

Letter to the Editor

Egg-allergic patients can be safely vaccinated against influenza*To the Editor:*

As the influenza vaccine contains residual egg protein, its administration to egg-allergic patients had always raised theoretical concerns about anaphylaxis.¹ We report our experience with the vaccination of egg-allergic patients with a trivalent inactivated seasonal influenza vaccine administered during 5 seasons (2007-2011) and summarize the current published clinical experience with these patients.

We conducted a prospective cohort study recruiting and vaccinating egg-allergic patients in 2010-2011 and 2011-2012 in 5 Canadian hospitals (Montreal, Quebec City, Sherbrooke, Edmonton, and Vancouver). *Egg allergy* was defined as a history of at least 1 sign or symptom of allergy (cutaneous, ocular, respiratory, gastrointestinal, or cardiovascular symptoms) occurring within 60 minutes of egg ingestion, and the confirmation of persistent sensitization to egg (within 6 months of vaccination) shown by a skin prick test response to egg at least 3 mm larger than that of the saline control within 10 to 15 minutes, or an egg-specific IgE level of 0.35 kU/L or more (UniCAP, Pharmacia). In 2010-2011, we recruited all patients with allergy to egg, whereas in 2011-2012, the recruitment focused on patients with severe allergic reaction defined as the occurrence of anaphylaxis or cardiorespiratory symptoms upon egg ingestion. In both years, patients (or their parents/legal guardian if minor patients) had to provide written consent for the collection of data on adverse events occurring within 24 hours following vaccination. We also performed a retrospective cohort study of all egg-allergic patients referred for administration of seasonal influenza at the Sainte-Justine Hospital in Montreal, during the 2007-2008, 2008-2009, and 2009-2010 vaccination seasons. The definition of egg allergy and the threshold for skin prick test were the same as previously described, but the method of detection of specific IgE was the Immulite immunoassay system (Siemens, Muenchen, Germany).

For both cohorts, patients were examined immediately before vaccination, remained under observation for 60 minutes post-vaccination, and were then reexamined for any sign of allergic reaction. The vaccine used during all 5 seasons was the split-virion trivalent inactivated influenza vaccine Fluviral manufactured by GSK (Quebec City, Quebec, Canada). The ovalbumin content for the lots used was provided by the manufacturer: 0.09 µg/mL in 2007-2008, 0.03 µg/mL in 2008-2009, 0.31 µg/mL in 2009-2010, up to 0.2 µg/mL in 2010-2011, and up to 0.06 µg/mL for 2011-2012. The primary outcome was the occurrence of anaphylaxis according to the Brighton Collaboration definition.² The study was approved by the ethics boards of all participating hospitals.

Over 5 influenza seasons, 457 doses of trivalent inactivated seasonal influenza vaccines were administered to 367 patients among whom 132 (153 doses) had a history of severe allergy to egg (see Table E1 in this article's Online Repository at www.jacionline.org). Four patients reported mild allergic-like symptoms after previous influenza vaccination (1 urticaria, 2 vomiting, and 1 eczema), but none experienced an adverse event when given the current vaccine. While 13 patients developed mild

allergic-like symptoms in the 24 hours following vaccination, none of the 367 patients developed anaphylaxis.

We then did a literature review and retrieved articles in English or French in which at least 25 egg-allergic patients had been vaccinated. PubMed was searched with the following MESH: (influenza AND (vaccination or vaccine)) AND (egg AND (allergy OR allergic)). Further studies or conference abstracts were identified by citations in retrieved articles and by consultation with experts. Among the 87 articles retrieved from PubMed, 16 were studies including the vaccination of 25 or more egg-allergic patients. We additionally found 10 conference abstracts of studies with the same minimal number of patients. Together, these 26 studies and the current study have enrolled 4172 patients including 513 who were identified as patients with a history of severe reactions (Table I). These patients received a total of 4729 doses, and none developed anaphylaxis. With no anaphylaxis after 4729 doses of vaccine, the 95% Clopper-Pearson exact CI of the risk of anaphylaxis ranges from 0% to 0.08% (or 0 to 1 of 1250 doses).³ For the 597 doses administered to the 513 patients with a history of severe allergic reaction to egg, the exact 95% CI of the risk of anaphylaxis ranges from 0% to 0.62% (or 0 to 1 of 161 doses). Their risk of anaphylaxis is in fact smaller as many studies in Table I had patients with severe allergy but simply did not report the information regarding their number.

The clinical experience with influenza vaccination in egg-allergic patients in our cohorts and in other studies displayed in Table I has limitations. The amount of ovalbumin varied in the different influenza vaccines used and was sometimes unknown or low. Patients rarely had a recent positive food challenge confirming the persistence of egg allergy. Some studies included young children with atopic conditions (eg, atopic dermatitis) who had never eaten eggs but had a positive skin test result and high levels of egg-specific IgE. These sensitized patients are typically managed with recommendations of food avoidance as if they were allergic, although the diagnosis of allergy for these patients may be inaccurate. Despite these limitations, the patients in Table I are representative of patients managed as egg-allergic and the large number vaccinated with no ensuing anaphylaxis constitutes a strong scientific basis for new recommendations.

Egg allergy is the second most frequent food allergy and affects 1% to 2% of young children.⁴ While most patients will eventually develop tolerance to eggs, it will still be present in more than 60% by 6 years of age.⁵ In the United States, this grossly corresponds to 150,000 to 250,000 influenza vaccine-eligible preschoolers. Many of these patients have not benefited from the influenza vaccine in the past because of the fear of anaphylaxis or the difficulty of accessing an allergist as is often recommended.¹ Paradoxically, given their young age and the high rate of concurrent asthma, these patients have a higher risk of complications from influenza and are among those most likely to benefit from this vaccine.⁶ The evidence gathered over the past 15 years is overwhelmingly reassuring that this risk is minimal. The published number of egg-allergic patients safely vaccinated against influenza is nearly 4 times as large as the number that ended the precautions regarding measles, mumps and rubella (MMR) vaccine (4172 vs 1227).⁷ There will always be a very small risk of anaphylaxis associated

TABLE I. Published studies with 25 or more egg-allergic patients vaccinated against influenza

Reference	No. of patients		No. of doses	
	All	Severe allergy	All	Severe allergy
Bierman CW, Shapiro GG, Pierson WE, Taylor JW, Foy HM, Fox JP, et al. Safety of influenza vaccination in allergic children. <i>J Infect Dis</i> 1977;136:S652-55.	28	1	28	1
James JM, Zeiger RS, Lester MR, Fasano MB, Gern JE, Mansfield LE, et al. Safe administration of influenza vaccine to patients with egg allergy. <i>J Pediatr</i> 1998;133:624-8.	83	27	83	27
Zeiger RS. Current issues with influenza vaccination in egg allergy. <i>J Allerg Clin Immunol</i> 2002;110:834-40.	28	NR	28	
Dorsey MJ, Song L, Geha T, Timmons A, Oettgen H, Schneider L. Influenza vaccine in 55 patients with egg allergy. <i>J Allergy Clin Immunol</i> 2005;115:S250.	37	NR	37	
Hotte SL, Lejtenyi C, Primeau MN. A 6 years experience with influenza vaccination in egg allergic patients. <i>J Allergy Clin Immunol</i> 2008;121:S239.	115	NR	173	
Esposito S, Gasparini C, Martelli A, Zenga A, Tremolati E, Varin E, et al. Safe administration of an inactivated virosomal adjuvanted influenza vaccine in asthmatic children with egg allergy. <i>Vaccine</i> 2008;26:4664-8.	44	11	44	11
Park AY, Pien GC, Stinson R, Brown-Whitehorn, Spengel JM. Administration of influenza vaccine to patients with egg allergy. <i>J Allergy Clin Immunol</i> 2008;121:S240.	45	NR	45	
Saltzman RW, Park AY, Pien GC, Stinson R, Spengel JM. Administration of influenza vaccine to pediatric patients with egg allergy. <i>J Allergy Clin Immunol</i> 2009;123:S175.	349	NR	349	
Thanik ES, Cox AL, Sampson HA. Administration of a low egg-containing influenza vaccine [Fluarix] in an egg-allergic pediatric population. <i>J Allergy Clin Immunol</i> 2010;125:AB25.	214*	NR	214	
Chung EY, Huang L, Schneider L. Safety of influenza vaccine administration in egg-allergic patients. <i>Pediatrics</i> 2010;125:e1024-30.	171	NR	171	
Gagnon R, Primeau MN, Des Roches A, Lemire C, Kagan R, Carr S, et al. Safe vaccination of patients with egg allergy with an adjuvanted pandemic H1N1 vaccine. <i>J Allergy Clin Immunol</i> 2010;126:317-23.	830	164	830	164
Greenhawt MJ, Chernin AS, Howe L, Li JT, Sanders G. The safety of the H1N1 influenza A vaccine in egg allergic individuals. <i>Ann Allergy Asthma Immunol</i> 2010;105:387-93.	105	25	105	25
Leo SH, Dean J, Chan ES. Safety of H1N1 and seasonal influenza vaccines in egg allergic patients in British Columbia. <i>Allergy Asthma Clin Immunol</i> 2010;6:P4.	81*	NR	81	
Pien GC, LeBenger KS, Carotenuto DR, Difilippi M, Scolpino D, Simmons JM, et al. Coordination of multidisciplinary resources for vaccination of egg-allergic individuals during an H1N1 (novel) influenza pandemic. <i>Allergy Asthma Proc</i> 2010;31:507-10.	62	NR	62	
Siret-Alatrasta A, Bouali F, Demoly M, Bousquet PJ, Demoly P. The 2009-2010 H1N1 vaccination campaign for patients with egg allergy in a region of France. <i>Allergy</i> 2011;66:298-9.	53	NR	53	
Boden SR, LaBelle VS, Sedlak DA, Kim EH, Vickery BP, Burks AW. Safe administration of flu vaccine in egg-allergic patients. <i>J Allergy Clin Immunol</i> 2011;127:AB114.	101	NR	206	
Paschall VL, Siles RI, Bhatti H, Nolder PJ, Melton AL. Do egg-specific IgE levels predict reactions to seasonal influenza or H1N1 vaccination? <i>J Allergy Clin Immunol</i> 2011;127:AB182.	62	NR	131	
Owens G, MacGinnitie A. Higher-ovalbumin-content influenza vaccines are well tolerated in children with egg allergy. <i>J Allergy Clin Immunol</i> 2011;127:264-5.	64	NR	96	
Howe LE, Conlon AS, Greenhawt MJ, Sanders GM. Safe administration of seasonal influenza vaccine to children with egg allergy of all severities. <i>Ann Allergy Asthma Immunol</i> 2011;106:446-7.	204	27	204	27
Webb L, Petersen M, Boden S, LaBelle V, Bird JA, Howell D, et al. Single-dose influenza vaccination of patients with egg allergy in a multicenter study. <i>J Allergy Clin Immunol</i> 2011;128:218-9.	152	34	292	34
Pitt T, Kalicinsky C, Warrington R, Cisneros N. Assessment of epicutaneous testing of a monovalent influenza A (H1N1) 2009 vaccine in egg allergic patients. <i>Allergy Asthma Clin Immunol</i> 2011;7:3.	59	NR	59	
Schuler JE, King WJ, Dayneka NL, Rastelli L, Marquis E, Chad Z, et al. Administration of the adjuvanted pH1N1 vaccine in egg-allergic children at high risk for influenza A/H1N1 disease. <i>Can J Pub Health</i> 2011;102:196-9.	62	NR	62	
Forsdahl BA. Reactions of Norwegian children with severe egg allergy to an egg-containing influenza A (H1N1) vaccine: a retrospective audit. <i>BMJ Open</i> 2012;2:e000186.	80	19	80	19
Fung I, Spengel JM. Administration of influenza vaccine to pediatric patients with egg-induced anaphylaxis. <i>J Allergy Clin Immunol</i> 2012;129:1157-9.	56	56	119	119
Khan FS, Virant FS, Furukawa CT, Altman LC, Williams PV, Kennedy MS, et al. Influenza vaccine administration in egg allergic children. <i>J Allerg Clin Immunol</i> 2012;129:AB70.	643	NR	643	
Wainwaring Upton JE, Hummel DB, Kasprzak A, Atkinson AR. No systemic reactions to influenza vaccination in egg-sensitized tertiary care pediatric patients. <i>Allerg Asthma Clin Immunol</i> 2012;8:2.	77	17	77	17
Des Roches A, Paradis L, Gagnon R, Lemire C, Begin P, Carr S, et al. Egg-allergic patients can be safely vaccinated against influenza. <i>J Allergy Clin Immunol</i> 2012 (current study).	367	132	457	153
Totals	4172	513	4729	597

NR, Not reported.

*Number of doses, as number of patients not reported.

with influenza or any other vaccination, but there is now robust evidence that egg-allergic patients, even those with severe allergy, can be safely vaccinated against influenza. The risk of

anaphylaxis appears sufficiently low for patients with egg allergy to be vaccinated like all other individuals, without requiring administration by an allergist.

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TABLE E1. Characteristics of egg-allergic patients vaccinated against seasonal influenza between 2007 and 2011

	n (%)							
	All patients				Patients with severe allergy			
	Retrospective	Prospective		Total (N = 367)	Retrospective	Prospective		Total (N = 132)
	2007-2008 to 2009-2010 (n = 137)	2010-2011 (n = 187)	2011-2012 (n = 43)		2007-2008 to 2009-2010 (n = 31)	2010-2011 (n = 58)	2011-2012 (n = 43)	
Sex								
Male	87 (63)	98 (52)	28 (65)	213 (58)	23 (74)	29 (50)	28 (65)	80 (61)
Age (y)								
<2	29 (21)	21 (11)	6 (14)	56 (15)	5 (16)	4 (7)	6 (14)	15 (11)
2-4	53 (39)	72 (39)	11 (26)	136 (37)	14 (45)	16 (28)	11 (26)	41 (31)
5-11	51 (37)	64 (34)	18 (42)	133 (36)	11 (36)	22 (38)	18 (42)	51 (39)
>12	4 (3)	30 (16)	7 (16)	41 (11)	1 (3)	16 (28)	7 (16)	24 (18)
Skin prick test to egg								
≥3 mm	137 (100)	181 (97)	39 (91)	357 (97)	31 (100)	55 (95)	39 (91)	125 (95)
≥10 mm	71 (52)	72 (39)	14 (33)	157 (43)	22 (71)	22 (38)	14 (33)	58 (44)
Egg IgE (kUA/L)*								
<0.35	1 (1)	14 (7)	2 (5)	17 (5)	0	7 (12)	2 (5)	9 (7)
0.35-<2	22 (18)	20 (11)	2 (5)	44 (12)	2 (9)	8 (14)	2 (5)	12 (9)
2-<7	27 (22)	27 (14)	7 (16)	61 (17)	8 (36)	6 (10)	7 (16)	21 (16)
7-17	31 (25)	15 (8)	1 (2)	47 (13)	5 (23)	4 (7)	1 (2)	10 (8)
17.5-99	43 (35)	18 (10)	7 (16)	58 (16)	7 (32)	7 (12)	7 (16)	16 (16)
Tolerate baked goods†	49 (36)	53 (28)	12 (28)	114 (31)	6 (19)	18 (31)	12 (28)	36 (27)
Naive to flu vaccine	84 (61)	81 (43)	11 (26)	176 (48)	17 (55)	28 (48)	11 (26)	56 (42)
Vaccinated								
Single dose	227 (100)‡	170 (91)	41 (95)	438 (96)‡	52 (100)‡	45 (78)	41 (95)	138 (91)‡
2 doses (10% + 90%)	0	17 (9)	2 (5)	19 (4)	0	13 (22)	2 (5)	15 (9)
Allergic symptoms ≤24 h following influenza vaccination (all were mild)	0	9 (5)	4 (9)	13 (6)	0	2 (3)	4 (9)	6 (6)

Significant differences with *P* values <.05 between severe and nonsevere egg-allergic patients are indicated in bold characters.

*Measured with UniCAP for 2010-2011 and 2011-2012 and with Immulite for 2007-2010.

†There were 114 patients (including 36 severe cases) who had challenge with a baked good and tolerated it well. While the tolerance to baked goods in patients with severe allergy may suggest milder severity, this does not rule out the risk of severe reaction to uncooked egg proteins.

‡Some patients had more than 1 dose over several seasons. Percentage calculated on the total number of doses administered.