Rate of Recurrence of Adverse Events Following Immunization

Results of 19 Years of Surveillance In Quebec, Canada

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Background: While adverse events following immunization (AEFI) are frequent, there are limited data on the safety of reimmunizing patients who had a prior AEFI. Our objective was to estimate the rate and severity of AEFI recurrences.

Methods: We analyzed data from the AEFI passive surveillance system in Quebec, Canada, that collects information on reimmunization of patients who had a prior AEFI. Patients with an initial AEFI reported to the surveillance system between 1998 and 2016 were included. Rate of AEFI recurrence was calculated as number of patients with recurrence/total number of patients reimmunized.

Results: Overall, 1350 patients were reimmunized, of which 59% were 2 years of age or younger. The AEFI recurred in 16% (215/1350) of patients, of whom 18% (42/215) rated the recurrence as more severe than the initial AEFI. Large local reactions extending beyond the nearest joint and lasting 4 days or more had the highest recurrence rate (67%, 6/9). Patients with hypotonic hyporesponsive episodes had the lowest rate of recurrence (2%, 1/50). Allergic-like events recurred in 12% (76/659) of patients, but none developed anaphylaxis. Of 33 patients with seizures following measles mumps rubella with/without varicella vaccine, none had a recurrence. Compared with patients with nonserious AEFIs, those with serious AEFIs were less often reimmunized (60% versus 80%; rate ratio: 0.8; 95% confidence interval: 0.66–0.86).

Conclusions: Most patients with a history of mild or moderate AEFI can be safely reimmunized. Additional studies are needed in patients with serious AEFIs who are less likely to be reimmunized.

Key Words: vaccination, safety, adverse event, recurrence, surveillance

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Most routine vaccines require the administration of several doses to develop optimal protection against the targeted disease(s). However, the occurrence of an adverse event following immunization (AEFI) with a vaccine dose often raises concerns regarding the safety of subsequent doses. Although studies have shown that health care providers (HCPs) have concerns when immunizing patients who had a previous AEFI,[1–3] the literature on the safety of reimmunizing these patients is scarce.[4] For common AEFIs, the literature provides limited information on the risk of recurrence specific to each vaccine, and there are few studies on recurrence of rare but serious AEFIs.[4] These knowledge gaps may negatively impact immunization programs because patients with AEFI may fail to complete their vaccine series and therefore remain susceptible to vaccine preventable diseases.[3,5]

In the province of Quebec (Canada), among the patients who had an AEFI reported to the passive vaccine adverse event reporting system, public health units are encouraged to follow up those who require additional doses to complete the series of vaccine(s) temporally associated with their AEFI[6,7] (Supplemental Digital Content 1, http://links.lww.com/INF/D241 (form) and Table, Supplemental Digital Content 2, http://links.lww.com/INF/D242). This follow-up is encouraged since 1998 and aims to record whether the patients were reimmunized and the outcome of reimmunization. The objective of this study was to estimate the rate of AEFI recurrence using the data collected between 1998 and 2016 by this provincial surveillance system.

MATERIALS AND METHODS

Study Population, Setting and Design

In Quebec, HCPs are legally required to report any unusual or severe AEFI if they suspect a link between the vaccine and the adverse event.[6,7] All AEFI reports are validated by a public health physician or nurse, and if the AEFI fulfills the criteria for reporting (eg, fever ≥39.0°C, local reaction extending beyond the nearest joint or lasting 4 days or longer), the AEFI is entered in an electronic database[6,7] (see form, Supplemental Digital Content 1, http://links.lww.com/INF/D241). The information recorded includes data on the patient; the vaccine(s) administered and the reported AEFI (see form, Supplemental Digital Content 1, http://links.lww.com/INF/D241). The severity of the AEFI is rated by the reporting HCP as mild (did not impair daily activities), moderate (impaired daily activities) or severe (prevented daily activities). A serious AEFI (SAE) is defined as a condition that was fatal or life threatening, required hospitalization for more than 24 hours or resulted in permanent disability[8] (see form, Supplemental Digital Content 1, http://links.lww.com/INF/D241). For anaphylaxis, the level of diagnostic certainty is assessed using the Brighton Collaboration's case definition.[9,10]

Since 1998, public health units are encouraged to follow-up patients requiring additional doses of the vaccine(s) temporally associated with the reported AEFI to complete their recommended immunization schedule (Table, Supplemental Digital Content 2, http://links.lww.com/INF/D242). Public health nurses call these

patients after the expected date of the next vaccine dose to ascertain whether the patient was reimmunized and whether the AEFI recurred. In some cases, information about reimmunization can be directly communicated to public health by the HCP. The information about reimmunization is entered as free text in the patient's initial AEFI report.

Data Collection

This retrospective study included patients with an AEFI entered into the surveillance system's electronic database between January 1, 1998, and December 31, 2016, and who required additional doses of the vaccine(s) temporally associated with their AEFI. Patients with an AEFI associated with influenza vaccine only were excluded as this vaccine is reformulated every year. For patients requiring several additional doses of a vaccine, the analysis only considered the first additional dose. For patients with more than one AEFI reported, only the most severe AEFI (considered as the main reason for reporting) was included in the analysis. Allergic symptoms, anaphylaxis and rash without pruritus were all categorized as allergic-like events (ALE). Vaccines were classified based on their antigens given that the Quebec vaccine schedule and the vaccine brands available in Quebec have changed during the study period. Recurrence was defined as the occurrence of the same AEFI following reimmunization with a vaccine containing at least one of the antigens temporally associated with the initial AEFI. Severity of AEFI recurrence was based on patient or HCP report and coded as less, equally or more severe than the initial AEFI.

Statistical Analysis

The rate of AEFI recurrence (number of patients with AEFI recurrence divided by the total number of patients reimmunized) by vaccine type, patient characteristics (eg, age, sex) and characteristics of the AEFI (eg, type, severity) were compared using rate ratios (RR) and their 95% confidence intervals (95% CIs), 2-tailed χ^2 or Fisher exact tests. Statistical significance was defined as $P < 0.05$. Analyses were conducted with SAS version 9.4 (SAS Institute, Cary, NC).

Ethical exemption was obtained from the Laval University Research Ethics Board as this study only involved secondary analysis of denominalized data.

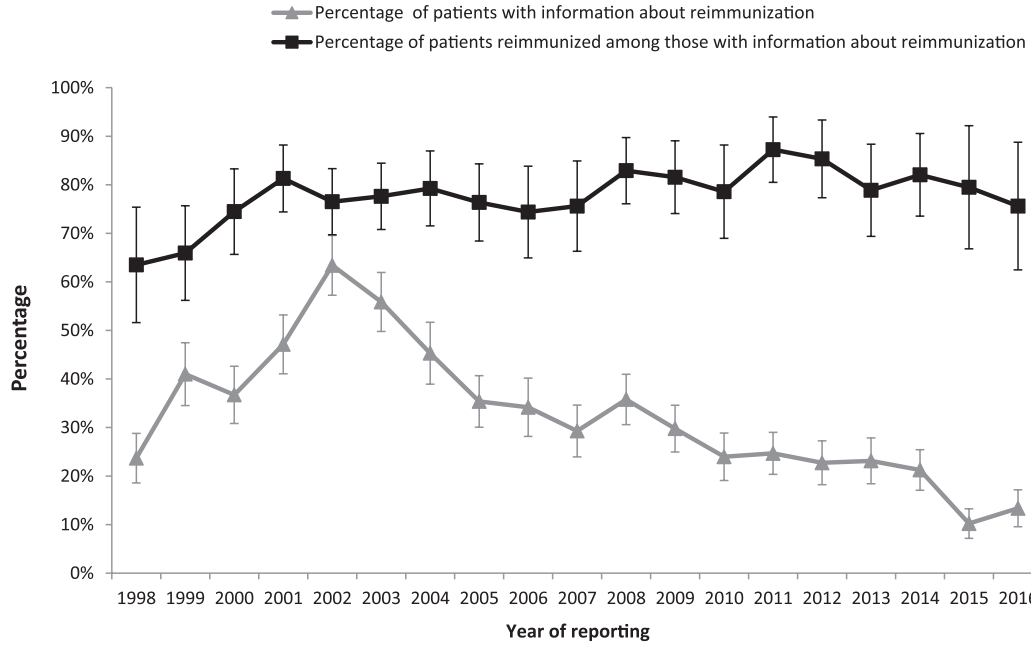
RESULTS

Between 1998 and 2016, the database included 5600 patients who required 6786 additional doses of the vaccine(s) temporally associated with their AEFI. Information about reimmunization was available for 1731 patients (31% overall, varying annually between 12% and 63%; Fig. 1). Compared with these patients, the 3869 patients without information about reimmunization were more frequently 2 years of age or younger (67.4% versus 54.1%; $P < 0.001$), more frequently male (45.7% versus 41%; $P = 0.001$) and more likely to have had a SAE (11.8% versus 9.6%; $P = 0.01$; Table 1).

Reimmunization and AEFI Recurrence: Overall Results

Among the 1731 patients included in the analyses, 1350 (78%) were reimmunized and received 78% of the 2169 required additional doses (Table 2). The majority (59%, 803/1350) of reimmunized patients were children 2 years of age or younger, and the most common category of AEFI was ALE (49%, 659/1350). Overall, a recurrence occurred in 16% (215/1350) of patients (Table 2), 41% and 18% of which were rated as equally and more severe than the initial AEFI, respectively.

Compared with patients 2 to 17 years of age or 18 years of age or older, those 2 years of age or younger were more often reimmunized (65% and 68% versus 86%; $P < 0.001$) and less likely to have a recurrence (23% and 29% versus 12%; $P < 0.001$; Table 2). Gender did not influence reimmunization (76% of males versus 81% of females; $P = 0.3$) or recurrence (15.6% of males



Percentage of patients with information about reimmunization= number of patients with information on reimmunization /number of patients requiring additional doses of vaccine

Percentage of patients reimmunized among those with information about reimmunization = number of patients reimmunized / number of patients with information on reimmunization

FIGURE 1. Description of reimmunization and recurrence per study year.

TABLE 1. Characteristics of the Patients With AEFI Who Required Additional Doses of Vaccine

Characteristics	Information About Reimmunization: Present (n = 1731), n (%col)	Information About Reimmunization: Absent (n = 3869), n(%col)	*P* Value
Age at immunization (yr)			
0–1.9	937 (54.1)	2605 (67.4)	
2–17	540 (31.2)	722 (18.6)	<0.001
≥18	254 (14.7)	542 (14.0)	
Sex			
Female	1021 (59.0)	2099 (54.3)	0.001*
Male	710 (41.0)	1767 (45.6)	
Unknown	0	3 (0.1)	
Vaccines†			
DTaP/dTap combinations	631 (36.5)	1901 (49.1)	
PCV	307 (17.7)	594 (15.4)	
Rotavirus	89 (5.1)	174 (4.5)	
MMR±V	342 (19.8)	766 (19.8)	
HepB±A	657 (38.0)	880 (22.7)	
HPV	136 (7.9)	302 (7.8)	
Other vaccines	7 (0.4)	0	
Type of AEFI			
ALE	820 (47.4)	1533 (39.6)	
Injection site reactions			
Large local reaction	240 (13.9)	712 (18.4)	
Cellulitis	18 (1.0)	201 (5.2)	
Sterile abscess/nodule	23 (1.3)	52 (1.3)	<0.001
Infectious abscess	5 (0.3)	16 (0.4)	
Systemic adverse events			
Diarrhea/vomiting	95 (5.5)	163 (4.2)	
Fever	92 (5.3)	270 (7.0)	
Seizures	67 (3.9)	232 (6.0)	
Persistent crying	58 (3.4)	102 (2.6)	
Hypotonic hyporesponsive episode	56 (3.2)	102 (2.6)	
Arthralgia/arthritis	44 (2.4)	54 (1.4)	
Thrombocytopenia	15 (0.8)	30 (0.9)	
Other AEFIs	203 (11.7)	398 (10.3)	
Severity of the initial AEFI			
Mild (did not impair daily activities)	354 (20.4)	1229 (31.8)	0.003
Moderate (impaired daily activities)	280 (16.2)	1001 (25.9)	
Severe (prevented daily activities)	111 (6.4)	258 (6.6)	
Unknown	986 (57.0)	1381 (35.7)	
Serious AEFI (SAE)‡			
Yes	166 (9.6)	455 (11.8)	0.01*
No	1565 (90.4)	3396 (87.8)	
Unknown	0	18 (0.4)	

*Patients with an unknown status were not considered when estimating the *P* value.

†Not mutually exclusive.

‡Serious AEFI: condition that was fatal or life threatening, required hospitalization for more than 24 hours or resulted in permanent disability.

versus 16.2% of females; $P = 0.7$; Table 2). The proportion of patients reimmunized was inversely proportional to the severity of the initial AEFI (89%, 76% and 64% of patients with mild, moderate and severe AEFIs were, respectively, reimmunized; $P < 0.001$), but the rate of recurrence was not significantly different whatever the severity (18%, 15% and 8% of recurrences in patients with mild, moderate and severe AEFIs, respectively; $P = 0.1$). Patients with SAEs were less often reimmunized than those without SAEs (60% versus 80%; RR: 0.8; 95% CI: 0.66–0.86) but had fewer recurrences (8% versus 17%; RR: 0.5; 95% CI: 0.25–0.95; Table 2).

Among all AEFIs, patients with hypotonic hyporesponsive episode (HHE) were the most likely to be reimmunized (89%; 95% CI: 78.1–96.0) and the least likely to have a recurrence (Table 2). Only 1 of 50 (2%; 95% CI: 0.1%–10.6%) patients with HHE who were reimmunized had a recurrence. This recurrence occurred in a 4-month-old boy receiving his second doses of pneumococcal conjugate vaccine (PCV) and full-content diphtheria-tetanus-acellular pertussis (DTaP)–containing vaccine.

The rate of AEFI recurrence was similar between vaccines and varied from 8% to 22%. Patients with an AEFI following full-content or reduced-antigen diphtheria-tetanus-acellular pertussis (DTaP/dTap)–containing vaccines were the most likely to be reimmunized (90%; 95% CI: 87.4–92.2), and those with an AEFI following rotavirus vaccine were the least likely to be reimmunized (53%; 95% CI: 41.9 to 63.5; Table 2) especially if they had diarrhea/vomiting. Among patients with diarrhea/vomiting, only 35% (10/29) were reimmunized with rotavirus vaccine compared with 94% (29/31) and 88% (14/16) of patients reimmunized with DTaP/dTap-containing vaccines and PCV, respectively (Table 3).

Recurrence per Type of AEFI

Among the 820 patients with ALEs, 659 (80%) were reimmunized of which 76 (12%; 95% CI: 9.2–14.2) had a recurrence

TABLE 2. Reimmunization and Rate of Recurrence Depending on the Characteristics of the Vaccinee and Initial AEFI

	Percentage Reimmunized (n/N)*	Percentage of Recurrences or Rate of Recurrence (n/N)†	Percentage of Recurrences With a Greater Severity (n/N)‡§
Total number of patients requiring additional vaccine doses	78 (1350/1731)	16 (215/1350)	18 (36/203)
Age groups (yr)			
<2	86 (803/937)	12 (95/803)	11 (10/90)
2–17	65 (369/540)	23 (85/369)	25 (19/76)
≥18	68 (173/254)	20 (34/173)	21 (7/34)
Sex			
Female	76 (778/1021)	16 (126/778)	17 (19/115)
Male	81 (572/710)	16 (89/572)	19 (17/88)
Vaccines			
DTaP/dTap-containing vaccines	90 (568/631)	13 (74/568)	11 (8/73)
PCV	82 (253/307)	10 (25/253)	21 (5/24)
Rotavirus	53 (47/89)	11 (5/47)	0 (0/2)
MMR±V	78 (267/342)	8 (22/267)	14 (3/22)
Hep B±A	68 (448/657)	23 (102/448)	23 (22/96)
HPV	75 (102/136)	22 (22/102)	25 (4/16)
Other vaccines	86 (6/7)	0 (0/6)	NA
Type of AEFI			
ALE	80 (659/820)	12 (76/659)	20 (14/70)
Injection site reactions			
Large local reaction	84 (203/240)	22 (44/203)	9 (4/42)
Cellulitis	67 (12/18)	8 (1/12)	0 (0/1)
Sterile abscess/nodule	91 (21/23)	48 (10/21)	22 (2/9)
Infectious abscess	80 (4/5)	25 (1/4)	0 (0/1)
Systemic adverse events			
Diarrhea/vomiting	78 (74/95)	24 (18/74)	13 (2/16)
Fever	77 (71/92)	15 (11/71)	22 (2/9)
Seizures	73 (49/67)	6 (3/49)	0 (0/3)
Persistent crying	84 (49/58)	16 (8/49)	13 (1/8)
Hypotonic hyporesponsive episode	89 (50/56)	2 (1/50)	0 (0/1)
Arthralgia/arthritis	55 (24/44)	25 (6/24)	0 (0/6)
Thrombocytopenia	47 (7/15)	29 (2/7)	50 (1/2)
Other AEFIs	63 (127/203)	27 (34/127)	29 (10/34)
Severity of the initial AEFI			
Mild (did not impair daily activities)	89 (314/354)	18 (56/314)	23 (11/48)
Moderate (impaired daily activities)	76 (212/280)	15 (31/212)	12 (3/25)
Severe (prevented daily activities)	64 (71/111)	8 (6/71)	33 (2/6)
Unknown	76 (753/986)	23 (174/753)	16 (20/124)
Serious AEFI			
Yes	60 (100/166)	8 (8/100)	25 (2/8)
No	80 (1250/1565)	17 (207/1250)	16 (34/207)

*Percentage reimmunized = number of patients reimmunized/total number of patients with information on reimmunization.

†Percentage of recurrences (rate of recurrence) = number of patients with recurrence/total number of patients reimmunized.

‡Percentage of recurrences with greater severity = number of recurrence more severe than the initial AEFI/total number of recurrences with information on severity.

§The denominator can be lower than the total number of recurrences because the severity of the recurrence was sometimes not reported.

ALE indicates allergic-like event; Hep B±A, hepatitis B with or without hepatitis A antigen; HPV, human papilloma virus; NA indicates not applicable.

(Table 2). The rate of ALE recurrence varied from 5% to 25% between vaccines (Table 3). Patients whose ALE onset occurred within an hour of immunization were as likely to be reimmunized as those with onset 1–3 hours or ≥4 hours postimmunization and had no greater rate of recurrence (Table 4). Among the 18 patients with reported anaphylaxis, 3 met the Brighton Collaboration level 1 of diagnostic certainty, 8 met level 2, 6 met level 3 and 1 did not have a description of signs and symptoms (Table, Supplemental Digital Content 3, http://links.lww.com/INF/D243). A medical assessment was done for 2, 4, 4 and 1 patients, and reimmunization performed in 0, 3, 4 and 1 patients, respectively. None of 8 reimmunized patients had a recurrence. Reimmunization was withheld in 3 patients: 1 was considered immune to the targeted vaccine preventable disease based on serum antibody titers, and 2 had positive skin testing to the vaccine.

Large local reactions recurred in 44 of 203 reimmunized patients (22%; 95% CI: 16.2–28.0; Table 2). The rate of recurrence varied from 7% to 33% between vaccines (Table 3). Large local reactions that extended beyond the nearest joint and lasted 4 days or more recurred in 6(67%) of 9 patients compared with 13% (5/39) when it did not go beyond the nearest joint and lasted <4 days (RR = 2.9; 95% CI: 1.4–5.8).

Among the 92 patients with fever, 71 (77%) were reimmunized, and recurrences occurred in 11 (15%; 95% CI: 8.0–26.0). The rate of recurrence varied from 0% to 15% between vaccines (Table 3). The proportion of patients reimmunized and the rate of fever recurrence did not differ by the recorded level of temperature (39°C–40.4°C versus ≥40.5°C).

No recurrences occurred among 11 patients with afebrile seizures who were reimmunized compared with 3 recurrences

TABLE 3. Reimmunization and Recurrence per Type of Vaccine (Not Mutually Exclusive) and Type of AEFI*

AEFI	DTaP/dTap-Containing Vaccines, % (n/N)	PCV, % (n/N)	Rotavirus, % (n/N)	MMR±V, % (n/N)	Hep B±A, % (n/N)	HPV, % (n/N)
ALE						
Percentage reimmunized*	92 (230/250)	83 (123/149)	92 (23/25)	82 (162/195)	71 (231/326)	78 (51/65)
Percentage of recurrences†	10 (23/230)	11 (14/123)	9 (2/23)	5 (8/162)	17 (39/231)	24 (12/51)
Percentage of recurrences with greater severity‡§	10 (2/21)	23 (3/13)	NR	33 (2/7)	25 (9/36)	8 (1/12)
Large local reactions						
Percentage reimmunized*	91 (108/118)	90 (28/31)	NA	79 (16/20)	74 (66/89)	94 (16/17)
Percentage of recurrences†	13 (15/108)	7 (2/28)	NA	33 (5/15)	32 (21/66)	13 (2/15)
Percentage of recurrences with greater severity‡§	7 (1/15)	0 (0/2)	NA	0 (0/5)	15 (3/20)	NR
Fever						
Percentage reimmunized*	94 (29/31)	63 (12/19)	50 (2/4)	71 (20/28)	72 (23/32)	50 (1/2)
Percentage of recurrences†	14 (4/29)	17 (2/12)	0 (0/2)	15 (3/20)	13 (3/23)	0 (0/1)
Percentage of recurrences with greater severity‡§	25 (1/4)	50 (1/2)	NA	0 (0/2)	50 (1/2)	NA
Diarrhea/vomiting						
Percentage reimmunized*	94 (29/31)	88 (14/16)	35 (10/29)	100 (4/4)	84 (32/38)	80 (8/10)
Percentage of recurrences†	14 (4/29)	7 (1/14)	10 (1/10)	0 (0/4)	31 (10/32)	38 (3/8)
Percentage of recurrences with greater severity‡§	0 (0/4)	0 (0/1)	0 (0/1)	NA	11 (1/9)	0 (0/1)
Seizures						
Percentage reimmunized*	76 (16/21)	56 (10/18)	0 (0/11)	75 (33/44)	33 (1/3)	0 (0/1)
Percentage of recurrences†	19 (3/16)	10 (1/10)	NA	0 (0/33)	0 (0/1)	NA
Percentage of recurrences with greater severity‡§	0 (0/3)	NR	NA	NA	NA	NA

* Vaccine categories are not mutually exclusive as vaccines are frequently coadministered.

*Percentage of reimmunized= number of patients reimmunized /total number of patients with information on reimmunization

†Percentage of recurrences (rate of recurrences) = number of patients with recurrence/total number of patients reimmunized

‡Percentage of recurrences with greater severity = number of recurrence more severe than the initial AEFI/total number of recurrences with information on severity

§The denominator can be lower than the total number of recurrences because recurrence severity was sometimes not reported

ALE, allergic-like event; Hep B±A, hepatitis B with or without hepatitis A antigen; HPV, human papilloma virus; NA, not applicable; NR, not reported; PCV, pneumococcal conjugate vaccine.

TABLE 4. Rate Ratios (RR) Comparing Reimmunization and Recurrence by Type of AEFI

AEFI	Percentage Reimmunized (n/N)	RR (95% CI)	Percentage of Recurrence (n/N)	RR (95% CI)
Allergic-like event (ALE)				
Time from immunization to onset of the initial ALE (hr)				
<1	82 (157/192)	1.0 (0.93–1.09)	8 (13/157)	0.6 (0.34–1.09)
1–3	79 (85/107)	1.0 (0.88–1.09)	7 (6/85)	0.5 (0.23–1.21)
≥4	81 (399/493)	Reference	13 (54/399)	Reference
Severity of the initial ALE				
Mild	90 (189/212)	Reference	15 (29/189)	Reference
Moderate	80 (95/119)	0.9 (0.81–0.99)	7 (7/95)	0.5 (0.22–1.06)
Severe	72 (23/32)	0.8 (0.65–1.01)	4 (1/23)	0.3 (0.04–1.98)
Large local reactions				
Nature of the large local reaction				
Not beyond the nearest joint and lasting <4 days	87 (78/90)	Reference	23 (18/78)	Reference
Not beyond the nearest joint and lasting ≥4 days	87 (72/83)	1.0 (0.89–1.12)	24 (17/72)	1.1 (0.57–1.83)
Beyond the nearest joint and lasting <4 days	81 (39/48)	0.9 (0.80–1.09)	13 (5/39)	0.6 (0.22–1.38)
Beyond the nearest joint and lasting ≥4 days	67 (6/9)	0.8 (0.48–1.23)	67 (4/6)	2.9 (1.44–5.79)
Fever				
Temperature				
39°C–40.4°C	84 (46/55)	Reference	20 (9/46)	Reference
≥40.5°C	71 (12/17)	0.8 (0.61–1.17)	8 (1/12)	0.4 (0.06–3.04)
Seizures				
Type of seizures				
Febrile	77 (36/47)	Reference	8 (3/36)	Reference
Afebrile	69 (11/16)	0.9 (0.62–1.29)	0 (0/11)	0

among 36 patients (8%; 95% CI: 1.8–22.5) with febrile seizures. These 3 recurrences of febrile seizures occurred among patients reimmunized with DTaP/dTap-containing vaccines administered with or without concurrent PCV. None of the 33 patients reimmunized with measles mumps rubella vaccine with or without varicella antigen (MMR±V; Table 3) had a recurrence of febrile seizure including 18 patients with onset of febrile seizures between day 5 and day 12 following their first MMR±V immunization.

Diarrhea/vomiting recurred in 18 of 74 reimmunized patients (24%; 95% CI: 15.1–35.7; Table 2). The rate of recurrence varied from 0% to 38% between vaccines (Table 3).

DISCUSSION

This is one of the largest studies to estimate the rate of AEFI recurrence per type of AEFI and vaccine, a key element for the

decision regarding further immunization of patients who had a prior AEFI. Overall, 16% of patients had a recurrent AEFI, of whom 18% rated the recurrence as more severe than the initial AEFI, respectively. The rate of AEFI recurrence was similar between vaccines and between AEFIs except for large local reactions extending beyond the nearest joint and lasting 4 days or more, which were associated with the highest rate of recurrence (67%). No patient with anaphylaxis experienced a recurrence. Among patients with nonanaphylactic ALEs, 12% had a recurrence, of which 20% were considered more severe than the initial ALE. None of the 33 patients with febrile seizures following the first dose of MMR±V (recommended in Quebec at 12 months of age) had a recurrence following administration of the second dose (recommended at 18 months of age; Table, Supplemental Digital Content 2, http://links.lww.com/INF/D242).

ALEs often raise concerns about the rate of anaphylaxis upon reimmunization. Our results and those of previous studies show that while recurrence of nonanaphylactic events may happen, anaphylaxis following reimmunization is rare.[4,11–17] This reassuring finding is likely related to 2 factors. First, most reported ALEs following immunization are mild or moderate. Based on the experience with penicillin, food and insect venom allergies mild or moderate events will either not recur[18–21] or will generally result in recurrences with similar severity (stereotypic) as the first event[22–27] and not in anaphylaxis. Second, most ALEs following immunization are unlikely to be IgE mediated. They usually began more than 1 hour following immunization, a timing inconsistent with an IgE-mediated hypersensitivity to vaccine components.[11,13,16,17] This is further supported by the fact that skin tests with the vaccines temporally associated with the ALE are generally negative even in patients with reported anaphylaxis.[11–13,16] The current management algorithms suggest that precautions (skin testing with the vaccine, graded dose reimmunization or serologic testing for immunity to the vaccine) are needed for the few patients with a severe clinical presentation[9] and/or onset of their ALE within 1 to 4 hours of immunization but are generally unnecessary for other patients.[11,28]

Similar to other studies,[13,29–31] we found that large local reactions extending beyond the nearest joint and lasting 4 days or more (referred to as extensive limb swelling) recurred frequently (67%). Fortunately, recurrent extensive limb swellings are usually not accompanied by systemic adverse events and resolve without sequelae.[29,30,32] Further studies are needed to understand the mechanism of these reactions and identify interventions reducing these recurrences. For extensive limb swellings following administration of DTaP-containing vaccines, reimmunization with lower-antigen formulations (dTap) reduces the rate of recurrence.[29,30] However, the low antigen-content formulations have been confirmed to provide protective levels of antibody in patients 4 years of age or older, but data is lacking for infants.[33–35]

Patients with a history of HHE were the most likely to be reimmunized. This probably results from the clear recommendations to reimmunize these children issued since 1998[32,36] after various studies showed that the condition was benign and recurred in less than 1% of children.[4,37–39]

Rotavirus vaccine was readministered to 53% of patients overall and to only 35% of those with diarrhea/vomiting. The reasons of this lower reimmunization rate were not captured in this study. However, the narrow window to complete the rotavirus series (before 8 months of age) and perceptions that rotavirus gastroenteritis is not a severe disease in Canada may be contributing factors.[40,41]

This study had limitations. It was based on a passive surveillance system that does not capture all AEFIs, and only 31% of eligible patients were followed up. While our participants may not be representative of all patients with AEFIs, they are likely representative of the rate of recurrence of those with similar conditions. Nearly 40% of patients with severe or serious AEFIs were not reimmunized, and they may have been at greater risk of recurrence than those who were. This would underestimate the rate of recurrence in this subgroup. However, it is reassuring to see that most patients with severe events can be safely reimmunized given that the 60% who were reimmunized had fewer recurrences than patients with mild or moderate events. We were not able to estimate the rate of recurrence of rare and severe AEFIs (eg, Guillain–Barré syndrome, Kawasaki disease) because information about reimmunization was available in less than 4 patients. Collection of reimmunization data was not standardized, and many reports missed information on AEFI severity. Additionally, the information on AEFI recurrence and its severity was mostly obtained from patients and relied on their memory and perception that may or may not be consistent with objective clinical severity. When several vaccines were coadministered at a given visit, it was impossible to determine which vaccine(s) caused systemic AEFIs (initial or recurrent). Difference between the formulations of vaccines associated with the initial AEFI and those used for reimmunization is also a methodologic caveat that may have underestimated the rate of recurrence of a specific systemic AEFI associated with a given vaccine/product. However, our results likely represent the rate observed in real-life practice where vaccine coadministration is frequent and various vaccine formulations are available. Given that the potential confounders of AEFI recurrence are unknown, we presented crude estimates and performed stratified analyses. It should be noted that details such as administration of analgesics/antipyretics were not recorded in the database.

Our results suggest that despite the rate of recurrence, most patients with a history of mild or moderate AEFI can be safely reimmunized. The vaccine-specific rates of recurrence of specific AEFIs we have estimated should be helpful to vaccine providers but often included a small number of patients limiting the statistical power. Additional studies are needed to improve the precision of these estimates and to better assess the rate of recurrence in patients with serious AEFIs as they are often not reimmunized.[4,13] Rare and serious AEFIs require the surveillance of a large-source population to be identified.[42,43] Despite their limitations, passive vaccine adverse event reporting systems may be the only way to access these patients in sufficient numbers to obtain robust estimates of their rate of recurrence. Therefore, adapting these systems to include a systematic and standardized follow up of patients with rare or serious AEFIs could be the only way to ever provide empiric data to clinicians.

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