists,[6] which is similar to that recommended by the CSACI.[7] This study included allergic patients never previously vaccinated against influenza (naive patients) and those vaccinated in the past without having an allergic reaction. The control subjects were recruited during the same period primarily from a single public health mass-vaccination center in Quebec City, whereas a few others were recruited from day care centers or through radio advertisements. While waiting for their vaccination, patients with egg allergy and control subjects (or their parents/legal guardian if minor patients) were invited by research nurses to provide written consent for the collection of data on adverse events occurring within the 24 hours after vaccination. There was no blinding of the immunizations and observations between patients with egg allergy and control subjects. The study was approved by the ethic boards of the 6 participating hospitals and that of the public health clinic.

Confirmation of egg allergy

IgE-mediated egg allergy was defined as a minimum of 1 sign or symptom occurring within 60 minutes of egg ingestion and confirmation of sensitization to eggs (within 6 months of the vaccination) shown by an SPT response to hens' eggs at least 3 mm larger than that elicited by the saline control within 10 to 15 minutes or an egg-specific IgE level of 0.35 kU/L or greater (UniCAP; Pharmacia, Uppsala, Sweden). Because patients who had never ingested eggs might have been sensitized without having had the opportunity to display clinical allergy, we applied more stringent inclusion criteria to this group. These patients and those with an uncertain clinical history of allergic reactions to eggs were required to have both a positive SPT response and a serum egg-specific IgE level (measured by means of UniCAP) of 2 kU/L or greater if the patient was less than 2 years old and 7 kU/L or greater for older patients.

Vaccination of patients with egg allergy and control subjects

We applied the clinical approach published by Erlewyn-Lajeunesse et al,[6] which recommended administering the influenza vaccine in a single dose (followed by 60 minutes of observation) to patients at low risk of an anaphylactic reaction if the vaccine contained less than 1.2 μg/mL egg protein. Low-risk patients were those who previously had mild gastrointestinal or dermatologic reactions after egg ingestion or those who had never eaten egg but were found to be sensitized, as demonstrated by means of SPT responses and IgE levels. Patients at higher risk included those who experienced systemic allergic reactions to eggs involving the cardiorespiratory system or those with uncontrolled asthma. As recommended, for patients in the higher-risk group, the vaccine was divided into 2 doses (10% and 90%) administered at 30-minute intervals, with 60 minutes of observation after the second dose.

The vaccine studied was a monovalent pH1N1 vaccine adjuvanted with ASO3, a squalene-based adjuvant (Arepanrix; GlaxoSmithKline, Mississauga, Ontario, Canada). This vaccine requires the mixing of the antigen to an equal volume of adjuvant. The ovalbumin content of the antigen component of Arepanrix was provided by the manufacturer and was less than 0.03 μg/mL in all lots used.

For both allergic patients and control subjects, the vaccine was administered intramuscularly according to the dosage recommended by the manufacturer (ie, 0.25 mL for children <10 years old and 0.5 mL for those ≥10 years old). All participants remained under observation for 60 minutes after vaccination. The participants were examined immediately before the vaccination and 60 minutes later. They were contacted by telephone 24 to 48 hours later to collect data on adverse events that might have developed between 1 and 24 hours after vaccination.

Outcomes

The primary outcome was the occurrence of an anaphylactic reaction according to the criteria of the Brighton Collaboration. The Brighton Collaboration criteria for anaphylaxis require the sudden onset and rapid progression of signs and symptoms involving more than 1 system. The level of diagnostic certainty of anaphylaxis depends on which body systems are affected during the reaction and the severity of observed symptoms (minor or major).[16]

Expanded vaccination of patients with egg allergy

The Quebec Ministry of Health and Social Services, the Association of Allergists and Immunologists of Quebec, and the Quebec Association of Paediatricians organized special clinics throughout the province where patients could be rapidly vaccinated if the vaccination of the first 900 patients with egg allergy by allergist investigators showed an acceptably small risk of anaphylaxis. In these clinics vaccination was done by nurses under the supervision of physicians (general physicians, pediatricians, internists, or allergists). These physicians were only assessing patients with comorbid conditions that might have precluded their vaccination (eg, presence of bronchospasm) and were responsible for treating adverse events occurring during the 60 minutes after vaccination. Vaccine was administered in a single dose or in divided doses (10% to 90%) according to the protocol previously described.

A mandatory surveillance program was organized to ensure the safety of this rapid vaccination campaign. Data on the total number of patients vaccinated and the details regarding any adverse events requiring treatment had to be faxed within 24 hours of each vaccination session. These reports were analyzed daily by the provincial safety monitoring committee. Results were disseminated electronically 3 times per week to all public health units and all physicians supervising the vaccination clinics. These clinics started on November 17, 2009.

RESULTS

A total of 1076 patients with egg allergy were recruited, none of whom had a history of an allergic reaction to any prior

TABLE I. Published studies with 30 or more patients with egg allergy vaccinated against influenza

Authors, year	No.	Characteristics of patients	Egg protein content	No. with reactions	Reaction to vaccination
Bierman et al,[8] 1977	130	Allergic to eggs, chicken, or feathers with a negative skin test response to the vaccine	Unreported	6/130	Three had a delayed cutaneous reaction: ● One had eczema 24 h later. ● One had limited urticaria starting 8 h after vaccination. ● One had urticaria starting 4-6 h after vaccination, which evolved to erythema multiforme a few days later.
James et al,[9] 1998	83	Median age, 3 y with egg allergy, nearly all with asthma; all patients had documented IgE reactivity to egg, as determined by means of SPTs or RASTs 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	0.02-1.2 μg/mL	8/83	In patients ≤8 y of age: ● Mild throat itching, cough, and wheeze after first dose ● Small hive that resolved before second dose ● Small hive that resolved before second dose ● Delayed emesis, mild cough, and wheeze In patients >8 y of age: ● Local pruritus 18 h later ● Delayed fussiness ● Mild URI symptoms after 2-dose protocol ● 10-mm Erythema at injection site >1 h after vaccination
Dorsey et al,[10] 2005	32 + 5	Patients with confirmed diagnosis of egg allergy: ● 32 with negative SPT responses to vaccine ● 5 with positive SPT responses to vaccine	4.9-14.6 μg/mL	0/37	Initially included 55 patients, but 18 patients with positive SPT responses to vaccine were not vaccinated.
Hotte et al,[11] 2006	115	82% with signs or symptoms compatible with clinical history of egg allergy, 18% never been exposed to eggs, with diagnosis on the basis of a positive SPT response, increased serum specific IgE level, or both done as part of an assessment for moderate-to-severe atopic dermatitis	Unreported	3/115	● One had a small urticarial plaque to the chin 15 min after vaccine that lasted 15 min. ● One had a single urticarial plaque to the forehead that disappeared within 30 min. ● One had a single urticarial lesion that resolved quickly.
Esposito et al,[12] 2008	44	Asthmatic children with egg allergy ≥3 y old administered a virosomal vaccine with very low egg protein content	Inflexal Berna (1 ng per dose)	3/44	● One had mild bronchospasm. ● One had mild erythema. ● One had mild bronchospasm.
Park et al,[13] 2008	45	Children with confirmed diagnosis of egg allergy	Unreported	1/45	● One had diffuse hives. ● Fourteen had local erythema or hives.
Saltzman et al,[14] 2009	349	Patients with confirmed diagnosis of egg allergy; the 58 children with positive skin test responses to vaccine received 3 graded vaccination doses	Unreported	10/349	● Two had eczema flares. ● Eight patients had hives at the injection site or distant from it. ● Four had redness at the injection site.
Chung et al,[15] 2010	171	Retrospective assessment of medical charts of patients with confirmed egg allergy vaccinated between 2002 and 2003 and 2008 and 2009; excluded 88 patients with positive vaccine skin test responses	Unreported	29/171 (17%) localized; 7/171 (4%) systemic	● Six systemic reactions within 30 min after 10% of the dose included wheezing, eczema exacerbation, or hives on face/chest. ● One systemic reaction occurred >30 min after 90% of the dose and caused hives and facial flushing.

influenza vaccine they might have received. Two hundred forty-six vaccinated patients were excluded from analysis (Fig 1). Reasons for exclusion were as follows: tolerance to egg ingestion (n = 27), negative SPT response and IgE level of less than 0.35 kU/L (n = 42), and unclear history of egg ingestion (n = 1). For patients with unclear clinical history or who had never eaten eggs, 153 did not have a positive SPT response and a serum egg-specific IgE level of 2 kU/L or greater if the patient was less than 2 years old and 7 kU/L or greater for older patients: 133 of them had only a positive SPT response, 7 had only the positive serum egg-specific IgE level, and 13 had negative results on both tests; 19 took antihistamines before vaccination; and 4 were unable to provide information regarding previous influenza vaccination. This left 830 confirmed allergic patients for the analysis.

Table II shows the characteristics of the 830 confirmed allergic patients and their 393 control subjects. Among patients with egg allergy, 72% were naive to influenza vaccine, 63% were male, 55% were 5 years old or less, 65% reported other food allergies, 20% reported environmental allergies, and 50% had a history of bronchial hyperactivity. Only 9% required the vaccine to be administered in divided doses (10% and 90%). Among the 830

patients, 154 (100 who had eaten eggs before and 54 who had never eaten eggs) had both positive SPT responses and significantly increased egg-specific IgE levels (≥2 kU/L if the patient was <2 years old and ≥7 kU/L for older patients). The 393 recruited control subjects were equally distributed between sexes, and their age distribution was similar to that of patients with egg allergy.

None of the patients with confirmed egg allergy had anaphylaxis (risk, 0/830; 95% CI, 0% to 0.4%). During the 60 minutes after vaccination, 17 (2%) patients with egg allergy had signs/symptoms compatible with an allergic reaction and included in the Brighton Collaboration criteria: 1 had mild abdominal pain, 13 had cutaneous symptoms (2 had generalized hives), and 3 had respiratory symptoms (hoarse voice, sensation of throat closure, and wheezing; Table III). The frequency of these signs/symptoms was twice as high for patients previously vaccinated against influenza compared with patients who were naive to this vaccine (3.4% vs 1.5%); however, this was not significant ($P = .12$). Antihistamines were administered to 1 patient with angioedema, 1 patient with urticaria, and 1 patient with ocular pruritus. Salbutamol was administered to the patient with mild wheezing who had known asthma, who hyperventilated after his injection, and whose respiratory distress was deemed related to anxiety by the attending clinician. The patient recovered uneventfully within 1 to 2 hours. Among control subjects, no anaphylaxis occurred, and the proportion of patients who presented with signs/symptoms compatible with an allergic reaction was similar (3.1%) to that observed in patients with egg allergy. None required treatment. During the 60 minutes after vaccination, 10 (1.2%) patients with egg allergy and 5 (1.3%) control subjects had cutaneous signs/symptoms not included in the Brighton Collaboration criteria, which consisted of localized hives or pruritus away from the injection site (5 vs 0, respectively) and nonspecific rash without pruritus (5 vs 5, respectively).

During the next 23 hours, the proportion of patients with egg allergy and control subjects who had at least 1 symptom compatible with an allergic reaction were similar (13.7% vs 14.7%, $P = .63$). Among patients with egg allergy, antihistamines were taken by 8 patients with a dermatologic complaint, and salbutamol was taken by 2 patients (1 with cough and hoarseness and the other with mild dyspnea). All recovered uneventfully without requiring any medical visits. One control subject required assessment for symptoms compatible with oculorespiratory syndrome (red eyes, nasal congestion, dry cough, hoarseness, difficulty breathing, throat tightness, bronchospasm, stridor, edema of the upper airway, and tachypnea). The greater number of symptoms at 60 minutes than at 24 hours can be explained by the longer period of follow-up. The majority of the symptoms at 24 hours were gastric problems or minor respiratory problems (sneezing, runny nose, or cough). Because those symptoms at 24 hours were equally reported in both groups (control subjects and allergic patients), they are most likely unrelated to allergy but are either nonallergic adverse events caused by the vaccine or caused by something other than the vaccine. With a longer period of follow-up (23 hours vs 1 hour), we expected more adverse events.

Between November 17, 2009, and February 10, 2010, 3640 additional patients with egg allergy were vaccinated by nurses under physician supervision, according to the same clinical guidelines. Nearly two thirds of these patients had not been previously vaccinated against influenza. The diagnosis of egg allergy was self-reported, and no confirmation was sought.

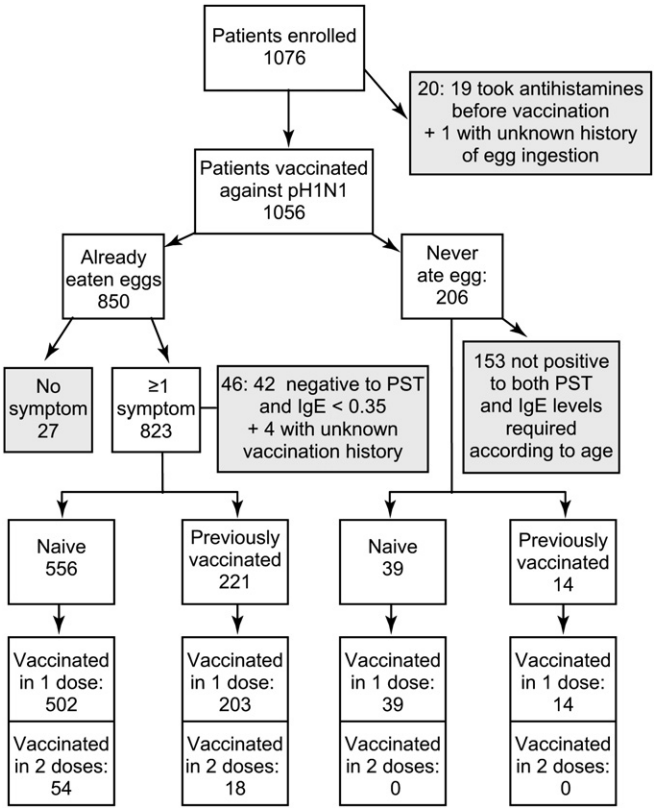

FIG 1. Distribution of patients with egg allergy. Patients excluded from the analysis are shaded in *gray*. *PST,* Skin prick test.

Patients with a history of egg intolerance were not included in this group.

Among these 3640 patients, 2 (0.05%) had symptoms treated with epinephrine, although none fulfilled the Brighton criteria for anaphylaxis. The first was a 45-year-old woman with a history of allergic rhinitis and asthma triggered by aeroallergens treated with cetirizine continuously and salbutamol when needed. When eating eggs, she had diarrhea and vomiting. She had a positive test result to eggs 16 years before, but her most recent test result 1 year before vaccination was negative, and her allergist was planning a diagnostic food challenge. Twenty minutes after receiving 10% of the vaccine dose, she complained of a tingling sensation of her tongue. The tingling progressed to her mouth and throat over 10 to 15 minutes, and she complained of dyspnea. The physical examination showed no angioedema of the mouth or throat, no wheezing, and no abnormal lung findings. Her blood pressure and heart rate remained normal (103-133/79-86 mm Hg and 75-79 beats/min, respectively) throughout the episode, and there was no cutaneous involvement. Despite the absence of objective signs, given the persistence of her symptoms, she was administered a first dose of epinephrine at the vaccination site. Five minutes later, she felt better, but numbness persisted in her tongue. She received a second dose of epinephrine and was transferred to the emergency department for observation, where she recovered uneventfully.

The second patient was a 3-year-old boy never previously vaccinated against influenza with a history of angioedema after ingestion of hardboiled egg. Thirty minutes after vaccination, the child began crying continuously for 30 minutes. The physician

TABLE II. Characteristics of patients with confirmed egg allergy and control subjects

	Allergic patients			Control subjects (n = 393), no. (%)
	Naive subjects (n = 595), no. (%)	Vaccinated subjects (n = 235), no. (%)	Total subjects (n = 830), no. (%)	
Sex				
Male	377 (63)	143 (61)	520 (63)	202 (51)
Female	218 (37)	92 (39)	310 (37)	191 (49)
Age (y)				
<2	145 (24)	28 (12)	173 (21)	83 (21)
2-4	177 (30)	103 (44)	280 (34)	141 (36)
5-11	196 (33)	81 (34)	277 (33)	88 (22)
≥12	77 (13)	23 (10)	100 (12)	79 (20)
Allergy to products other than egg				
Food allergy	378 (66)	158 (67)	536 (65)	9 (2)
Drug allergy	27 (5)	10 (4)	37 (4)	32 (8)
Respiratory allergy	120 (20)	48 (20)	168 (20)	19 (4)
Other allergy	19 (3)	9 (4)	28 (3)	3 (1)
Underlying disease				
Asthma	282 (47)	135 (57)	417 (50)	
SPT				
Positive (≥3 mm)	568 (95)	228 (97)	796 (96)	
UniCAP (kUA/L)				
<0.35	64 (13)	23 (5)	87 (18)	
0.35-<2	112 (23)	43 (9)	155 (32)	
2-<7	77 (16)	19 (4)	96 (20)	
7-17.4	56 (12)	19 (4)	75 (16)	
≥17.5	46 (10)	20 (4)	66 (14)	
Never ate egg	39 (7)	14 (6)		
Tolerate eggs in baked goods (eg, muffins and cookies)				
Yes	187 (39)	64 (35)	251 (30)	NA
No/never tried	289 (61)	121 (65)	410 (70)	
Vaccinated				
Single dose	541 (91)	217 (92)	758 (91)	393 (100)
10% to 90%	54 (9)	18 (8)	72 (9)	

NA, Not applicable.

reported wheezing and thoracic indrawing. The child was treated with epinephrine and salbutamol and was kept under observation for 4 hours, during which time he received 5 additional treatments with salbutamol before recovering fully.

Among the 3,641 vaccinated patients, 69 (1.9%) others had mild signs/symptoms compatible with an allergic reaction: 42 (1.2%) had skin involvement, 17 (0.5%) reported throat tingling/tightening, and 7 (0.2%) reported cough. These patients were treated with antihistamines, and 4 of the 7 with cough were given salbutamol.

DISCUSSION

We report the largest prospective study published to date on influenza vaccination of patients with egg allergy. None of the 830 patients with confirmed egg allergy had symptoms meeting the Brighton Collaboration criteria for anaphylaxis. A few patients presented with mild and limited signs/symptoms resolving spontaneously or with antihistamines/salbutamol. The frequency of adverse events at 60 minutes and 24 hours was similar to that in the control group, suggesting no additional risk in patients with egg allergy. The frequency of adverse events was not higher in the 9% of patients vaccinated with divided doses and those who received a single dose, suggesting that they too would likely have tolerated the full dose as a single injection. Naive patients were not at greater risk than patients previously vaccinated against influenza. In the expanded vaccination of more than 3,600 patients self-reporting egg allergy, none met the criteria for anaphylaxis, although epinephrine was administered to 3 patients.

The criteria defined by the Brighton Collaboration Allergic Reactions Working Group are very close to those published by the National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network.[17] In both classifications it is emphasized that to diagnose anaphylaxis, the reaction should be of sudden onset and show a rapid progression of symptoms. Although the National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network criteria suggest a diagnosis of anaphylaxis after an accidental exposure to allergens if reduced blood pressure is the only sign after exposure to an allergen, the Brighton Collaboration criteria require the involvement of 2 or more organ systems. This is important because the context of immunization (eg, anxiety or use of a needle) is often favorable to vagal reactions causing low blood pressure alone without any other signs of possible allergic reaction. In our study none of our patients with egg allergy experienced low blood pressure after vaccination.

Several limitations of this study warrant consideration. A first limitation is the possibility that patients previously vaccinated against influenza (28% of our cohort) were at lower risk of anaphylaxis than those naive to influenza vaccine. However, it is

TABLE III. Signs/symptoms compatible with allergic manifestations (classified into minor and major criteria of the Brighton Collaboration) at 60 minutes and 24 hours after vaccination in patients with egg allergy and control subjects

	At 60 min		At 24 h	
Signs/symptoms	**Allergic patients (n = 830), no. (%)**	**Control subjects (n = 393), no. (%)**	**Allergic patients (n = 830), no. (%)**	**Control subjects (n = 393), no. (%)**
Gastrointestinal total	1 (0.1)	1 (0.3)	44 (5.3)	23 (5.9)
Diarrhea	0	0	9	7
Abdominal pain	1	0	27	14
Nausea	0	0	16	4
Vomiting	0	1	2	1
Dermatologic or mucosal total	13 (1.6)	6 (1.5)	18 (2.2)	3 (0.8)
Minor criteria total	11 (1.3)	6 (1.5)	10 (1.2)	2 (0.5)
Generalized pruritus without skin rash	0	0	0	0
Generalized prickling sensation	0	0	0	0
Localized injection site urticaria	0	1	3	1
Red and itchy eyes	3	0	6	1
Major criteria total	2 (0.2)	0	8 (1.0)	1 (0.3)
Generalized hives or generalized erythema	2	0	2	0
Angioedema localized or generalized	0	0	0	0
Generalized pruritus with skin rash	0	0	7	1
Respiratory total	3(0.4)	2 (0.5)	31 (3.7)	22 (5.6)
Minor criteria total	2 (0.2)	02 (0.5)	28 (3.4)	18 (4.6
Persistent dry cough	0	0	8	4
Hoarse voice	1	0	3	3
Difficulty breathing without wheeze or stridor	0	0	0	0
Sensation of throat closure	1	1	0	0
Sneezing and rhinorrhea	0	1	20	14
Major criteria total	1 (0.1)	0	3 (0.4)	4 (1.0)
Bilateral wheeze	1	0	2	1
Stridor	0	0	0	3
Obvious upper airway swelling (tongue, throat, uvula, and larynx)	0	0	1	1
Respiratory distress (≥2 of tachypnea, increased use of accessory respiratory muscles, recession, cyanosis, and grunting)	0	0	1	0
Cardiovascular	0	0	0	0
Minor: reduced peripheral circulation as indicated by ≥2 of tachycardia, capillary refill time >3 s, or decreased level of consciousness				
Major: hypotension based on measurement or clinical diagnosis of uncompensated shock				
Signs/symptoms in ≥2 systems	0	3 (0.8)	21 (2.5)	10 (2.6)
Meeting Brighton Collaboration criteria for anaphylaxis	0	0	0	0
Total	17 (2)	12 (3.1)	114 (13.7)	58 (14.7)

None of the differences were significant.

more likely the current egg allergy status of the patient (still presenting clinical symptoms of allergy after egg ingestion) that drives the risk of anaphylaxis than its prior history of vaccination. Similarly, despite fairly stringent criteria to confirm egg allergy, 30% of our cohort tolerated extensively heated eggs and might therefore have been at lower risk. The other 70% of patients with egg allergy were completely avoiding eggs and did not undergo confirmatory food challenges. We therefore cannot identify the actual number of patients still truly allergic to eggs. It is also possible that patients with the most severe past reactions avoided vaccination altogether, limiting our capacity to generalize these results. Nevertheless, among the 154 patients with a high positive predictive value of true allergy (positive SPT response to hens' egg and a serum egg-specific IgE level ≥2 kU/L if the patient was <2 years old and ≥7 kU/L for older patients), no severe reactions were observed at either 60 minutes or 24 hours. In addition, although the expanded vaccination of more than 3600 patients with self-reported egg allergy might have included several nonallergic patients or others in whom tolerance developed over time, this is likely representative of the larger population of patients currently considered allergic to eggs. Although not quantifiable, many of them were likely truly allergic and therefore do contribute to the evidence that allergic patients can be safely vaccinated against influenza. Therefore this study provides strong evidence that this adjuvanted monovalent pH1N1 influenza vaccine (Arepanrix) was safe to administer to patients with egg allergy. Our results are in line with those from previous studies including 30 patients or more (Table I), suggesting that seasonal influenza vaccines are safe in patients with egg allergy when the egg content is less than 1.2 μg/mL.[8-15] However, we cannot generalize our results to all seasonal influenza vaccines.

Because all antigen lots used in our study had less than 0.030 μg/mL ovalbumin, which had to be mixed with an equal volume

of adjuvant, the actual content of ovalbumin in the delivered vaccine is less than 0.015 μg/mL. Although the reported ovalbumin content of 2009-2010 US Food and Drug Administration–approved monovalent A/H1N1 vaccine was close (varying between 0.003 and 0.064 μg/mL) to that in our study, it was much higher in some trivalent seasonal influenza vaccines, reaching 1.08 to 1.42 μg/mL.[18] Further studies should assess the risk after administration of vaccines with ovalbumin content closer to the 1.2 μg/mL threshold described by James et al.[9]

For patients with egg allergy, access to influenza vaccination is severely limited if they require individual assessment by an allergy specialist annually. Because rapid access to vaccination was central to protect patients with egg allergy against the 2009 pH1N1 and because skin tests with the vaccine are potentially unreliable, we used the approach recommended by a group of British allergists and supported by the CSACI. After the initial results showed no anaphylaxis, we were able to safely vaccinate more than 3,600 additional persons without requiring an allergist to assess each patient. Without this process, those patients would not have had timely access to vaccination. The same issues exist with seasonal influenza vaccination and deprive patients with egg allergy of adequate protection, many of whom are also affected by asthma. In addition, the issue of safe influenza vaccination of the patient with egg allergy will be a concern during the next pandemic, particularly if it is more severe than the 2009 pandemic. Similar studies with seasonal or future pandemic candidate influenza vaccines should be conducted to assess the safety and feasibility of vaccinating patients with egg allergy without requiring an individual investigation by allergy specialists.

Collaborators from the different sites are as follows: CHUQ-CHUL (Dr Jacques Hébert, Dr Pierre-Michel Bédard, and Dr Aubert Lavoie), Montreal Children's Hospital (Dr Bruce Mazer, Dr Christine M. C. Kusker, Dr Christine Lejtenyi, Dr Reza Alizadehfar, Dr Francisco Noya, Dr Elaine Medoff, and Dr Karen Sigman), Hôpital Ste Justine (Dr Martin Blauière, Dr Louis Paradis, and Dr Allison Kukhta), CHUS (Anne Farrands and Marguerite Plante), and Stollery Children's Hospital (Dr Timothy Vander Leek and Dr Per Lidman). We also thank Dr Normand Dubé from the Association des Allergologues et Immunologues du Québec.

Clinical implications: The risk of anaphylaxis after influenza vaccination of patients with egg allergy appears small, but further studies with seasonal vaccines are needed.

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