

Letter to the Editor

Allergic symptoms after pandemic influenza vaccination rarely mediated by vaccine-specific IgE

To the Editor:

In 2009, anaphylaxis and allergic-like reactions to the AS03-adjuncted monovalent pandemic H1N1 (pH1N1) vaccine were frequent.¹⁻³ They constituted 40% of all adverse event notifications in Canada, with a rate of anaphylaxis 20 times greater than the historical average.^{2,3} This vaccine (Arepanrix; Glaxo-SmithKline, Laval, Quebec, Canada) accounted for more than 96% of the doses administered in Canada.

Among patients aged 10 to 64 years who presented allergic symptoms less than 24 hours following pH1N1 vaccination, we estimated the proportion who had an IgE-mediated allergy to the pH1N1 vaccine. These cases were compared with a control group of individuals, frequency-matched for age and sex, with no such history. Participants were investigated between January and March 2011 (13-18 months after vaccination). A description of the reaction was obtained from cases by using a standardized questionnaire. Skin prick test (SPT) and intradermal test (IDT) were performed by using Arepanrix (mixed antigen + AS03-adjunct) or its separate components (the antigen alone, the AS03-adjunct alone), positive (histamine), and negative (saline) controls. SPT was performed by using full-strength products, and IDT was performed by injecting 0.02 mL at 1:100 dilution. Reactions to both SPT and IDT were observed at 10 minutes: the result was positive if, compared with saline, the SPT wheal was 3 mm or more, or if the IDT wheal was 5 mm or more. All were considered negative in the absence of a flare (erythema). Skin testing result was considered positive when both the mixed vaccine and at least 1 component (antigen or adjuvant) were also positive. Skin testing result was considered indeterminate when tests were positive for the vaccine or one of its components but not both. Skin testing result was considered negative when skin tests were negative to the 3 products (antigen, adjuvant, and vaccine).

We tested 95 cases and 37 controls, most of whom were women (83%) with a mean age of 38 years. While 50% of both cases and controls reported at least 1 allergy, self-reported food intolerances (34% vs 14%; $P = .02$) and prior anaphylaxis (22% vs 0%; $P < .001$) were more frequent among cases. These anaphylaxis were attributed to various antigens (eg, foods, drugs, etc). Fish and egg allergy were reported by only 3% of the cases (Table I).

Among cases, 52% had their symptom onset less than 1 hour following vaccination (Table I). Mucocutaneous symptoms were reported by 88% of the cases; 44% reported urticaria, and 39% had angioedema affecting the throat (31%), lips (29%), tongue (23%), or eyelids (20%) (Table I). A sensation of throat closure or dysphagia was reported by 40% to 45% of the cases, 48% complained of dyspnea, 18% of dry persistent coughing, and 22% of wheezing. Injection site reactions were frequent (63%), but few involved localized pruritic rash (13%). Symptoms lasted an average of 5 hours, 66% received antihistamines, 20% were given epinephrine, and 4% were hospitalized. For 22 cases, their reaction was considered anaphylactic.

Positive skin test results were observed in 4 (4%) cases (see Table E1 in this article's Online Repository at www.jacionline.org).

and 1 (3%) control (Fisher exact test, $P = .99$). Among cases, 1 was positive to the antigen, 2 to the adjuvant, and 1 to both components, while the positive control had a positive IDT result to the adjuvant. Seven cases (7%) and 1 control (5%) had indeterminate results, while the remaining 84 cases (88%) and 35 controls (95%) had negative skin test results, including all cases with egg or fish allergy. Among the 22 cases who had a reaction compatible with anaphylaxis as assessed by the allergist after his evaluation, 2 (9%) had a positive skin test result and 1 (5%) had an indeterminate result. Among the 19 patients who had received epinephrine for their symptoms, 1 (5%) had indeterminate and 2 (10%) had positive skin test results.

Seasonal influenza vaccination was offered to 83 cases (87%), and 25 (27%) accepted to be revaccinated with the trivalent split 2011-2012 seasonal influenza vaccine (Fluviral, GlaxoSmithKline). Two (8%) revaccinated cases had indeterminate skin test results (one prick positive to the antigen and adjuvant but negative to the mixed product, and the other had a positive IDT result to the adjuvant) while the remainder were negative (92%), 3 of which were consistent with anaphylaxis. Five cases presented delayed self-limiting allergic-like symptoms despite negative ($n = 4$) or indeterminate ($n = 1$) skin test results (Table E1), none of which were likely due to an IgE-mediated allergy. No reaction was observed among the 3 revaccinated cases of anaphylaxis.

In this study, 4% of the cases had positive skin test results suggestive of an IgE-mediated hypersensitivity to the pH1N1 vaccine, a proportion that was similar among controls (3%). While 5 cases reported symptoms after revaccination with the seasonal vaccine containing the same pH1N1 antigen, none appeared attributable to a type I hypersensitivity, suggesting that IgE-mediated allergy to the pandemic vaccine was uncommon. This result is similar to those reported in other vaccine studies.^{4,5}

Skin testing with the implicated vaccine is currently the recommended approach to investigate suspected IgE-mediated reactions to vaccines.^{6,7} Vaccines, however, are not standardized for skin testing, and results are often difficult to correlate with a diagnosis of vaccine allergy. False-positive results are unlikely to happen with full-strength SPT but may occur at a frequency of 10% to 15% with IDTs with the influenza vaccine diluted 1:100.^{8,9} The 7 participants with discordant results between the vaccine and its components were considered indeterminate. Although we cannot rule out that mixing the antigen and the adjuvant exposes new allergenic epitopes, they likely represent false-positive results. Though unlikely, indeterminate or negative results do not rule out an IgE-mediated allergy to vaccine metabolites and do not exclude the possibility of recurrences upon revaccination if other mechanisms are involved.⁶

It has historically been assumed that allergic reactions to vaccination are due to allergenic components of vaccines such as egg, yeast, gelatin, latex, or antibiotics.^{6,7} The presence of an adjuvant derived from shark liver oil also raised concerns for patients allergic to fish. In our study, allergies to egg or fish were reported by only 3% of the cases, all of whom had negative skin test results with the vaccine. These background allergies are unlikely to have played a significant

TABLE I. Characteristics of cases and symptoms after the administration of the 2009 adjuvanted pandemic A/H1N1 vaccine, by interval between vaccination and symptom onset

	n (%)				All cases (N = 95)
	Interval between vaccination and onset of symptoms				
	<1 h (n = 49)	1-3 h (n = 12)	4-11 h (n = 14)	12-23 h (n = 19)	
Patient characteristics					
Female	42 (86)	11 (92)	12 (86)	14 (74)	79 (84)
Mean age (y)	34	41	34	41	37
First dose of influenza vaccine ever	27 (55)	4 (33)	9 (64)	11 (58)	51 (54)
Allergy diagnosed by physician	22 (45)	8 (67)	7 (50)	8 (42)	45 (48)
Aeroallergens	14 (29)	4 (33)	5 (36)	4 (22)	27 (29)
Drugs	12 (25)	7 (58)	3 (21)	4 (22)	26 (28)
Any food allergy	8 (16)	2 (17)	1 (7)	1 (6)	12 (13)
Eggs	2 (4)	0 (0)	0 (0)	0 (0)	2 (2)
Fish	3 (6)	0 (0)	0 (0)	0 (0)	3 (3)
Shellfish	3 (6)	1 (8)	0 (0)	0 (0)	4 (4)
Other allergy	39 (80)	11 (92)	10 (71)	15 (79)	75 (80)
Allergic rhinitis	9 (18)	2 (17)	3 (21)	3 (16)	17 (18)
Eczema	8 (16)	2 (17)	0 (0)	2 (11)	12 (13)
Asthma	13 (27)	3 (25)	0 (0)	7 (37)	23 (24)
Symptoms to pandemic vaccine					
Local reaction*	29 (59)	39 (75)	12 (86)	10 (53)	60 (64)
Ocular symptoms†	14 (29)	4 (33)	4 (29)	8 (42)	30 (32)
Red itchy eyes	7 (14)	3 (25)	1 (7)	2 (11)	13 (14)
Redness	12 (24)	3 (27)	4 (31)	6 (32)	25 (27)
Pruritus	8 (16)	3 (27)	1 (7)	2 (11)	14 (15)
Discharge	4 (8)	2 (18)	2 (14)	5 (26)	13 (14)
Pain/burning	11 (23)	4 (36)	3 (21)	3 (16)	21 (23)
Cardiovascular	28 (57)	7 (58)	4 (29)	4 (21)	43 (46)
Palpitations	21 (49)	5 (42)	3 (21)	3 (16)	32 (36)
Feeling faint/fainted	20 (41)	5 (42)	3 (21)	2 (11)	30 (32)
Respiratory‡	34 (69)	7 (58)	5 (36)	9 (47)	55 (59)
Nasal congestion/rhinorrhea/sneezing	5 (11)	4 (36)	3 (23)	3 (17)	15 (17)
Sore throat	10 (21)	1 (9)	3 (23)	4 (21)	18 (20)
Cough	11 (22)	0 (0)	2 (15)	3 (17)	16 (18)
Difficulty breathing	30 (61)	5 (42)	4 (29)	7 (37)	46 (49)
Chest tightness	17 (35)	3 (25)	3 (21)	5 (26)	28 (30)
Wheezing	10 (20)	3 (25)	2 (14)	5 (26)	20 (21)
Tachypnea	23 (49)	6 (50)	3 (21)	6 (32)	38 (41)
Cyanosis of extremities	7 (16)	2 (17)	1 (7)	2 (11)	12 (13)
Mucocutaneous§	44 (90)	11 (92)	14 (100)	16 (84)	85 (90)
Angioedema	17 (35)	4 (33)	7 (50)	9 (47)	37 (39)
Eyelid swelling	6 (13)	2 (17)	4 (29)	6 (32)	18 (20)
Lip swelling	11 (24)	4 (33)	6 (43)	5 (26)	26 (29)
Tongue swelling	12 (26)	3 (25)	2 (14)	4 (21)	21 (23)
Throat swelling	17 (39)	5 (42)	1 (8)	4 (21)	27 (31)
Sensation of throat tightening	28 (58)	5 (42)	3 (21)	5 (26)	41 (44)
Difficulty swallowing	25 (53)	4 (33)	3 (23)	4 (21)	36 (40)
Hoarseness	13 (28)	2 (20)	4 (31)	2 (11)	21 (24)
Any skin rash	26 (53)	10 (83)	9 (64)	11 (58)	55 (59)
Pruriginous skin rash (urticaria)	17 (35)	8 (67)	7 (50)	10 (53)	42 (45)
Gastrointestinal	19 (39)	4 (33)	1 (7)	3 (16)	27 (28)
Abdominal pain or diarrhea	6 (12)	3 (25)	1 (7)	1 (5)	11 (12)
Nausea or vomiting	17 (35)	2 (17)	0 (0)	2 (11)	21 (22)

Italicized values are part of the prior, non-italicized category.

*Local reaction is defined as any of the following symptoms at the injection site: pain, swelling, pruritus, nonpruriginous rash, redness and/or tingling.

†Ocular symptoms also include palpebral edema for which results are also included in mucocutaneous symptoms.

‡Respiratory symptoms include any of the following symptoms: dry persistent coughing, dyspnea, wheezing, tachypnea, cyanosis of the extremities and/or chest tightness, sneezing, nasal congestion, rhinorrhea and/or sore throat.

§Mucocutaneous symptoms include: angioedema or skin rash (pruriginous or nonpruriginous).

||Angioedema includes: facial edema (eyelid, lips, or head/neck), edema of the tongue or throat, hoarseness, difficulty swallowing and/or a sensation of throat tightening.

role in the occurrence of allergic-like symptoms to the pandemic vaccine. However, the history of prior anaphylaxis to different allergens in 20% of the cases suggests susceptibility due to unidentified mechanisms. We conclude that IgE-mediated allergies to the pandemic vaccine were rare and that reactions in our patients were either coincidental or attributable to other immunologic reactions to the vaccine that have yet to be determined.

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Isabelle Rouleau, MSc^a

Gaston De Serres, MD, PhD^{a,b}

Jean Philippe Drolet, MD, FRCPC^a

Devi Banerjee, MD, FRCPC^c

Chantal Lemire, MD, FRCPC, FAAAAI^d

Andrew Moore, MD, FRCPC^e

Louis Paradis, MD, FRCPC, FAAAAI^f

Reza Alizadhefar, MD, FRCPC, FAAAAI^g

Anne Des Roches, MD, FRCPC, FAAAAI^h

Edmond S. Chan, MD, FRCPC, FAAAAI^h

Donald Stark, MD, FRCPC, FAAAAIⁱ

Mélanie Benoit, BSc^a

Danuta M. Skowronski, MD, FRCPC^j

On behalf of the PCIRN (Public Health Agency of Canada–Canadian Institutes for Health Research Influenza Research) Network

From ^aCentre hospitalier universitaire de Québec, Laval University, Quebec City, Quebec, Canada; ^bthe Institut national de santé publique du Québec, Quebec City, Quebec, Canada; ^cMcGill University Health Center, McGill University, Montreal, Quebec, Canada; ^dCentre hospitalier universitaire de Sherbrooke, University of Sherbrooke, Sherbrooke, Quebec, Canada; ^eCentre affilié universitaire Hôpital Charles Lemoyne, Greenfield Park, Quebec, Canada; ^fCentre hospitalier universitaire de Montréal, Montreal University, Montreal, Quebec, Canada; ^gHôpital Ste-Justine, University of Montreal, Montreal, Quebec, Canada; ^hBC Children's Hospital, University of British Columbia, Vancouver, Canada; ⁱUniversity of British Columbia, Vancouver, Canada; and ^jBC Center for Disease Control, Vancouver, Canada. E-mail: gaston.deserres@ssss.gouv.qc.ca.

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Table E1. Symptoms following the pandemic vaccine of the four cases with positive skin test and of the five patients with allergic symptoms after revaccination with the seasonal vaccine

Pt	Description of symptoms following the pandemic vaccine	Skin testing results
Patients positive to skin testing		
A	F 41 years old. Post pandemic vaccine 45 minutes after vaccination, bilateral conjunctivitis, dry and persistent cough, sore throat, hoarseness, dyspnea, chest tightness. Numbness, prickling and weakness in both legs (difficulty in raising legs), and felt pressure behind head. Arthralgia, non-pruritic rash. Rash at the injection site.	Reconstituted vaccine IDT: 7 mm wheal / 8 mm flare Antigen SPT: 3mm wheal / 4 mm flare
B	F 43 years old with a history of eczema. Post pandemic vaccine Within 2 minutes after pandemic vaccination, chest and throat tightness, dizziness and dyspnea. Urticaria and facial angioedema, tachycardia, light headedness, tachypnea, cyanosis, difficulty swallowing and abdominal pain. Epinephrine was administered. Four to five hours later, reaction resumed and epinephrine was administered again.	Reconstituted vaccine IDT: 7 mm wheal / 8 mm flare Adjuvant IDT: 6 mm wheal / 10 mm flare
C	F 33 years old. Post pandemic vaccine Immediately after vaccination, feeling of heat and facial oedema. 10 minutes later, red non-itchy plaques on the trunk and legs, weakness, trembling and feeling faint. No adrenaline was administered. At the ER she was administered antihistamines, solucortef and prednisone.	Reconstituted vaccine IDT: 9 mm wheal / 10 mm flare Adjuvant IDT: 8 mm wheal / 12 mm flare
D	F 6 years. Post pandemic vaccine 3 minutes post-vaccination, sensation of throat tightening and difficulty swallowing, dyspnea, tachypnea and chest tightness. Epinephrine administered. Transferred to ER where she received epinephrine, cortisone and antihistamines. Patient had a history of food intolerances to peaches, gooseberry and penicillin, asthma, chronic bronchitis, depression. Atypical cholinesterase	Reconstituted vaccine SPT: 3 mm wheal / 25 mm flare Antigen SPT: 7 mm wheal / 6 mm flare Adjuvant SPT: 6 mm wheal / 25 mm flare
Patients with allergic symptoms after seasonal revaccination		
E	F 39 years. Post pandemic vaccine: Twelve hours after vaccination, the patient presented with fever, dizziness and a dry cough. She also had facial swelling, bilateral conjunctivitis (with pruritus, pain and discharge), hoarseness, dyspnea with wheezing, nasal congestion and chest tightness. Also reported nausea and vomiting. Post seasonal revaccination: within 30 minutes nausea, dizziness and headache which resolved 50 minutes later. Later that day, pruritus to the neck, a hoarse voice and headache.	Negative
F	F 48 years Post pandemic vaccine: Immediately after vaccination, the patient reported sublingual oedema and difficulty swallowing, diarrhea, nausea and vomiting. Post seasonal revaccination: Within 1 hour, sensation of sublingual oedema and pruriginous rash at the injection site which resolved without intervention 20 minutes later. Oedema was not objectivated by the allergist. At 20 hours, bilateral conjunctivitis with ocular pruritus, sore throat and cough	Negative
G	F 55 years Post pandemic vaccine: 17 hours post vaccination, bilateral conjunctivitis with pain, discharge and palpebral oedema, dyspnea with wheezing, chest tightness, hoarse voice and a sensation of oedema to lips, tongue and throat with dysphagia. Post seasonal revaccination 24 hours after vaccination: Bilateral conjunctivitis, ocular pruritus and palpebral oedema.	Negative
H	F 53 years Post pandemic vaccine: 8 hours post vaccination generalized urticaria, bilateral conjunctivitis with palpebral oedema, dyspnea with wheezing, hoarse voice, sensation of throat and chest tightness, tachycardia, fever, and fatigue Post seasonal revaccination: 8 hours after vaccination, urticarial lesion where the skin tests were done and a hoarse voice.	Negative
I	F 45 years Post pandemic vaccine: One hour post vaccination, pruriginous rash all over the body. Post seasonal revaccination: 6 hours post vaccination, generalized urticaria, palpitations, dyspnea without wheezing, dry and persistent cough. The rash, dyspnea and palpitations were short-lived. Considered anxiety-related by the patient and allergist.	Indeterminate