Original Article

Clinical Approach Used in Medical Consultations for Allergic-Like Events Following Immunization: Case Series Report in Relation to Practice Guidelines

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What is already known about this topic? The Joint Task Force on Practice Parameters (JTFPP) guidelines on the management of allergic-like events (ALEs) after immunization are based on the likelihood of anaphylaxis identified through the time to symptom onset ($\leq$ or $>$4 hours) and number of systems involved (1 or $\geq$2 systems).

What does this article add to our knowledge? In actual practice, most patients did not experience anaphylaxis but were managed as if they had. Management appeared to be the same regardless of the time to symptom onset or number of systems involved. Recurrences of ALEs mostly occur in patients with onset of their initial ALE within 1 hour after immunization. In patients with delayed ALEs ($>$4 hours), an IgE-mediated reaction is unlikely; in that context, skin testing can be misleading and should be limited to patients meeting a specific case definition of anaphylaxis.

How does this study impact current management guidelines? The definition of anaphylaxis in the JTFPP guidelines seems too nonspecific and may warrant revisiting. The 4-hour interval currently used to identify IgE-mediated vaccine reactions seems too long; the standard 1-hour interval used for other injected products is likely also appropriate for vaccines. Restricting skin testing and graded dose reimmunization to patients with onset $\leq$1 hour (probably IgE mediated) or to anaphylaxis (regardless of the time to symptom onset) is likely sufficiently cautious to avoid anaphylaxis at reimmunization.

BACKGROUND: The Joint Task Force on Practice Parameters (JTFPP) guidelines for the investigation and reimmunization of patients who experienced allergic-like events (ALEs) after immunization are predicated on the likelihood of anaphylaxis, assessed through the time to symptom onset (≤ or >4 hours) and number of systems involved.

OBJECTIVE: The objectives of this study were to compare the management of a series of patients with ALE in actual practice relative to JTFPP guidelines and to discuss key concepts and considerations in their use.

METHODS: This retrospective study was based on a chart review of patients who consulted for suspected vaccine-associated ALEs at a large allergy department in Canada.

RESULTS: Only 3 of the 135 patients who presented ALEs after immunization were referred for suspected anaphylaxis. There was no significant difference in the frequency of skin testing or reimmunization of patients whatever the time to symptom onset or number of systems involved in the ALE. Eight patients whose initial ALE occurred within 1 hour after immunization had a recurrence on reimmunization. Another patient whose initial ALE occurred 10 hours after influenza immunization had throat tightening and difficulty swallowing without objective signs.

CONCLUSIONS: Most ALEs after immunization are not suggestive of anaphylaxis and should not be managed as such. The definition of anaphylaxis in the JTFPP guidelines is nonspecific and may need to be revisited. Restricting skin testing and graded dose reimmunization to patients whose ALE onset is ≤1 hour (compatible with IgE-mediated reaction) and to those

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Abbreviations used
AEFI- Adverse event following immunization
ALE- Allergic-like event
DTaP- Diphteria (D), tetanus (T), acellular pertussis (aP) vaccine
JTFPP- Joint Task Force on Practice Parameters (representing the American Academy of Allergy, Asthma and Immunology, the American College of Allergy, Asthma and Immunology, and the Joint Council of Allergy, Asthma and Immunology)
MMR- Measles mumps rubella vaccine
ORS- Oculorespiratory syndrome

meeting specific clinical criteria for anaphylaxis (whatever the timing) is likely a sufficiently sensitive and cautious approach. **(J Allergy Clin Immunol Pract 2016;■:■-■)**

Key words: *Vaccine; Allergy; Adverse event; Vaccine safety*

After injection site reactions, fever, and general malaise, allergic-like events (ALEs) are the most frequently reported adverse events following immunization (AEFI).[1-3] Because of the fear of anaphylaxis on reimmunization, patients who experienced an ALE after immunization often receive a presumptive diagnosis of vaccine allergy accompanied by precautionary interruption of immunization until their evaluation by an allergist.

Anaphylaxis is an acute hypersensitivity reaction with multiorgan-system involvement that can present as, or rapidly progress to, a life-threatening event.[4] Anaphylaxis is often caused by immediate hypersensitivity reactions triggered by IgE, and for injected allergens, symptom onset typically occurs within minutes and almost always within 1 hour of exposure.[4-6] Delayed reactions may be caused by other mechanisms and are less likely to be life threatening. Anaphylaxis to vaccines in particular typically begins within 30 minutes after immunization, but can have an onset several hours later.[7-10] In patients with a history of an ALE, the risk of anaphylaxis on re-exposure to the vaccine depends on the mechanism (IgE mediated or not) and severity of the initial ALE (anaphylaxis or not).

Several guidelines have been proposed to provide safe reimmunization to patients with a history of an ALE after immunization.[11-13] The guidelines of the Joint Task Force on Practice Parameters (JTFPP) focus on anaphylaxis, and the clinician must foremost address the question: "Are the nature and timing of the reaction consistent with anaphylaxis?"[11] A "probable anaphylactic reaction" is defined as a reaction occurring within 4 hours of exposure and affecting 2 or more systems (dermatologic, respiratory, cardiovascular, or gastrointestinal), whereas a "possible anaphylactic reaction" is a reaction occurring within 4 hours after immunization that affected 1 system or a reaction occurring more than 4 hours after immunization but affecting 2 or more systems. For patients who need further doses, those whose reaction is not consistent with anaphylaxis should be revaccinated with a full dose of the implicated vaccine without further investigation.[11] For those whose reaction is consistent with probable or possible anaphylaxis, the management is more cautious. When possible, serology should assess whether the patient is protected from the disease prevented by the vaccine. If serology is not available or shows antibody titer below protective levels, the allergist should perform skin testing to assess possible IgE response to the vaccine or its components. Testing begins with a skin prick test with the vaccine, followed if negative by an intradermal test with the vaccine diluted at 1:100.[11,12] Patients with negative skin tests can be reimmunized with a single full dose of vaccine but should remain under observation for at least 30 minutes. In patients with positive skin tests, reimmunization can be avoided or administered in graded doses depending on the severity of the initial ALE, the risk (severity and incidence) of the vaccine-preventable disease, and the patient's preference.[11,12] The JTFPP practice guidelines are mainly based on an expert opinion, and their real-world compliance as well as their clinical impact have not been formally evaluated.

There is a paucity of literature describing the clinical management of patients who experienced ALEs after immunization. The objectives of this study were (1) to describe the clinical approach used to manage patients with an ALE after immunization in a large department of allergy in Canada, (2) to compare this approach with the management algorithm proposed by the JTFPP, (3) to assess the safety of reimmunization, and (4) to discuss key concepts of the JTFPP guidelines that may need to be revisited.

METHODS

This retrospective study included patients who consulted one of the 8 allergists of the Laval University Teaching Hospital (now called Centre Hospitalier Universitaire de Québec—Université Laval) in Quebec City, Canada, for an ALE after immunization between January 1, 2008, and December 31, 2011. Patients whose reason for consultation made reference to vaccine(s) were identified from the appointment listings of the allergy clinic. Their medical charts were retrieved and anonymized. Baseline characteristics, clinical data, test results, and reimmunization status were extracted using a standardized form. We excluded patients who consulted for nonallergic AEFI (eg, local reaction), those who consulted only for allergy to a specific vaccine component (eg, eggs), and those consulting for conditions or treatments possibly interfering with immunization response (eg, immune deficiency).

The need for additional doses of vaccine was based on the Quebec recommended immunization schedule.[14] Given annual reformulation of influenza vaccine, we considered that additional doses were always indicated for this vaccine. Reimmunization was defined as the administration of the vaccine(s) implicated in the ALE or another vaccine sharing common antigens. We calculated the proportion of patients who had an immediate ($\leq$4 hours) or delayed reaction (>4 hours), who had serologic testing for one or more of the vaccine antigens, who were skin tested, and who were revaccinated. Skin tests consisted of a prick test with vaccine diluted at 1:10 followed if negative by an intradermal test with vaccine diluted at 1:100. A positive skin test was defined as a wheal $\geq$3 mm compared with the saline control surrounded by flare and/or erythema.[12] Recurrence of an ALE was defined as any allergic symptom within 24 hours after reimmunization.

Proportions were compared using χ^2 or Fisher exact tests when indicated. Statistical testing was bilateral with significance set at $P < .05$. The study protocol was approved by the hospital research ethics board.

RESULTS

During the 4 study years, there were 362 appointments for which a vaccine-related issue was identified as a possible reason for consultation. Of these, 227 were excluded: 22 patients did not come to their appointment, 8 did not consult for a vaccine-

TABLE I. Characteristics of patients who consulted an allergist for an allergic-like event after immunization

	Influenza N = 56 n (col%)	DTaP-Hib-P dTap-P N = 37 n (col%)	MMR N = 12 n (col%)	PCV N = 14 n (col%)	HPV N = 15 n (col%)	Hep A+B Hep B N = 22 n (col%)	Other vaccines N = 17 n (col%)	Any vaccine N = 141 n (col%)
Sex								
Male	7 (12)	18 (50)	9 (75)	7 (50)	1 (7)	7 (32)	6 (35)	39 (28)
Female	49 (88)	19 (50)	3 (25)	7 (50)	14 (93)	15 (68)	11 (65)	102 (72)
Age group								
0-4 y	4 (6)	27 (90)	11 (92)	14 (100)	0	0	5 (29)	42 (30)
5-17 y	2 (6)	3 (10)	0	0	15 (100)	15 (68)	5 (29)	38 (27)
≥18 y	50 (88)	7	1 (8)	0	0	7 (32)	7 (42)	61 (43)
Medical history*								
Atopic dermatitis	3 (5)	3 (8)	0	2 (14)	1 (7)	0	3 (18)	10 (7)
Asthma	9 (16)	3 (8)	0	0	1 (7)	3 (14)	3 (18)	18 (13)
Allergic rhinitis	7 (12)	1 (3)	0	0	2 (13)	2 (9)	1 (6)	13 (9)
Food allergy	4 (7)	3 (8)	0	0	2 (13)	2 (9)	2 (12)	12 (9)
Drug allergy	8 (14)	3 (8)	1 (8)	1 (7)	1 (7)	2 (9)	3 (18)	15 (11)
Other allergy	7 (12)	4 (11)	2 (17)	0	3 (20)	3 (14)	3 (18)	18 (13)

DTaP-Hib-P, Diphteria (D), tetanus (T), acellular pertussis (aP), *Haemophilus* influenzae type B (Hib) and poliomyelitis (P) vaccine; *dTap-P*, reduced antigen diphteria (d), tetanus (T), acellular pertussis (ap), and poliomyelitis (P) vaccine; *Hep A+B*, hepatitis A and B vaccine; *HPV*, human papilloma virus vaccine; *MMR*, measles mumps rubella vaccine; *PCV*, pneumococcal conjugated vaccine.
*Some patients had more than 1 atopic condition or allergy and were counted more than once.

related issue, and 41 lacked the necessary information in their medical chart to contribute to analysis. The remaining 156 excluded patients never actually experienced an ALE after immunization: 7 attended for immune deficiency, 9 had experienced a large local reaction to a previous vaccine with no allergic sign or symptom, and 140 consulted for a declared allergy to a vaccine component: egg (108), antibiotics (10), thimerosal (8), mercury (7), latex (4), or other products (3).

After these exclusions, there remained 135 patients who experienced 141 ALEs (6 patients had 2 separate episodes involving different vaccines) after immunization with 173 vaccines.

Patient characteristics

Among these 135 patients, 57% were children. Females consulted 2.6 times more often than males (72% vs 28% $P < .001$) (Table I). Children younger than 5 years of age consulted for routine childhood vaccines (diphteria, tetanus, acellular pertussis [DTaP], *Haemophilus* influenzae type B and poliomyelitis vaccine; measles mumps rubella vaccine [MMR]; and pneumococcal conjugated vaccine), whereas adults mostly (82%) consulted in relation to the influenza vaccine. A history of atopy (dermatitis, asthma, or rhinitis) was reported by 24% (n = 33) of patients, and 27% (n = 37) reported a history of allergy to at least one other trigger.

Description of the ALEs

The interval between immunization and symptom onset was specified for 99 (70%) ALEs; the median interval was ≤2 hours for all vaccines except influenza (4 hours) and MMR (24 hours) (Table II). The median duration of symptoms was <7 days for all vaccines except MMR for which the median symptom duration was 12.5 days.

Signs and symptoms were described in the medical chart for 85% (120/141) of ALEs. Among the 21 patients who had no description of symptoms, 3 allegedly consulted for anaphylaxis after different vaccines (MMR, influenza, or yellow fever). Among the 120 patients with clinical descriptions, rash was the sign most frequently reported (overall 57%, range 42% to 80% depending on the implicated vaccine); rash was generalized in 24 (17%) patients and 7 (9%) had concomitant pruritus (Table II). Respiratory symptoms were reported in 35% of ALEs (range, 10% to 53%) and gastrointestinal symptoms in 6%. Cardiovascular symptoms (loss of consciousness, tachycardia) were reported by 2 patients. Most ALEs (n = 87, 73%) involved only one of the aforementioned systems. In 33 (27%) patients, symptoms involved 2 or more systems of which 23 (70%) had onset within 4 hours (16 within 1 hour), 3 (9%) had onset >4 hours, and 7 (21%) had no information on the time to onset of symptoms. No patient was hospitalized because of the ALE, but 18% (n = 25, 11 with immediate reactions involving ≥2 systems) had an emergency department visit and 10% (n = 14, 9 with immediate reactions involving ≥2 systems) received adrenaline.

The influenza vaccine was involved among 56 patients who most often reported respiratory symptoms (50%) followed by rash (45%) and ocular symptoms (13%). Nineteen (34%) of these patients presented ocular and/or respiratory symptoms within 24 hours after immunization, a clinical presentation compatible with the diagnosis of oculorespiratory syndrome (ORS), but this diagnosis was only mentioned once.

A total of 118 skin tests were undertaken for the 173 vaccines associated with the initial ALEs: 17 of 22 (77%) among ALEs meeting the "probable," 34 of 41 (83%) among ALEs meeting the "possible" JTFPP case definition for anaphylaxis, 24 of 37 (65%) among patients meeting neither case definition, and 43 of 73 (59%) among patients who could not be classified (time to onset or number of systems unavailable). Of the 118 skin prick tests conducted, 98% were negative as were 71% of the ensuing 116 intradermal tests. Of those that were positive either by the skin prick or intradermal test, the "probable," "possible," and neither case definition for anaphylaxis was met by 8 of 17 (47%), 9 of 34 (26%), and 7 of 24 (29%), respectively.

TABLE II. Clinical presentation of allergic-like events per vaccine

	Influenza N = 56 n (col%)	DTaP-Hib-P dTap-P N = 37 n (col%)	MMR N = 12 n (col%)	PCV N = 14 n (col%)	HPV N = 15 n (col%)	Hep A+B Hep B N = 22 n (col%)	Other vaccines N = 17 n (col%)	Any vaccine N = 141 n (col%)
Time to symptom onset								
≤1 h	16 (29)	11 (30)	2 (17)	5 (36)	5 (33)	8 (36)	8 (47)	41 (29)
1-3 h	5 (9)	6 (16)	0	2 (14)	3 (20)	4 (18)	1 (6)	16 (11)
≥4 h	17 (30)	12 (32)	6 (50)	5 (36)	3 (20)	5 (23)	2 (12)	42 (30)
Missing	18 (32)	8 (22)	4 (33)	2 (14)	4 (27)	5 (23)	6 (35)	42 (30)
Mean (median)	53.9 (4.0)	12.4 (1.1)	26.0 (24.0)	9.4 (1.9)	4.2 (1.0)	8.0 (2.0)	5.6 (0.5)	27.6 (2.5)
Duration of symptoms								
<1 d	7 (12)	4 (11)	0	3 (21)	1 (7)	3 (14)	3 (17)	15 (11)
1-6 d	9 (16)	6 (16)	1 (8)	5 (36)	4 (27)	8 (36)	2 (12)	25 (18)
≥7 d	2 (4)	5 (13)	3 (25)	4 (29)	1 (7)	2 (9)	4 (24)	15 (11)
Missing	38 (68)	22 (60)	8 (67)	2 (14)	9 (60)	9 (41)	8 (47)	86 (61)
Mean (median)	5.1 (1.2)	5.9 (3.0)	26.3 (12.5)	6.8 (4.0)	6.5 (2.0)	1.9 (2.0)	8.5 (6.0)	7.4 (2.0)
Medical consultation*	9 (16)	8 (23)	3 (25)	5 (36)	4 (27)	6 (27)	5 (29)	31 (22)
Medical office	4 (7)	2 (7)	2 (17)	2 (14)	0	1 (5)	1 (6)	9 (6)
Emergency department	7 (12)	6 (20)	1 (8)	3 (21)	4 (27)	5 (23)	5 (29)	25 (18)
Adrenaline	6 (11)	1 (3)	1 (8)	0	4 (27)	2 (9)	3 (18)	14 (10)
Number of systems involved								
1 system	33 (59)	26 (70)	7 (58)	11 (79)	5 (33)	16 (73)	10 (59)	87 (62)
≥2 systems	14 (25)	7 (19)	1 (8)	2 (14)	9 (60)	5 (23)	3 (18)	33 (23)
Not mentioned	9 (16)	4 (11)	4 (34)	1 (7)	1 (7)	1 (4)	4 (23)	21 (15)
Symptoms								
Anaphylaxis†	1 (2)	0	1 (8)	0	0	0	1 (5)	3 (2)
Rash‡	25 (45)	22 (73)	8 (67)	11 (79)	12 (80)	15 (68)	8 (42)	81 (57)
Localized	2 (4)	2 (7)	1 (8)	1 (7)	1 (7)	1 (5)	0	6 (4)
Generalized	4 (7)	10 (33)	1 (8)	9 (64)	4 (27)	5 (23)	3 (16)	24 (17)
Unspecified	19 (34)	10 (33)	6 (50)	1 (7)	7 (47)	9 (41)	5 (26)	51 (36)
Angioedema	6 (11)	1 (3)	1 (8)	0	3 (20)	1 (5)	0	11 (8)
Ocular‡	7 (13)	2 (7)	0	1 (7)	1 (7)	0	0	10 (7)
Red/itchy/watery eyes	4 (7)	1 (3)	0	1 (7)	0	0	0	5 (4)
Palpebral edema	3 (5)	2 (7)	0	1 (7)	1 (7)	0	0	6 (4)
Respiratory‡	28 (50)	3 (10)	1 (8)	0	7 (53)	6 (27)	7 (37)	49 (35)
Sore throat	5 (9)	0	1 (8)	0	0	3 (14)	4 (21)	10 (7)
Cough	4 (7)	1 (3)	0	0	0	1 (5)	0	6 (4)
Lip/tongue/throat swelling	5 (9)	0	1 (8)	0	0	4 (18)	3 (16)	10 (7)
Wheezing	2 (4)	1 (3)	0	0	0	0	0	3 (2)
Hoarseness/stridor								
Cyanosis	1 (2)	0	0	0	0	0	1 (5)	2 (1)
Dyspnea/chest tightness	17 (2)	2	1 (8)	0	7	4 (5)	4 (5)	29 (1)
Gastrointestinal‡	2 (4)	3 (10)	0	2 (14)	2 (13)	3 (14)	0	9 (6)
Nausea/vomiting	2 (4)	2 (7)	0	1 (7)	2 (13)	2 (9)	0	7 (5)
Diarrhea	0	1 (3)	0	1 (7)	0	1 (5)	0	2 (1)
Abdominal pain	0	0	0	0	0	0	0	0
Cardiovascular‡	1§ (2)	0	0	0	0	1‖ (5)	0	2 (1)
Others/Missing‡	12 (21)	7 (23)	3 (25)	4 (29)	4 (27)	5 (23)	7 (37)	21 (15)

DTaP-Hib-P, Diphteria (D), tetanus (T), acellular pertussis (aP), *Haemophilus* influenzae type B (Hib) and poliomyelitis (P) vaccine; *dTap-P*, reduced antigen diphteria (d), tetanus (T), acellular pertussis (ap), and poliomyelitis (P) vaccine; *Hep*, hepatitis A and B vaccine; *HPV*, human papilloma virus vaccine; *MMR*, measles mumps rubella vaccine; *PCV*, pneumococcal conjugated vaccine. Others: fever, chill, myalgia, fatigue, metallic taste in the mouth, tremor, headaches, paresthesia.

*Total can be lower than the sum of medical office and emergency department consultations because some patients consulted both at the medical office and emergency department.

†Patients declared that they had anaphylaxis with no further description of symptoms.

‡Multiple answers were allowed, so total (any vaccine) can be lower than the sum of individual signs/symptoms.

§Loss of consciousness.

‖Tachychardia.

TABLE III. Management of allergic-like events (ALEs) by time to symptom onset and by type of vaccine

	Time to symptom onset					Type of vaccines			
	≤1 h N = 55 n (col%)	1-4 h N = 21 n (col%)	>4 h N = 50 n (col%)	Unknown N = 47 n (col%)	*P* value	Influenza vaccine* N = 56 n (col%)	Other vaccines N = 117 n (col%)	*P* value	Total N = 173 n (col%)
Serology	2 (4)	0	0	1 (2)		0	3 (3)	.6	3 (2)
Skin testing									
Prick									
Done	39 (71)	15 (71)	32 (64)	32 (68)	.9	33 (59)	85 (73)	.07	118 (68)
Negative	38 (97)	15 (100)	32 (100)	31 (97)		33 (100)	83 (98)		116 (98)
Intradermal									
Done	38 (69)	15 (71)	32 (64)	31 (66)	.9	33 (59)	83 (71)	.1	116 (67)
Negative	26 (68)	11 (73)	20 (63)	25 (81)		16 (27)	66 (80)		82 (71)
Vaccines to be readministered†	N = 35	N = 18	N = 38	N = 37		N = 50	N = 78		N = 128
Readministered	34 (97)	15 (83)	34 (89)	32 (86)	.3	43 (86)	72 (92)	.2	115 (90)
Injected as									
1 dose	18 (53)	9 (60)	17 (50)	22 (69)		15 (35)	51 (71)		66 (57)
2 split doses	2 (6)	2 (13)	3 (9)	4 (12)		6 (14)	5 (7)		11 (10)
4 split doses	14 (41)	4 (27)	14 (41)	6 (19)		22 (51)	16 (22)		38 (33)
Recurrences	8 (24)	0	1 (3)	1 (3)	.05‡	7 (16)	3 (4)	.06	10 (9)

*All influenza vaccines (seasonal and pandemic).
†N = 128 vaccine doses due to be readministered at the time of consultation at the allergist office.
‡*P* value comparing ALEs with the onset of symptoms ≤ 1 h with ALEs with onset >1 h after immunization.

Management of patients requiring additional doses

A total of 102 patients required the administration of 150 additional doses of vaccines of which 128 doses (50 seasonal influenza vaccines and 78 doses of other vaccines) were due to be administered at the time of consultation at the allergy clinic. Only 3 patients had prior serology to determine whether they had pre-existing protection against the vaccine target disease. Reimmunization was performed for 90% (115/128) of eligible doses. The percentage of reimmunizations did not vary by onset interval (97% in those with onset ≤1 hour, 83% for 1-4 hours, 89% for >4 hours, and 86% for those with an unknown interval; $P = .3$) or by type of vaccine (86% for seasonal influenza vaccines and 92% for other vaccines; $P = .2$) (Table III).

Among the 49 patients with an immediate reaction (≤4 hours) who were reimmunized, 8 (16%) experienced a recurrence, all of whom had onset of their initial AEFI ≤1 hour after immunization. No preschool children experienced recurrence: 6 recurrences were adult patients reimmunized with influenza vaccines and 2 (1 preadolescent, 1 adult) with hepatitis B vaccines. Reimmunization with graded doses was interrupted in 2 patients who presented throat tingling or lingual edema; both were successfully treated with antihistamines (Table IV).

Among the 34 patients with a delayed reaction (>4 hours) who were reimmunized, 1 had throat tightening and difficulty swallowing with onset 15 minutes after immunization without any observable abnormal sign and a slow response to hydroxyzine and prednisone (Table IV). A patient with an unspecified time to onset had a large injection site reaction and received ibuprofen and cetirizine 10 mg orally.

Adherence to the JTFPP guidelines

Among patients eligible for reimmunization, 83 had a description of an ALE including both the time to symptom onset and the number of systems involved. Management of these patients is presented in Figure 1, *A* and *B*. Overall, 19 of 83 (23%), 31 of 83 (37%), and 33 of 83 (40%) met the probable, possible, or neither categories for likelihood of anaphylaxis defined by the JTFPP (specified in Table V).

There was no significant difference in the management of patients across these JTFPP categories for the likelihood of anaphylaxis defined by the time to onset or the number of systems involved. Skin testing was undertaken for 80% (47/59) of vaccines involved in the ALE with onset ≤4 hours and 68% (28/41) for those with later onset ($P = .20$), and for 73% (54/74) of those with 1 system and 80% (21/26) of those with 2 systems involved ($P = .43$).

For vaccines associated with an ALE with onset ≤4 hours after immunization, skin testing was undertaken in 81% (30/37) of those with 1 system and 77% (17/22) of those with 2 systems involved ($P = .73$). For vaccines associated with an ALE with later onset, skin testing was conducted in 65% (24/37) and 100% (4/4), respectively ($P = .13$). Patients were reimmunized as often for vaccines involved with an ALE with immediate (45/59 = 76%) or late onset (29/41 = 71%) ($P = .54$) or those involving 1 (54/74 = 73%) or 2 systems (20/26 = 77%) ($P = .37$). For vaccines associated with an ALE with onset ≤4 hours, reimmunization was undertaken in 75% (9/12) of those who had no skin test and 77% (36/47) of those who had a skin test ($P = .90$) including 69% (11/16) of those with a positive skin test and 81% (25/31) of those with negative results ($P = .37$). Reimmunization was administered as a single full dose only for vaccines with negative skin test results whatever the number of systems involved.

DISCUSSION

This paper describes the real-world experience of a large series of patients consulting allergists for ALEs after immunization.

TABLE IV. Patients with AEFI on reimmunization by interval between immunization and symptom onset in the initial ALE

ID. Vaccine: Interval immunization to symptom onset; Initial ALE presentation	Skin test	Reimmunization doses	Vaccine/antigen: AEFI after reimmunization
1. Hepatitis B: During immunization; Generalized rash and pruritus	Positive prick test	4 graded doses	Hepatitis B: After first dose erythema to the neck After second dose injection site erythema with satellite urticaria and throat tingling. *Reimmunization interrupted* and hydroxyzine 20 mg orally administered. 1 h later a decrease of symptoms
2. Hepatitis A and B: 2 min after immunization; Numbness and tingling of the tongue, iron taste, and dryness in the mouth. Lasted 24 h	Negative	1 dose	Hepatitis B: 5 min after immunization, light tingling to the lips and tongue, metallic taste in the mouth. Disappeared in 30 min
3. Seasonal influenza: 5 min after immunization; Generalized pruritus and edema of the face, tongue, lips, hands, and feet	Not done	4 graded doses	Pandemic influenza: Tingling of the face and lips, numbness of the tongue and lips after the fourth dose
4. Seasonal influenza: 5-10 min after immunization; Anaphylactic shock (no other information)	Positive intradermal test	4 graded doses	Pandemic influenza: Tingling in the mouth after the fourth dose
5. Pandemic influenza: 10 min after immunization; Tongue edema which lasted 20 min and resolved without treatment	Positive intradermal test	2 graded doses	Seasonal influenza: After first dose tongue edema *Reimmunization interrupted*. Administration of cetirizine 20 mg
6. Seasonal influenza: 15 min after immunization; Erythema of cheeks and neck, facial edema, tingling, and tightening of the throat. Benadryl and epinephrine administered. 2 d after immunization, recurrence of facial symptom, and left cheek dysesthesia. 1 dose of epinephrine administered	Negative	1 dose	Seasonal influenza: 20 min after immunization, numbness of the left cheek and lip, tongue tingling. BP 129/79, pulse 58/min, O_2 sat 98% 50 min after immunization throat tingling, numbness to both cheeks and lips. BP 129/69, pulse 55/min, O_2 sat 99%
7. Seasonal influenza: 30 min after immunization; Tachycardia, sensation of deafening	Positive intradermal test	4 graded doses	Seasonal influenza: 5 min after first dose, dizziness with facial flushing. BP 140/83, pulse 108/min, O_2 sat 99%. Disappeared in 15 min 1 min after second dose flushing lasts approximately 1 min Third and fourth dose uneventful
8. Pandemic influenza: 30-60 min after immunization; Erythema on the face and chest	Positive intradermal test	4 graded doses	Seasonal influenza: 8 h after immunization edema of the throat and chin; received hydroxyzine 20 mg, salbutamol, and beclomethasone orally. Resolution the following morning
9. Seasonal influenza: 10 h after immunization; Erythema and pruritus of the face and neck	Negative	1 dose	Seasonal influenza: 15 min after immunization throat tightening, difficulty to swallow. BP 137/94, pulse 105/min, O_2 sat 99%. No change at 35 min after immunization 1 h and 20 min post vac. Atarax (hydroxyzine) 25 mg orally + prednisone 50 mg orally 1 h and 50 min after immunization: throat tightening persists but has decreased lightly
10. HPV: time to symptom onset unspecified; Rapidly progressive peribuccal edema	Negative	1 dose	HPV: 30 min after immunization shoulder to elbow injection site erythema treated with ibuprofen and cetirizine 10 mg orally

AEFI, Adverse event following immunization; *ALE*, allergic-like event; *BP*, blood pressure; *HPV*, human papilloma virus vaccine.

Although the likelihood of anaphylaxis is at the crux of the JTFPP criteria for determining appropriate management, few patients in the current series consulted for this syndrome but nearly all were managed as if they had. Skin testing was performed comparably often for patients with immediate or delayed reactions and those with 1 or 2 systems involved. Furthermore,

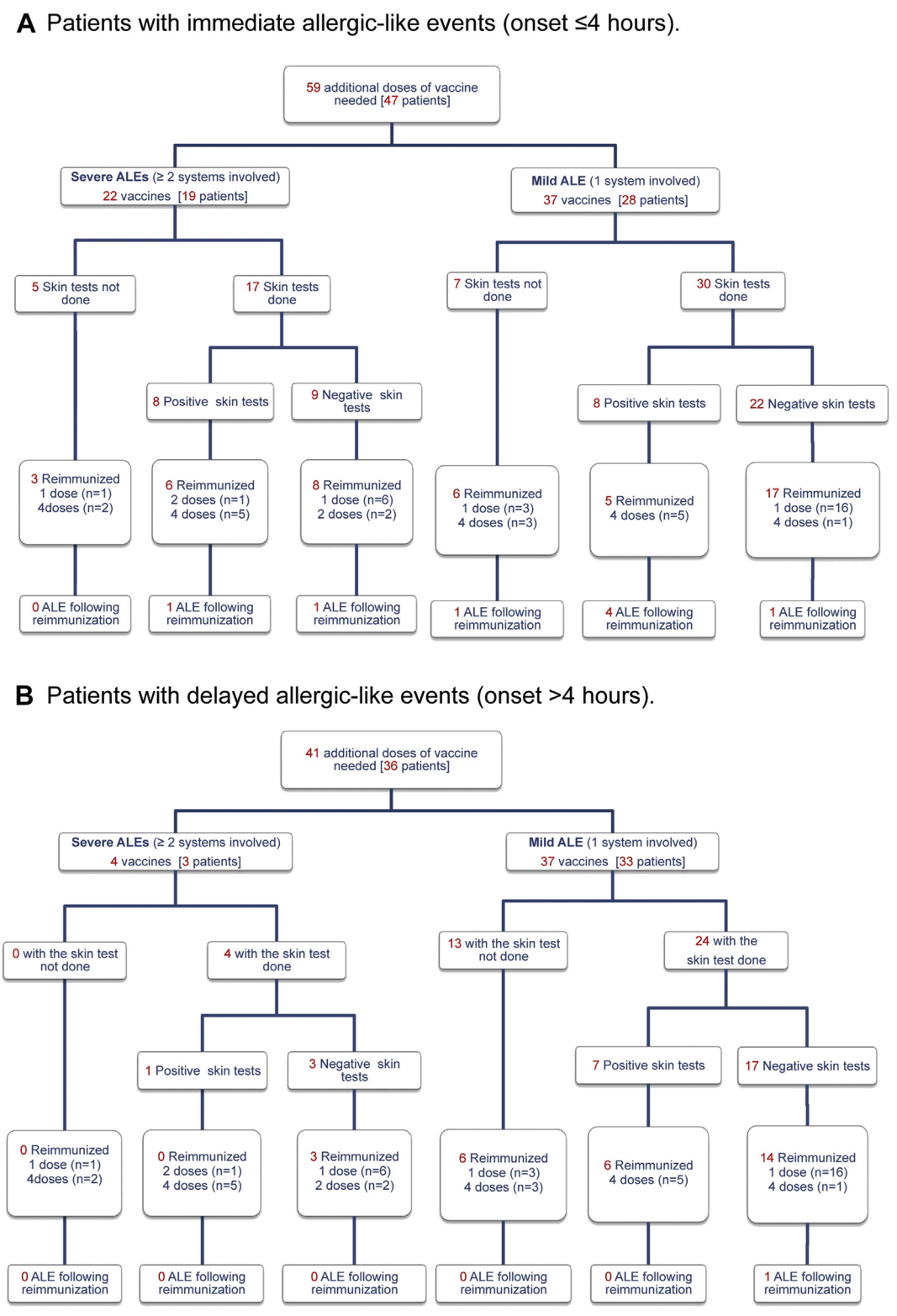

FIGURE 1. A, Management of patients with immediate allergic-like events (≤4 hours) after vaccination. **B**, Management of patients with delayed allergic-like events (>4 hours) after vaccination.

TABLE V. JTFPP criteria and practice guidelines for the management of allergic-like events in relation to likelihood of IgE-mediated anaphylaxis after reimmunization

JTFPP clinical criteria				JTFPP practice guideline		
					Action based on skin test result	
JTFPP anaphylaxis category	Timing (hours after exposure)	Severity (number of systems involved)	Vaccine-preventable target disease serology result	Immediate action or assessment	Negative	Positive
Probable	≤4	≥2	Protected	No further immediate action*	Not applicable	
	≤4	≥2	Unprotected or unavailable	Skin testing to assess IgE response†	Revaccinate single full dose; observe 30 min‡	Forego vaccine or receive in graded doses§
Possible	≤4	1	Protected	No further immediate action*	Not applicable	
	>4	≥2	Unprotected or unavailable	Skin testing to assess IgE response†	Revaccinate single full dose; observe 30 min‡	Forego vaccine or receive in graded doses§
Neither	>4	<2	Not applicable	Revaccinate single full dose as indicated per usual without further monitoring	Not applicable	

*Depending on the reliability and anticipated duration of antibody protection against the target vaccine preventable disease and other benefit-risk considerations.
†Testing begins with a skin prick test with diluted/undiluted vaccine or its components, followed if negative by an intradermal test with the vaccine diluted at 1:100.
‡Patients with negative skin tests can be revaccinated with a single full dose of vaccine but should remain under observation for at least 30 min.
§Patients with positive skin tests may forego the implicated vaccine or receive it in graded doses balancing the risk and severity of the allergic reaction versus the vaccine preventable disease and patient preference.

the decision to reimmunize appeared to be independent of the time to symptom onset, the number of systems affected in the initial ALE, or the skin test results. However, reimmunization was administered as a single full dose among those with negative skin test results and with graded doses for those who were skin test positive. Of 49 patients with immediate reactions (≤4 hours) who were reimmunized, 2 (4%) had their graded dose reimmunization interrupted and 6 (12%) experienced mild symptoms that self-resolved or were easily treated with antihistamines. Among the 34 patients with delayed reaction who were reimmunized, 1 experienced throat tightness without any objective sign of pharyngeal edema and recurrence of an ALE was unclear. These results corroborate the current clinical understanding that with adequate precautions the vast majority of patients who experience an ALE after immunization can be safely revaccinated.[11,15-18]

When evaluating patients who had an ALE after immunization, 2 clinical situations appear to require a cautious clinical management with skin testing and graded doses reimmunization depending on the results: IgE-mediated reactions to the vaccine because of their significant risk of recurrence on re-exposure to the implicated antigen and anaphylaxis (IgE mediated or not) because of their severity.

Typically, IgE-mediated reaction after an injected allergen occurs within 1 hour of the injection[5,6,19]; this 1-hour window is currently used for the diagnosis of type I hypersensitivity to most nonvaccine products.[20,21] Although the JTFPP guidelines categorize reactions per onset ≤4 hours or >4 hours, 1 hour seems a more appropriate cutoff to apply to patients consulting for nonanaphylactic reactions to vaccines. In the field of food and insect sting allergy, patients with mild to moderate allergic events after a first exposure will experience recurrences of similar severity (stereotypic) that are unlikely to progress to anaphylaxis,[22-25] and this probably applies to vaccines as well. When this small probability of patients with mild to moderate IgE-mediated reactions to develop anaphylaxis if revaccinated is compounded to the small probability that a reaction with onset past 1 hour is IgE mediated, the 1-hour cutoff appears reasonably cautious. In our study, the risk of recurrence of allergic symptoms on reimmunization was 23% (8/34) in patients whose first episode occurred within 1 hour of immunization but was null among the 15 patients with onset 1-4 hours after immunization. Although acknowledging that there are too few patients to draw robust conclusions, our findings support the 1-hour cutoff for nonanaphylactic ALEs.

In ALEs with a time to symptom onset >1 hour, the complexity resides in identifying patients who had anaphylaxis to vaccine. The JTFPP clinical criteria for possible anaphylaxis are broad without qualification of the severity of symptoms. In our case series that is likely representative of patients consulting allergists for an ALE after immunization, the ALEs were generally mild, and although no patients were given a diagnosis of anaphylaxis by the allergists, 60% (50/83) of the patients with description of their symptoms met the JTFPP case definition of probable (23%) or possible (37%) anaphylaxis. Given the rarity of anaphylaxis and considering that the later the onset of a reaction, the less likely is it to be caused by the vaccine; it seems useful to consider a more specific anaphylaxis case definition. The Brighton Collaboration has developed a case definition of anaphylaxis that is more specific with levels of diagnostic certainty based on the presence of major or minor symptoms

(Tables E1-E3, available in this article's Online Repository at www.jaci-inpractice.org).[4] In patients with a time to symptom onset >1 hour, this definition seems more appropriate. In addition to that, non−IgE-mediated reactions to the vaccine that can mimic anaphylaxis should be sought. For the influenza vaccine in particular, the ORS should be considered.[26] ORS typically starts 2-24 hours after immunization and often affects 2 systems causing bilateral conjunctivitis, facial edema, lingual and pharyngeal edema, and upper respiratory symptoms (cough, sore throat, hoarseness, dyspnea, chest tightness).[26] ORS is not IgE mediated and most patients with ORS can be safely reimmunized against influenza.[27-31]

Only 3 of the 37 vaccines required in patients with an ALE involving 1 system and with onset >4 hours after immunization were readministered in a single dose without prior skin testing, as recommended in the JTFPP guidelines. The remainder had skin testing (24/37) and/or graded dose reimmunization (9/37). In patients with mild delayed ALEs, skin testing is not justified by the severity of the reaction and should be avoided. In ALEs with a time to symptom onset >1 hour, the pretest probability of an IgE-mediated reaction is low and this decreases the positive predictive value of the skin test. With the vaccine diluted at 1:100, Wood et al[32] estimated the frequency of false positive intradermal tests at 15% and 5% in patients tested with influenza and DTaP/DT vaccines, respectively. These false positive results are harmful as they may increase the patients' anxiety and reluctance to be reimmunized. Graded dose reimmunization is safe and preferable to withholding immunization, but the administration of a single dose is also a minimal risk scenario that will reassure patients and community providers about the safety of future immunizations. Moreover, administration of a single dose should be preferred, as it has not been proven that graded immunization confers comparable immunity.

In this study, only 2% (3/141) of patients had serology to evaluate pre-existing protection against the disease(s) targeted by the implicated vaccine. Serology is theoretically appealing, but seems to have little clinical applicability. For childhood vaccines, serologic tests are not available for several antigens found in multicomponent vaccines and/or validated correlates of protection are lacking.[11] Influenza vaccines are reformulated and/or expire annually, and antibodies for antigens of the past season are not generally considered adequate the following season. Serological testing requires an additional visit and postpones reimmunization. Finally, reimmunization of patients even with positive serology may sometimes be considered because the durability of a protective level of antibodies is not known. When feasible, serology may still be worthwhile in patients who had anaphylaxis but, as reflected in the current case series, is likely to be of low utility for clinical decision making among most other patients.

This study has several limitations. Patients often consult allergists long after their ALE and may retain poor memory of their symptoms. Because of its retrospective nature, the information was not collected and/or recorded in a standardized manner by the clinicians. Charts sometimes lacked important information relevant to diagnosis and decision making that may have been collected during the visit without being recorded. In particular, the interval between immunization and onset of symptom was lacking for 28% of patients and is critical in the JTFPP management algorithm. For each vaccine, there were only a handful of patients evaluated and reimmunized across the 4 study years. The small sample size limits the statistical power of this study to assert the safety of reimmunization per product. Prick tests were performed with vaccine diluted at 1:10 in all patients that may not be as sensitive as undiluted product. However, patients with an IgE-mediated reaction were unlikely to be missed as all those with negative prick tests had an intradermal test with vaccine diluted at 1:100 per JTFPP guideline. Despite these caveats, our study puts into perspective key concepts and practical considerations of current JTFPP guidance that may warrant revisiting.

In conclusion, most ALEs after immunization are not suggestive of anaphylaxis and should not be managed as such. Restricting skin testing and graded dose reimmunization to patients whose ALE onset ≤1 hour (compatible with an IgE-mediated reaction) and to those meeting specific clinical criteria for anaphylaxis (whatever the timing) is likely sufficiently sensitive for identification of those at greatest risk of anaphylaxis at reimmunization. Reimmunization of patients not meeting these criteria with a single dose without prior skin testing incurs a very small risk of anaphylaxis and readiness to intervene early in the exceptional event of a severe reaction will further minimize the risk of serious outcome. Withholding recommended vaccines deprives patients from adequate protection against targeted diseases and is rarely necessary; even with severe cases, the cautious approach of using graded doses may trigger the recurrence of allergic symptoms but is unlikely to result in anaphylaxis.

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Brighton Collaboration Case Definition of Anaphylaxis

Source: Ruggeberg J, Gold M, Bayas J-M, Blum M, Bonhoeffer J, Friedlander S, et al. Anaphylaxis: case definition and guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine 2007;25:5675-84.

TABLE E1. Case definition of anaphylaxis

For all levels of diagnostic certainty
Anaphylaxis is a clinical syndrome characterized by
Sudden onset AND
Rapid progression of signs and symptoms AND
Involving multiple (≥2) organ systems, as follows
Level 1 of diagnostic certainty
≥1 major dermatological AND
≥1 major cardiovascular AND/OR ≥1 major respiratory criterion
Level 2 of diagnostic certainty
≥1 major cardiovascular AND ≥1 major respiratory criterion OR
≥1 major cardiovascular OR respiratory criterion AND
≥1 minor criterion involving ≥1 different system (*other than* cardiovascular or respiratory systems) OR
(≥1 major dermatologic) AND (≥1 minor cardiovascular AND/OR minor respiratory criterion)
Level 3 of diagnostic certainty
≥1 minor cardiovascular OR respiratory criterion AND
≥1 minor criterion from each of ≥2 different systems/categories

Note. The case definition should be applied when there is no clear alternative diagnosis for the reported event to account for the combination of symptoms.

TABLE E2. Major criteria used in the case definition of anaphylaxis

Dermatologic or mucosal
Generalized urticaria (hives) or generalized erythema
Angioedema,* localized or generalized
Generalized pruritus with skin rash
Cardiovascular
Measured hypotension
Clinical diagnosis of uncompensated shock, indicated by the combination of at least 3 of the following:
Tachycardia
Capillary refill time >3 s
Reduced central pulse volume
Decreased level of consciousness or loss of consciousness
Respiratory
Bilateral wheeze (bronchospasm)
Stridor
Upper airway swelling (lip, tongue, throat, uvula, or larynx)
Respiratory distress—2 or more of the following:
Tachypnoea
Increased use of accessory respiratory muscles (sternocleidomastoid, intercostals, etc.)
Recession
Cyanosis
Grunting

*Not hereditary angioedema.

TABLE E3. Minor criteria used in the case definition of anaphylaxis

Dermatologic or mucosal
Generalized pruritus without skin rash
Generalized prickle sensation
Localized injection site urticaria
Red and itchy eyes
Cardiovascular
Reduced peripheral circulation as indicated by the combination of at least 2 of
Tachycardia and
A capillary refill time of >3 s without hypotension
A decreased level of consciousness
Respiratory
Persistent dry cough
Hoarse voice
Difficulty breathing without wheeze or stridor
Sensation of throat closure
Sneezing, rhinorrhea
Gastrointestinal
Diarrhea
Abdominal pain
Nausea
Vomiting
Laboratory
Mast cell tryptase elevation > upper normal limit