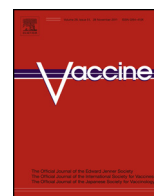




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Increased risk of anaphylaxis following administration of 2009 AS03-adjuvanted monovalent pandemic A/H1N1 (H1N1pdm09) vaccine

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ABSTRACT

Background: Anaphylaxis after trivalent influenza vaccination is typically reported at a rate of <1 per million doses. In Quebec, Canada, anaphylaxis following administration of the monovalent AS03-adjuvanted H1N1pdm09 vaccine was reported through passive surveillance at a rate of 8 per million doses administered. This was 20 times higher than the reporting rate for non-adjuvanted trivalent vaccines administered during the six previous seasons. However, adequate estimation of the incidence of anaphylaxis is hindered by wide variations in definitions and diagnosis.

Methods: Using the Brighton collaboration case definition of anaphylaxis, all cases with allergic symptoms (AS) reported to public health were reviewed to estimate the incidence of anaphylaxis following AS03-adjuvanted H1N1pdm09 vaccine.

Results: Among 752 reports of allergic symptoms, 33 were initially reported as anaphylaxis of which 20/33 (60%) met the Brighton definition (19/20 with certainty levels 1 or 2). A total of 38 additional cases with onset within 1 h of vaccination also met the Brighton definition of anaphylaxis (27 (71%) with certainty levels 1 or 2). The 58 cases meeting Brighton Level 1 or 2 criteria for anaphylaxis represent a 75% increase over the 33 passively reported and an incidence of 13 per million doses administered.

Conclusion: A substantial number of patients with early-onset allergic symptoms met the most specific levels of the Brighton case definition but were not reported as anaphylaxis. Based on this specific case definition, the incidence of anaphylaxis after AS03-adjuvanted H1N1pdm09 vaccine substantially exceeded that reported with seasonal influenza vaccines, a signal that warrants better understanding.

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1. Introduction

The 2009 emergence of pandemic H1N1 (H1N1pdm09) influenza led health authorities worldwide to undertake mass immunization campaigns. In Quebec, Canada, 4.2 million doses of an AS03-adjuvanted monovalent vaccine (Arepanrix[®], GSK) were administered in 2009. Two unadjuvanted vaccines were also available for use primarily in pregnant women (<4% of doses).

One-third of adverse events following immunization (AEFI) with pandemic vaccines reported to the passive surveillance system concerned allergy, a broad category of AEFI characterized by the presence of any allergic symptoms (AS). These events were reported on a standardized form using tick-boxes for three broad clinical presentations (anaphylaxis, oculo-respiratory syndrome (ORS), and allergy). For surveillance purposes, “allergy” refers to any symptom compatible with allergy and not with a confirmed, type I hypersensitivity. It includes bronchospasm, edema of the mouth/throat, facial/generalized edema, urticaria or pruritic rash, and any other suspected allergic reaction, but excludes non-pruritic rashes. ORS is a reaction to influenza vaccines which consists of a constellation of symptoms considerably overlapping those of allergy, and is reported in a distinct category of AEFI. ORS is defined by Canada’s National Advisory Committee on

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Immunization as the occurrence of bilateral red eyes, and/or facial swelling, and/or respiratory symptoms (cough, wheeze, chest tightness, difficulty breathing, difficulty swallowing/throat tightness, hoarseness or sore throat) with onset within 24 h of influenza immunization [1]. In addition to the three tick box reporting categories, details on the reactions can be added in a free text area.

The reported rate of all AEFI with the monovalent adjuvanted H1N1pdm09 vaccine was 50 per 100,000, which is 2.6 times that of the previous six years (19/100,000) with non-adjuvanted trivalent inactivated influenza vaccine (TIV). Symptoms compatible with allergy, such as urticaria and skin rashes, followed the general trend with a reporting rate 3.3-fold greater after H1N1pdm09 vaccination than with previous seasonal TIV. Most noteworthy, anaphylaxis was reported 20 times more frequently than in the previous six years, during which 4 cases had been passively reported among >10.4 million doses of TIV distributed (0.4/million doses).

Anaphylaxis typically presents as cutaneous and subcutaneous manifestations with cardiovascular or respiratory symptoms. It can be lethal if untreated but the compensatory release of endogenous epinephrine and angiotensin II will often lead to spontaneous recovery [2]. Underdiagnosis can occur in cases not exhibiting signs of uncompensated shock or in those with early administration of epinephrine, and an estimated 10–20% of anaphylaxis cases remain undiagnosed [2–5]. In Quebec, many patients with allergic symptoms reported after H1N1pdm09 vaccination appeared shortly after vaccination, implicated ≥2 organ systems, or required the administration of epinephrine, all of which suggested that anaphylaxis may have been underreported.

The diagnosis of anaphylaxis, ORS, or allergy is at the discretion of the reporting clinician and based on clinical judgment that is non-standardized or inconsistently applied. The Brighton Collaboration case definition (BCCD) for anaphylaxis was developed for use in immunization settings, where anaphylaxis may be anticipated and treated promptly [6] (Table 1). However, this definition is meant to diagnose anaphylaxis without attributing causality, and stipulates no time-limit after vaccination although anaphylaxis almost always occurs within 1 h of exposure to the triggering antigen.

In this study, we assess clinical features and estimates of anaphylaxis based on the Brighton collaboration case definition systematically applied to AS reports associated with AS03-adjuvanted H1N1pdm09 vaccine and notified to the Quebec passive AEFI surveillance system.

2. Methods

2.1. Data sources

In Quebec, clinician AEFI reporting to regional public health is mandatory. All cases reported as anaphylaxis, ORS, or allergy among patients immunized between October 25th and December 31st, 2009 were identified from the provincial AEFI database in May 2010.

Available narrative descriptions were reviewed to extract signs, symptoms, and medication used for treatment. Cases of anaphylaxis were evaluated based on the BCCD by combining signs and symptoms using a computer algorithm. The remaining cases were classified by reporting diagnosis, as ORS or allergy [1,6].

The number of doses administered by date of vaccination, proprietary name and lot number of the vaccine, gender and age of cases were extracted from the H1N1pdm09 immunization registry containing information on every vaccinated person in the province [7].

Table 1
Brighton collaboration case definition of anaphylaxis [6].

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 ≥1 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)		
	Minor criteria	Major criteria
Skin/mucosal	• Generalized pruritus without skin rash • Generalized prickle sensation • Localized injection site urticaria	• Generalized urticaria (hives) or generalized erythema • Angioedema^a, localized or generalized • Generalized pruritus with skin rash
Cardiovascular	• Red and itchy eyes • Reduced peripheral circulation as indicated by the combination of at least 2 of: ◦ Tachycardia ◦ A capillary refill time of >3 s without hypotension ◦ A decreased level of consciousness	• Measured hypotension • Clinical diagnosis of uncompensated shock, indicated by the combination of at least 3 of the following: ◦ Tachycardia ◦ A capillary refill time of >3 s ◦ Reduced central pulse volume ◦ Decreased level of consciousness, or loss of consciousness
Respiratory	• Persistent dry cough • Hoarse voice • Difficulty breathing without wheeze or stridor • Sensation of throat closure • Sneezing, rhinorrhea	• Bilateral wheeze (bronchospasm) • Stridor • Upper airway swelling (tongue, throat, uvula, or larynx) • Respiratory distress – 2 or more of the following: ◦ Tachypnea ◦ Increased use of accessory respiratory muscles (sternocleidomastoid, intercostals, etc.) ◦ Recession ◦ Cyanosis ◦ Grunting
Gastrointestinal	• Diarrhea • Abdominal pain • Nausea • Vomiting	

^a Not hereditary angioedema.

2.2. Statistical analyses

Rates were estimated by dividing the number of reports by the number of doses administered, and rescaled by 100,000 or 1 million doses, as indicated. Exact binomial 95% confidence intervals (CI) were calculated for rates, and crude rate ratios and their 95% CI were computed by Poisson regression. Characteristics of cases were compared using Fisher's exact test for categorical variables

and Kruskal–Wallis one-way analysis of variance for age, delay to onset, and duration of symptoms.

3. Results

Between October 25th and December 31st 2009, 4,199,866 doses (96.4% of all doses) of adjuvanted H1N1pdm09 vaccine (Arepanrix®; GlaxoSmithKline), 121,816 (2.7%) doses of unadjuvanted H1N1pdm09 vaccine (GlaxoSmithKline), and 35,937 (0.8%) doses of unadjuvanted H1N1pdm09 vaccine (Panvax®; CSL) were administered in Quebec. Twenty-two different lots of adjuvanted vaccine were distributed.

During the campaign, 752 (33%) of all AEFIs reported were for AS (17/100,000 doses) (Table 2). This rate was similar for both GSK adjuvanted and unadjuvanted vaccines (17 and 16 per 100,000 doses, respectively). It was higher for the CSL unadjuvanted vaccine, but with broad CI overlapping those of the two GSK products (30.6/100,000 doses, 95% CI: 15.2–54.7). Among these AEFI, 33 were reported as anaphylaxis (8/million doses), 263 as ORS (6/100,000 doses), and 456 as allergy (10/100,000 doses). Thirty-two of 33 anaphylaxis reports were associated with AS03-adjuvanted vaccine, and 1 with the unadjuvanted CSL vaccine.

During the first 4 weeks of the immunization campaign compared to weeks 5–10, the overall rate of AS was 2.2-fold higher (95% CI: 1.9–2.5) (Fig. 1) and was 2.3-fold higher for anaphylaxis (95% CI: 1.1–4.7). One lot of adjuvanted vaccine administered predominantly to women and healthcare workers (HCW) in the first 2 weeks of the immunization campaign (Lot 9A) was associated with 8 reported cases of anaphylaxis and a significantly higher rate of AS than other lots of adjuvanted vaccines (32.3 vs 14.9 per 100,000 doses; $p < 0.0001$) including lots also distributed in the first 4 weeks (21.6/100,000 doses) (135/418,483 vs 264/1,209,233; $p = 0.0002$).

3.1. Age and gender effect

Women/girls comprised the greater proportion of AEFI reports (74%) and, after adjusting for doses administered, were represented 2.5-fold more often than men/boys (95% CI: 2.1–2.9), 3.9-fold more among anaphylaxis reports (95% CI: 1.6–9.4). Rates were similar for boys and girls before puberty (<10 years old), but rates in females appeared increased from 10 years of age until 40–49 years before declining again after 50 years, remaining only slightly higher in women over 60 years (Fig. 1). This relationship was similar for anaphylaxis, ORS, and allergy. Self-reported HCW accounted for 15% of reports, of which 90% were women. Rates of AS were twice as high for HCW than for other vaccinees (RR: 2.0; 95% CI: 1.6–2.4) but this effect was only significant among women. Only 9 (1%) of all AS cases were pregnant: 7 had received the CSL unadjuvanted vaccine (64% of CSL AS reports), one (5%) had received the GSK unadjuvanted vaccine, and one received the adjuvanted vaccine ($p < .0001$).

3.2. Clinical presentation

A description of the event was available for 70% (530/752) of cases, including all those reported as anaphylaxis ($n = 33$), 150 cases of ORS (57%), and 347 cases of allergy (77%) (Table 2). All but one case of anaphylaxis and 24% (171) of all other cases had onset of symptoms <1 h after vaccination; 86 (12%) had onset between 1 and 4 h, 14% between 4 and 11 h, and 46% later than 12 h postvaccination.

Overall, 152 (29%) cases met the BCCD for anaphylaxis (Table 3). Among the 33 reported cases of anaphylaxis, 20 (61%) met the BCCD, whereas the 13 others experienced isolated respiratory symptoms for which 10 received epinephrine. For the other 132 cases meeting the BCCD, 38 (29%) experienced symptom onset <1 h postvaccination, 13 (10%), between 1–3 h and 81 (61%) at

≥4 h. In AS cases with onset >1 h postvaccination, ORS cases were more likely than allergy cases to meet the BCCD (60/150 = 40% vs 72/347 = 21%; $p < 0.0001$), although they were less likely to meet Level 1 diagnostic certainty (7/60 = 12% vs 33/72 = 46%; $p < 0.0001$). Compared to reported anaphylaxis cases, BCCD-based anaphylaxis cases had more skin/mucosal changes, but fewer respiratory symptoms (Table 4). Cases classified as ORS reported less conjunctivitis, hoarse voice and gastrointestinal symptoms, while cases re-classified as allergy had less pruritic rashes and conjunctivitis, but more sensations of throat closure, coughing and bronchospasm than those initially reported as such.

When considering only the 58 BCCD anaphylaxis cases with onset <1 h postvaccination, the rate of anaphylaxis was 13 cases per million doses administered (95% CI: 10–17 per million doses). Epinephrine was administered to only 45% (26/58) of the BCCD cases compared to 70% (23/33) of the patients initially reported as anaphylaxis. Among the 62 patients who received an injection of epinephrine within the hour postvaccination, 37% (23) were initially reported as anaphylaxis and 42% (26) met the BCCD. Most cases who received epinephrine and did not meet the BCCD had isolated respiratory symptoms (65%) or localized skin/mucosal involvement.

One fatal case of anaphylaxis was reported in an 80-year old male with underlying respiratory and vascular disease who presented dyspnea and wheezing 90 min postvaccination. On arrival at the hospital, he was hypertensive (BP: 187/102) and experiencing oxygen desaturation (O_2 sat. 60%). During intubation, he aspirated and subsequently showed edema of the airway, aspiration pneumonia, and died of renal failure approximately one week later. Because all symptoms were confined to the respiratory system, he did not meet the BCCD of anaphylaxis although he was reported as such.

4. Discussion

In the fall of 2009, numerous reports of AS following monovalent AS03-adjuvanted H1N1pdm09 vaccination were submitted to the passive AEFI surveillance system in Quebec. Anaphylaxis was initially reported at a rate of 8 per million doses administered (95% CI: 5–11), 20-fold higher than reported in the previous six years and substantially exceeding the expected rate of <1 case per million cited in the literature [8–11].

Typically, anaphylaxis caused by an injected antigen occurs shortly (<30 min) post-injection. While the BCCD identifies the clinical characteristics of anaphylaxis, it does not address causality and therefore includes no time criteria. Anaphylaxis occurring >1 h postvaccination, and meeting BCCD diagnostic certainty level 1 criteria, is likely a real case but is unlikely to be caused by vaccination [6]. Using the BCCD to ascertain cases, and considering only those that occurred <1 h postvaccination as causally-related, we estimated the incidence at 13 BCCD-defined cases of anaphylaxis per million doses administered, although including cases with later onset would have resulted in a rate 2–3-fold greater. The strict application of BCCD to all AS cases with symptom onset <1 h after vaccination identified nearly 2-fold more cases than reported suggesting that even amid the highly informed and monitored setting of a mass immunization campaign, anaphylaxis was underdiagnosed. The underdiagnosis of anaphylaxis is not unique to immunization [3–5].

Epinephrine is the main treatment for anaphylaxis and its early administration rapidly halts progression, but may contribute to an underestimation of anaphylaxis occurrence and risk [3]. In our series, many reported cases of anaphylaxis not meeting the BCCD only had respiratory symptoms and had received epinephrine. Without this treatment some may have progressed to fulfill

Table 2

Characteristics of cases by type of diagnosis reported.

	Anaphylaxis	Oculo-respiratory syndrome ^a		Allergy		All
	With complete description of events	Without description of event or delay to onset	With complete description of events	Without description of event or delay to onset	With complete description of event or delay to onset	All
	N = 33 N (%)	N = 113 N (%)	N = 150 N (%)	N = 109 N (%)	N = 347 N (%)	N = 752 N (%)
<i>Gender</i>						
Female	27 (82)	74 (65)	113 (75)	83 (76)	262 (76)	559 (74)
<i>Age category, years</i>						
<20	11 (33)	31 (27)	36 (24)	31 (28)	128 (37)	237 (32)
30–39	7 (21)	30 (27)	32 (21)	28 (26)	87 (25)	184 (24)
40–59	10 (30)	33 (29)	60 (40)	34 (31)	98 (28)	235 (31)
≥60	5 (15)	19 (17)	22 (15)	16 (15)	34 (10)	96 (13)
Mean age	34.1 ± 22.4	35.7 ± 21.5	38.0 ± 20.4	36.0 ± 20.7	31.2 ± 21.8 [†]	34.1 ± 21.5
<i>Other</i>						
History of allergy	16 (48)	21 (19)	75 (50) [†]	51 (47)	181 (52)	344 (46)
Chronic disease	10 (30)	16 (14)	51 (34) [†]	39 (36)	77 (22) [†]	193 (26)
Prior AEFI	0 (0)	2 (2)	7 (5)	4 (4)	18 (5)	31 (4)
<i>Vaccine administered</i>						
GSK, AS03–adjuvanted	32 (97)	107 (95)	144 (96)	102 (94)	336 (97)	721 (96)
GSK, unadjuvanted	0 (0)	3 (3)	3 (2)	5 (5)	9 (3)	20 (3)
CSL, unadjuvanted	1 (3)	3 (3)	3 (2)	2 (2)	2 (1)	11 (1)
<i>Delay to onset, in hours</i>						
<1	32 (97)	7 (6)	25 (17)	28 (26)	111 (32)	203 (28)
1–3	1 (3)	10 (9)	27 (18)	13 (12)	35 (10)	86 (12)
4–11	0 (0)	10 (10)	32 (21)	12 (11)	47 (14)	101 (14)
≥12	0 (0)	71 (63)	66 (44)	43 (39)	154 (44)	334 (46)
Missing		15 (13)	–	13 (12)		28 (4)
Mean ± s.d.	0.2 ± 0.3	21.1 ± 21.4	12.3 ± 20.0 [†]	16.3 ± 25.9	16.0 ± 21.0	15.2 ± 21.4
<i>Duration, in days</i>						
<1	16 (70)	10 (9)	20 (13)	17 (16)	85 (31)	148 (20)
1–2	3 (13)	14 (12)	47 (31)	12 (11)	73 (27)	148 (20)
3–7	3 (13)	6 (5)	46 (31)	24 (22)	73 (27)	152 (20)
≥7	1 (4)	4 (4)	19 (13)	24 (22)	43 (16)	90 (12)
Missing		79 (70)	18 (12)	32 (29)	75 (22)	214 (28)
Mean ± s.d.	1.1 ± 1.8	5.7 ± 13.4	3.8 ± 4.4 [†]	6.2 ± 7.5	4.0 ± 7.9 [†]	4.2 ± 7.5
Median	0.1	1	3	4	2	2

^a Using the National Advisory Committee on Immunization (NACI) definition: bilateral red eyes, and/or facial swelling, and/or respiratory symptoms (cough, wheeze, chest tightness, difficulty breathing, difficulty swallowing/throat tightness, hoarseness or sore throat) with onset within 24 h of influenza immunization.

[†] $p < .05$ (in comparing characteristics of cases with and without supporting description of event).

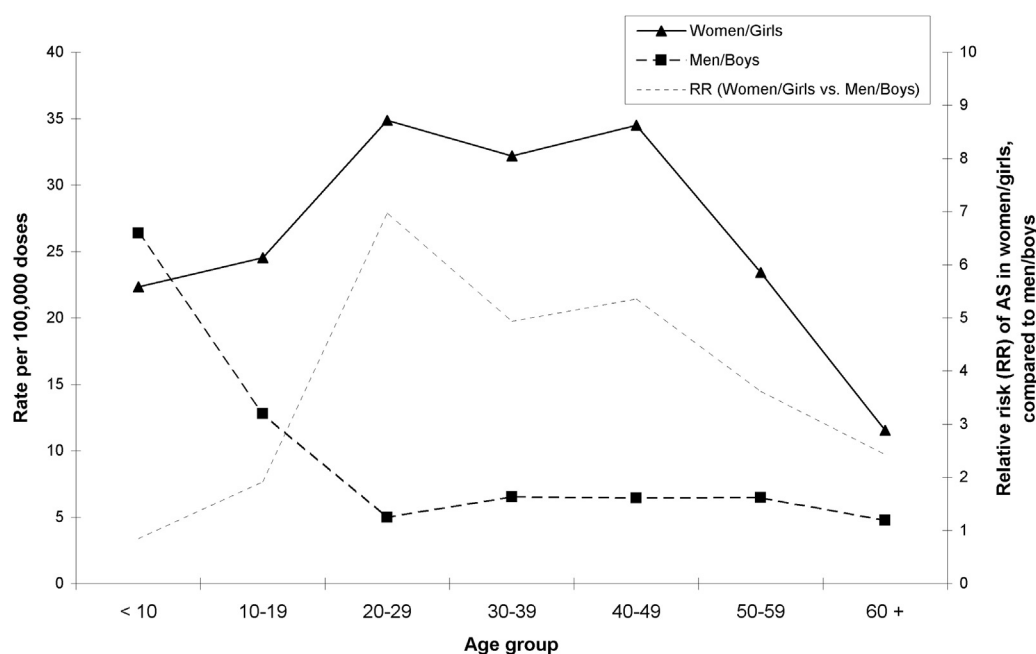


Fig. 1. Rates of allergic symptoms (AS) per 100,000 doses administered by age and gender, and dose-adjusted relative risk of AS in women/girls compared to men/boys.

Table 3

Cases meeting the Brighton Collaboration Case Definition of anaphylaxis, by type of diagnosis initially reported and interval between vaccination and symptom onset.

Brighton case definition met	Onset <1 h N = 136		Onset 1–3 h N = 62		Onset ≥4 h N = 299		Total N = 530
	Anaphylaxis		Anaphylaxis		Anaphylaxis		
		Oculo-respiratory syndrome ^a	Allergy	Oculo-respiratory syndrome ^a	Allergy	Oculo-respiratory syndrome ^a	
	N = 33	N = 25	N = 111	N = 27	N = 35	N = 98	
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	
Total	20 (61)	8 (32)	30 (27)	9 (33)	4 (11)	43 (44)	152 (29)
Certainty Level 1	8 (24)	1 (4)	11 (10)	1 (4)	2 (6)	5 (5)	48 (9)
Certainty Level 2	11 (33)	2 (8)	13 (12)	3 (11)	2 (6)	16 (16)	62 (12)
Certainty Level 3	1 (3)	5 (20)	6 (5)	5 (19)	0 (0)	22 (22)	42 (8)

^a Using the National Advisory Committee on Immunization (NACI) definition: bilateral red eyes, and/or facial swelling, and/or respiratory symptoms (cough, wheeze, chest tightness, difficulty breathing, difficulty swallowing/throat tightness, hoarseness or sore throat) with onset within 24 h of influenza immunization.

Table 4

Clinical presentation of all cases with allergic symptoms with diagnosis as reported to public health or restricted to those with symptom onset <1 h after vaccination and reclassified by standardized case definitions (Brighton case definition for anaphylaxis and NACI case definition for the oculorespiratory syndrome (ORS)).

	All cases with allergic symptoms by diagnosis as reported to public health				Cases with symptom onset <1 h after vaccination, reclassified according to standardized case definitions			
	Anaphylaxis	Oculo-respiratory syndrome ^a	Allergy	Total	Brighton anaphylaxis	Non-anaphylactic oculorespiratory syndrome ^a	Non-anaphylactic allergy	Total
	N = 33	N = 150	N = 347	N = 530	N = 58	N = 17	N = 93	N = 168
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	
<i>Dermatologic/mucosal</i>	16 (49)	105 (70)	265 (76)	386 (73)	45 (78)	9 (53)	28 (30)	82 (49)
Any pruritic rash	8 (24)	1 (1)	195 (56)	204 (38)	17 (29)	0 (0)	18 (19)	35 (21)
Angioedema, non respiratory	10 (30)	54 (36)	66 (19)	130 (25)	20 (34)	4 (24)	7 (8)	31 (18)
Red and/or itchy eyes	2 (6)	74 (49)	20 (6)	96 (18)	7 (12)	6 (35)	3 (3)	16 (10)
Pruritus, without generalized rash	0 (0)	6 (4)	43 (12)	48 (9)	9 (16)	1 (6)	10 (11)	20 (13)
Injection site urticaria	1 (3)	0 (0)	0 (0)	1 (0)	1 (2)	0 (0)	0 (0)	1 (1)
<i>Respiratory</i>	33 (100)	87 (58)	120 (35)	295 (55)	58 (100)	8 (47)	50 (54)	116 (69)
Angioedema (lip, tongue, throat, larynx)	16 (49)	8 (5)	55 (16)	78 (14)	20 (34)	0 (0)	20 (22)	40 (24)
Bronchospasm, wheezing	9 (27)	8 (5)	8 (2)	25 (5)	7 (12)	0 (0)	8 (9)	15 (9)
Dyspnea (without adventitious sounds)	18 (55)	49 (32)	35 (10)	99 (19)	26 (45)	5 (29)	16 (17)	47 (28)
Coughing	13 (39)	33 (22)	17 (5)	63 (12)	10 (17)	4 (24)	12 (13)	26 (15)
Sensation of throat closure	18 (55)	12 (8)	29 (8)	59 (11)	22 (38)	1 (6)	25 (27)	48 (29)
Hoarse voice	5 (15)	18 (12)	11 (3)	34 (6)	7 (12)	1 (6)	7 (8)	15 (9)
Tachypnea	3 (9)	0 (0)	0 (0)	3 (1)	2 (3)	0 (0)	1 (1)	3 (2)
Cyanosis	2 (6)	0 (0)	9 (3)	11 (2)	5 (9)	0 (0)	5 (5)	10 (6)
<i>Cardiovascular</i>	8 (24)	3 (2)	16 (5)	27 (5)	8 (14)	0 (0)	11 (12)	19 (11)
Decreased level/loss of consciousness	5 (15)	1 (1)	7 (2)	13 (2)	4 (7)	0 (0)	6 (6)	10 (6)
Tachycardia/palpitations	3 (9)	2 (1)	9 (3)	14 (3)	4 (7)	0 (0)	5 (5)	9 (5)
Measured hypotension	1 (3)	0 (0)	1 (0)	2 (0)	2 (3)	0 (0)	0 (0)	2 (1)
<i>Gastrointestinal</i>	7 (21)	27 (8)	28 (9)	62 (12)	19 (33)	2 (12)	2 (2)	23 (14)
Abdominal pain or diarrhea	7 (21)	28 (19)	27 (8)	62 (12)	19 (33)	2 (12)	2 (2)	23 (14)
Nausea or vomiting	5 (15)	25 (17)	21 (6)	51 (10)	16 (28)	1 (6)	1 (1)	18 (11)
<i>Health services required</i>								
Reported receiving epinephrine	23 (70)	4 (3)	38 (11)	65 (12)	26 (45)	1 (6)	35 (38)	62 (37)
Medical consultation	30 (91)	63 (42)	209 (60)	302 (57)	44 (76)	7 (41)	69 (74)	120 (71)
Hospitalization	1 (3)	3 (2)	4 (1)	8 (2)	1 (2)	1 (6)	1 (1)	3 (2)

^a Using the National Advisory Committee on Immunization (NACI) definition: bilateral red eyes, and/or facial swelling, and/or respiratory symptoms (cough, wheeze, chest tightness, difficulty breathing, difficulty swallowing/throat tightness, hoarseness or sore throat) with onset within 24 h of influenza immunization.

BCCD criteria, suggesting that the rate of anaphylaxis may be even higher than our BCCD-confirmed estimate of 13 cases per million. Conversely, lack of epinephrine use introduces another type of bias. The lower rate of epinephrine use in BCCD-confirmed cases compared to those initially reported as anaphylaxis (45% vs 70%) does not mean the former were not true anaphylaxis. The perception that anaphylaxis almost inexorably causes shock and death if left untreated is incorrect; anaphylaxis is often a self-resolving condition. Cases who spontaneously recovered may have been less likely to be reported as anaphylaxis, creating a reporting bias. Our findings on epinephrine use are consistent

with the published literature suggesting that only 30–45% of true anaphylaxis cases with other triggering antigens, receive epinephrine [12].

The underreporting of anaphylaxis does not appear to be specific to the pandemic vaccine, but may be more pronounced for influenza than for other vaccines. Between 2003 and 2008, the provincial passive surveillance system received 38 reports of AS implicating both skin/mucosal and respiratory systems. Among those, 4/19 (21%) cases following influenza vaccines were reported as anaphylaxis, while 13/19 (68%) cases following other vaccines were reported as such. This may be attributable, at least in part, to

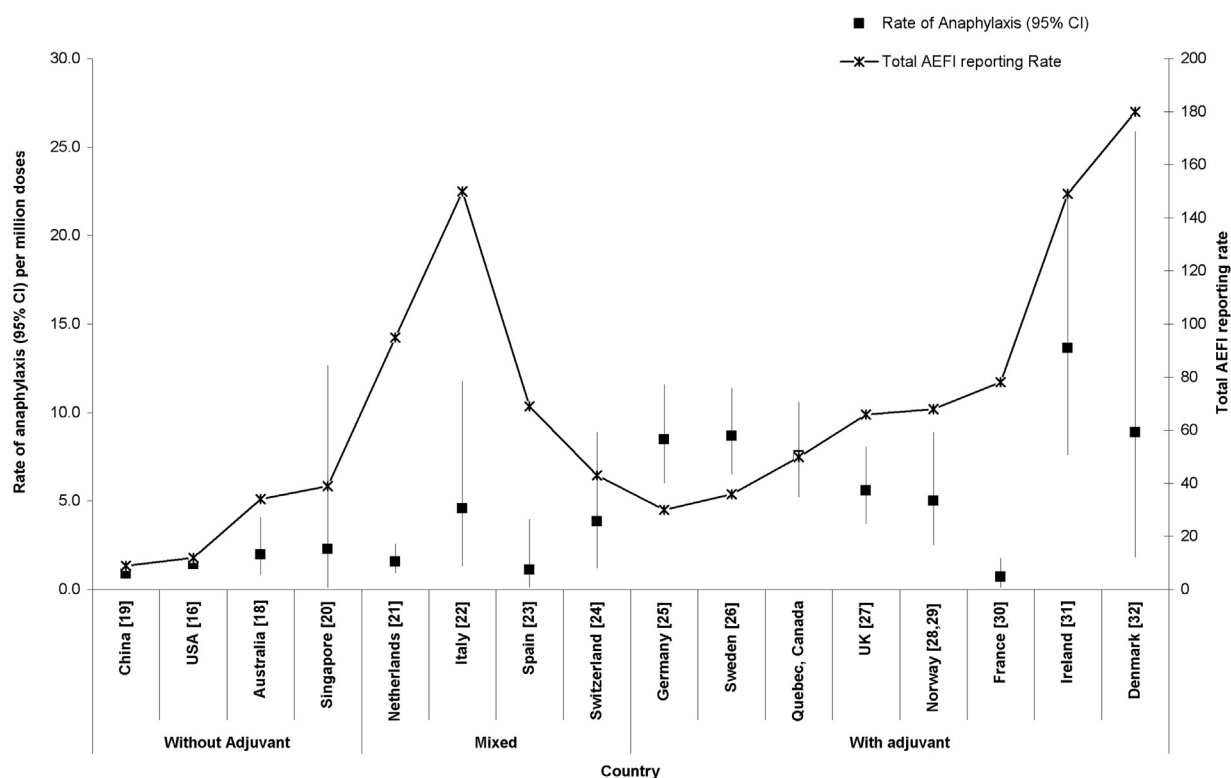


Fig. 2. Worldwide reporting rates of anaphylaxis following the administration of unadjuvanted and adjuvanted H1N1pdm09 monovalent influenza vaccines, per million doses administered.

the overlap between case definitions of anaphylaxis and ORS which per definition is only defined in relation to influenza vaccine. In our series, 95% of ORS cases had the concomitant presence of mucocutaneous and respiratory symptoms (facial edema/conjunctivitis and throat tightening, horse voice or dyspnea). Clinicians reporting AEFI for influenza vaccines are faced with choosing one diagnosis over another, and except for the notable absence of urticaria and pruritus in ORS, it is difficult to know what drives this decision.

The incidence of anaphylaxis, ORS and allergy was significantly affected by both gender and age. Cases were reported primarily by women (74%) who were, adjusting for doses administered, two-fold more likely than men to report any AS. Although it may reflect a greater female tendency to report, gender differences were greatest between 14 and 50 years of age, and may have a biological basis. Anaphylaxis and immediate hypersensitivity, but particularly drug allergy, also occur more frequently in women of childbearing age [13,14]. Although the reasons for this increased susceptibility are largely unknown, sex hormones have been shown to modulate immune responses as well as favoring Th2 cytokine profiles [14,15]. This sexual dimorphism in the risk of AS following immunization deserves more attention and may shed light on the causative mechanisms implicated in drug hypersensitivity reactions more generally.

The reporting rate of anaphylaxis following vaccination is not well quantified. Estimates vary from <1 to 10 per million doses of vaccine, but most are based on a small number of vaccinated individuals (relative to such a small rate), and are rarely specific to influenza vaccines [9–11]. The largest study was published by the US Vaccine Adverse Events Reporting System (VAERS) which received, between 1991 and 2001, 452 reports of “anaphylactoid reaction” following the administration of >1.9 billion doses of vaccine (0.2 cases/million doses distributed) [35]. Although half of the administered doses were influenza vaccines, an influenza-vaccine specific rate was not presented but would not exceed 1 case

per million doses. Universal vaccination with a novel adjuvanted vaccine in the pandemic context may have been associated with increased anxiety and public awareness, possibly contributing to enhanced AEFI reporting for both adjuvanted and unadjuvanted vaccines, particularly among HCW immunized during the first two weeks of the campaign [16,17]. However, rates of anaphylaxis following pandemic immunization were 20-fold greater than previously reported with seasonal vaccines, and while enhanced awareness surely led to an increase, it is unlikely to be the sole or predominant explanation.

We found no differences in rates between adjuvanted and unadjuvanted vaccines or between lots of AS03 adjuvant except for lot 9A, which had a rate of 19 reported anaphylaxis cases per million doses administered (1 in 52,000 vaccinees). Early in the campaign, health authorities considered withdrawal of lot 9A, but with initially suboptimal supply of vaccine rolled out at the height of the pandemic, the risk of contracting and dying from pandemic influenza remained higher than the risk of developing anaphylaxis, leaving the balance of risks and benefits in favor of keeping this vaccine lot in circulation [7]. The CSL unadjuvanted vaccine (Panvax, CSL Biotherapies) also had a higher rate of AS, which was mostly attributable to a higher rate of ORS (17 vs 6 per 100,000 doses; $p=0.01$). However, given its selective administration in pregnant women, the small number of doses administered, and the broad confidence intervals, this estimate should be interpreted cautiously. The Australian reporting rate of AEFI following pandemic immunization, where the CSL vaccine was administered to 3.5 million adults, was >10-fold higher than for seasonal TIV (34 vs 3 per 100,000 doses), suggesting this vaccine may have indeed been more reactogenic [18].

Countries which used AS03-adjuvanted pandemic vaccines reported anaphylaxis rates between 5 and 14 cases per million doses, which is consistent with our estimates, but higher than that reported by the manufacturer (Fig. 2) [16,18–32]. In their analyses,

Tavarès et al. could only confirm a quarter of cases using the BCCD, which led to a lower rate of 2 confirmed cases per million doses [33]. In our series, use of the BCCD similarly excluded 13 (39%) cases reported as anaphylaxis but when systematically applied to all AS reports, added 38 cases of anaphylaxis for a final rate of 13 per million doses. Rates of reported anaphylaxis following AS03-adjuvanted vaccines were similar in Quebec, Canada and throughout most of Europe, but are higher than those reported in Europe for the MF59-adjuvanted pandemic vaccine (3 per million doses) and for unadjuvanted pandemic vaccines used in the United States, China, and Australia (<1 per million) [16,18,19,34]. Rates of AEFI were 3-fold higher for AS03-adjuvanted than unadjuvanted pandemic vaccines administered in France (94 vs 34 per 100,000 doses), and 6-fold greater than for MF59 adjuvanted vaccines in the Netherlands (250 vs 40 per 100,000) [21,30]. Spontaneous reporting of AS in Canada, including anaphylaxis, returned to baseline levels the following season although the unadjuvanted seasonal TIV from the same manufacturer (GSK) included the same H1N1pdm09 strain. These observations suggest that the adjuvant, or characteristics associated with the monovalent adjuvanted formulation, may have contributed to the pandemic excess.

At this time, we cannot accurately estimate the proportion of reported AS cases which were biologically related to the AS03-adjuvant, or to the H1N1pdm09 antigen. Until now, adjuvanted vaccines have been mostly restricted to pandemic H5N1 and H1N1 vaccines or seasonal vaccines for the elderly. The squalene-based AS03 adjuvant is not currently used for seasonal TIV, although AS03-based formulations are still being developed [36]. A similar MF59-adjuvanted vaccine, previously used in the elderly, has recently demonstrated better protection in children than current subunit unadjuvanted vaccines and may soon be marketed for use in children. This safety signal, emerging from the broad-scale use of an AS03-adjuvanted influenza vaccine in children and younger adults, highlights the need for increased surveillance when introducing new adjuvants or adjuvanted vaccines into immunization programs or into new subgroups of the population.

Authors contributions

Gaston De Serres and Isabelle Rouleau had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Eveline Toth, Monique Landry and Suzanne Ménard were involved in the acquisition of data. Isabelle Rouleau and Manale Ouakki performed the statistical analyses. Isabelle Rouleau, Gaston De Serres, and Jean-Philippe Drolet performed the analysis and interpretation of data. Isabelle Rouleau drafted the manuscript. All authors carried out critical revision of the manuscript for important intellectual content. Gaston De Serres supervised the work.

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