Immunizing Patients With Adverse Events After Immunization and Potential Contraindications to Immunization

A Report From the Special Immunization Clinics Network

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Background: For patients who have experienced adverse events following immunization (AEFI) or who have specific medical conditions, there is limited evidence regarding the best approach to immunization. The Special Immunization Clinics (SICs) Network was established to standardize patient management and assess outcomes after reimmunization. The study objective was to describe the first 2 years of the network's implementation.

Methods: Twelve SICs were established across Canada by infectious diseases specialists and allergists. Inclusion criteria were as follows: local reaction ≥ 10 cm, allergic symptoms < 24 hours postimmunization, neurologic symptoms and other AEFI or medical conditions of concern. Eligible patients underwent a standardized evaluation, causality assessment was performed, immunization recommendations were made by expert physicians and patients were followed up to capture AEFI. After individual consent, data were transferred to a central database for analysis.

Results: From June 2013 to May 2015, 151 patients were enrolled. Most were referred for prior AEFI (132/151, 87%): 42 (32%) for allergic-like reactions, 31 (23%) for injection-site reactions, 20 (15%) for neurologic symptoms and 39 (30%) for other systemic symptoms. Nineteen patients (13%) were seen for underlying conditions that complicated immunization. Reimmunization was recommended for 109 patients, 60 of whom (55%) were immunized and followed up. Eleven patients (18%) experienced recurrence of their AEFI; none were serious (eg, resulting in hospitalization, permanent disability or death).

Conclusions: The most frequent reasons for referral to a SIC were allergic-like events and injection site reactions. Reimmunization was safe in most patients. Larger studies are needed to determine outcomes for specific types of AEFI.

Key Words: adverse event following immunization; immunization; consultation

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As rates of vaccine-preventable infections have declined, attention has shifted to the safety of recommended vaccines.[1] The continued success of immunization programs depends on maintaining confidence in the safety of recommended vaccines through augmented surveillance and research. Although immunizations are generally safe, adverse events following immunization (AEFI) do occur, and in rare cases they may be serious (eg, anaphylaxis).[2–5] Additionally, there is a growing population of patients with underlying medical conditions that may interfere with their response to immunizations or increase their risk of an AEFI. When AEFIs come to medical attention or when patients with certain medical conditions present for immunization, there is often uncertainty among healthcare providers and patients regarding the best approach to immunization. In some cases, healthcare providers may decide to delay or avoid further immunizations because of this uncertainty, leading to missed opportunities to immunize. Patients with prior AEFI and those with certain underlying medical conditions may benefit from assessment by a clinician with expertise in vaccine safety.[6]

Specialized immunization services have been established in a few countries, and their published experience suggests that most patients can be safely reimmunized after an AEFI.[7–10] However, data regarding the risk of recurrence of AEFI remain limited. Before 2013, services in Canada for patients who had experienced AEFI were only available in a few pediatric hospitals or through public health services in certain provinces. We conducted a survey of Canadian pediatricians in 2013 and found that 28% of general pediatricians who responded had encountered patients with potential contraindications to immunization or challenging AEFI that raised concerns about future immunizations.[11] Seventy-eight percent of respondents indicated that they would be somewhat or very

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likely to refer patients to a special immunization clinic, if one was available. These findings suggested a need to expand immunization services for these patients.

The Special Immunization Clinics (SICs) Network was established in 2013 at 12 centers in 6 Canadian provinces: British Columbia, Saskatchewan, Nova Scotia, Alberta (2 centers), Ontario (4 centers) and Quebec (3 centers) to provide standardized expert clinical assessment of patients with prior AEFI and underlying medical conditions that were potential contraindications to immunization, as well as to establish a platform for clinical vaccine safety research. SIC are coordinated by infectious diseases specialists in collaboration with allergists and other specialists with expertise in vaccine safety. Ten of 12 sites are based in pediatric tertiary care centers. The objective of this study was to describe the first 2 years of the network's implementation, the types of patients assessed for prior AEFI and potential contraindications to immunization, and their outcomes after immunization or repeat immunization.

METHODS

Study Design and Subjects

This was a prospective study of patients referred by a healthcare provider to one of 12 SIC between June 2013 and May 2015. Patients were eligible if they had a medical condition that was considered a potential contraindication to immunization or if they were referred for one of the AEFI listed in Table 1. Patients referred for vaccine hesitancy, needle phobia, a family history of AEFI or a personal history of conditions that are not considered contraindications to immunization in Canada (eg, mild egg allergy) were excluded. Seven sites enrolled exclusively children <18 years of age, while at the remaining 5 sites, patients of all ages were eligible.

Eligible patients underwent a standardized evaluation, which included completion of a medical questionnaire and physical examination. Recommendations for immunization or reimmunization were made by the SIC physician according to best practice, risk–benefit assessment and patient preference. To harmonize immunization recommendations across the network, management guidelines were developed for selected AEFI (eg, injection-site reactions, allergic-like events (ALEs), hypotonic-hyporesponsive episodes) and for patients with underlying medical conditions. After review of the literature and existing practice guidelines,[12–15] recommendations were drafted and discussed among the investigators and allergists to achieve consensus. Complex cases were discussed informally among all physician investigators to reach consensus on the best decision. Patients were contacted by telephone or email approximately 7 days after reimmunization to capture adverse events. Patients whose primary adverse event occurred more than 7 days after immunization were followed for up to 42 days after reimmunization.

After individual consent, the SIC nurse or physician completed a detailed data collection form, which included a description of the severity of the AEFI, causality assessment using the algorithm and checklist developed by the World Health Organization (WHO),[16] immunization recommendations and outcome of immunization or reimmunization. The form was transmitted to the SIC Network Data Center for entry into a central database (Microsoft Access). Ethical approval was received from the research ethics board at each participating site.

Data Source

Data were extracted from the central database on all patients referred to the SIC Network from June 2013 to May 2015 and who had been assessed by August 31, 2015. AEFI were categorized as follows: injection site reactions (ISRs) (ie, large local reactions, cellulitis, abscess, nodule), ALEs (ie, anaphylaxis, immediate hypersensitivity without anaphylaxis, idiopathic urticaria/angioedema, other allergic events), neurological events (eg, seizure, Guillain-Barré syndrome) and other systemic events (eg, thrombocytopenia, hypotonic-hyporesponsive episode). The case definition for AEFI was based on the SIC physician's diagnosis because patients were frequently seen months to years after the event and there was either insufficient information to apply an accepted case definition (eg, Brighton Collaboration definition) or no accepted case definition existed. "Immediate hypersensitivity without anaphylaxis" was diagnosed in patients who developed urticaria or other symptoms suggestive of an IgE-mediated reaction within 4 hours after immunization. Those with "other ALEs" presented with delayed onset of symptoms (> 12 hours after immunization) and/or with symptoms suggestive of non-IgE-mediated hypersensitivity (eg, erythema multiforme, serum sickness).

AEFI severity was reported according to the categories used by the Public Health Agency of Canada (PHAC): low impact (treated in vaccine clinic by on site staff, telephone advice from health professional, disabled <24 hours), moderate impact (unscheduled physician visit, ER services called to vaccine clinic but no further care needed, required new drug prescription, disabled 1–3 days), high impact (required ≥3 physician assessments, medical supervision out of hospital, hospitalized for ≤24 hours, disabled >3 days), serious (hospitalized >24 hours, life-threatening or fatal outcome, congenital abnormality, residual disability).

Assessment of a causal association between the immunization and adverse event was conducted by the site investigator. Results were reported as "consistent with causal association," "inconsistent with causal association," "indeterminate" and "unclassifiable" according to the WHO algorithm.[16]

Reimmunization recommendations and outcome were reported. Severity of AEFI recurrence was based on participant self-report and was recorded as follows: did not affect daily activities, limited daily activities or prevented daily activities. Participants were asked to rate the severity of the recurrence compared with the first occurrence as: milder, same severity or more severe.

Statistical Analysis

The analysis was descriptive. For patients with more than one AEFI, the most severe event was included in the analysis.

TABLE 1. Study Inclusion Criteria for Patients With Adverse Events Following Immunization

Adverse Event Type	Interval From Immunization to Symptom Onset	
	Inactivated Vaccines*	Live Vaccines†
Allergic-like symptoms	0–24 h	0–24 h
Fever ≥ 40.5°C	0–72 h	5–10 d
Injection site reaction	Any	Any
Erythema or swelling ≥ 10 cm		
Cellulitis, abscess, nodule, arthus reaction		
Seizure	0–72 h	5–10 d
Persistent inconsolable crying ≥ 3 h	0–48 h	0–48 h
Hypotonic-hyporesponsive episode	0–48 h	0–48 h
Arthralgia/arthritis	0–30 d	0–30 d
Unexpected AEFI of concern to the investigator	Any	Any

*Includes tetanus-diphtheria-acellular pertussis, inactivated influenza, pneumococcal conjugate, meningococcal conjugate, hepatitis B vaccine, human papillomavirus vaccine.

†Includes measles-mumps-rubella, varicella, rotavirus, yellow fever virus vaccines, live-attenuated influenza vaccine.

Patients with underlying conditions who also had a history of AEFI were included in the analysis of patients with AEFI. Analysis of patients referred for underlying medical conditions was stratified by the presence or absence of immunosuppression. Statistical analysis was conducted using SAS version 9.3 (SAS Institute, Cary, NC).

RESULTS

From June 2013 to May 2015, 269 patients were referred to a SIC clinic, of which 227 met the inclusion criteria, and 151 patients were enrolled by August 2015 (Fig. 1). Patients who declined to participate (49/227; 22%) did not differ significantly from participants in regards to gender or reason for referral. Nonparticipants were more likely to be adults (31% vs. 11% of participants; $P = 0.01$) and less likely to be from British Columbia (0% vs. 17%; $P < 0.01$). Most patients were seen for a history of AEFI (132/151; 87%), and 19 patients (13%) were referred for an underlying medical condition or pretransplant evaluation. Fifty percent of participants were male. The majority of participants were children; 48 (32%) were <2 years of age when they were screened, 87 (58%) were 2–17 years of age, 13 (9%) were 18–64 years of age and 3 (2%) were ≥65 years of age. There were 46 participants from Ontario, 34 from Nova Scotia, 26 from British Columbia, 24 from Quebec, 17 from Alberta and 4 from Saskatchewan. The recruitment rate among children <18 years of age (2013–2015) ranged from 1.4 per 100,000 in Quebec and Ontario to 18.4 per 100,000 in Nova Scotia.[17] The most common AEFI reported were ALE (42/132) and ISR (31/132) (Table 2).

Injection-site Reactions

Most ISR were large local reactions (defined as erythema and swelling ≥10 cm in diameter) (17/31; 55%), followed by sterile abscess with or without a nodule (5/31; 16%), cellulitis (5/31; 16%) and nodule without abscess (4/31; 13%). Among the large local reactions, erythema and/or edema crossed the joint in 5/17 cases and extended from joint to joint in 5/17 cases. The median interval from immunization to symptom onset was 18 hours [interquartile range (IQR) 3–24 hours] (Table 2). Severity was reported as low or moderate in 84% of cases, indicating minimal to no impact on daily activities. Trivalent inactivated influenza vaccine (TIV) was the immunization most frequently causally associated with ISR (15/31) (Table 3). The TIV product associated with the ISR was known in 9/15 patients: Fluviral (ID Biomedical Corporation of Quebec, Quebec, QC) (3), Vaxigrip (Sanofi Pasteur SA, Lyon, France) (3) and Agriflu (Novartis Vaccines and Diagnostics, Inc, Cambridge, MA) (3). Diphtheria-tetanus-acellular pertussis (DTaP/Tdap) vaccines were reported to be causally associated with ISR in 10 cases. Overall, immunization was reported as the cause of the ISR in 97% of cases (30/31); however, in no case was reimmunization contraindicated (Table 4).

Reimmunization was recommended to 27/31 patients with an ISR, 3 patients did not require further doses, and a recommendation was deferred in one case. At the time of this analysis, 17/27 were eligible for reimmunization, of whom 14/17 (82%) have been reimmunized and 3/17 (18%) remain unimmunized for other reasons or were lost to follow up. The ISR was of high impact or

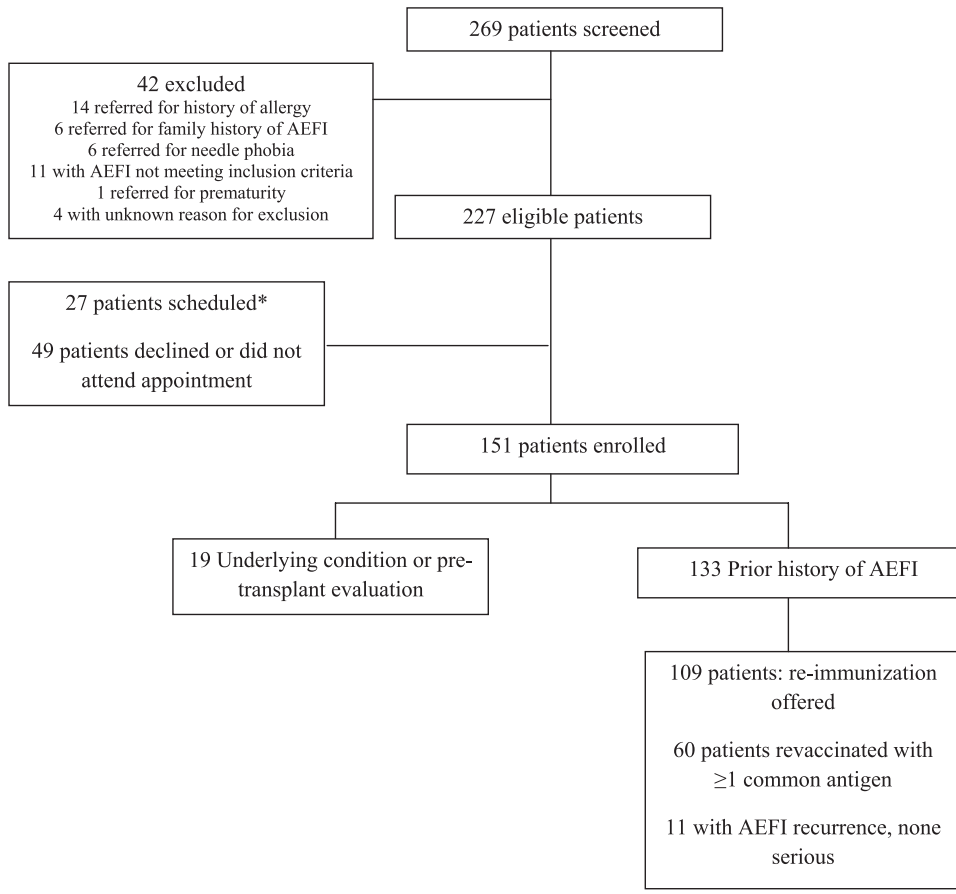

FIGURE 1. Summary of participants screened and enrolled in the Special Immunization Clinics Network (2013–2015). *Patients who are scheduled to be seen in the clinic after the data were locked on August 31, 2015.

TABLE 2. Stratified Analysis by Type of Adverse Event Following Immunization (N = 133)

	Injection-site Reaction	Allergic-like Events	Neurologic Events	Others*
	N = 31	N = 42	N = 20	N = 39
	n (%)	n (%)	n (%)	n (%)
Age in years, median (IQR)	4.2 (1.5–5.5)	2.0 (1.0–11.2)	1.1 (0.6–12.5)	1.0 (0.3–5.8)
Male sex	15 (48)	20 (48)	11 (55)	17 (44)
Interval from immunization to onset in hours, median (IQR)	18.0 (3.0–24.0)	2.0 (0.2–24.0)	24.0 (12.0–336.0)	9.0 (3.0–72.0)
Number of vaccines temporally associated with the AEFI				
1	24 (77)	16 (38)	10 (50)	16 (41)
2	5 (16)	13 (31)	5 (25)	8(21)
≥3	2 (6)	13 (31)	5 (25)	14 (36)
Unknown	0 (0)	0 (0)	0 (0)	1 (3)
Vaccine type				
DTaP/Tdap	11 (35)	19 (45)	10 (50)	24 (62)
PCV	6 (19)	14 (33)	6 (30)	16 (41)
Rotavirus	N/A	4 (10)	1 (5)	8 (21)
MMR/MMRV	4 (13)	14 (33)	4 (20)	8 (21)
Varicella	1 (3)	8 (19)	2 (10)	3 (8)
Men-C	1 (3)	7 (17)	5 (25)	8 (21)
HPV	1 (3)	4 (10)	1 (5)	4 (10)
Influenza	15 (48)	11 (26)	3 (15)	4 (10)
Other†	1 (3)	10 (24)	4 (20)	5 (13)
Severity				
Low impact	9 (29)	13 (31)	1 (5)	11 (28)
Moderate impact	17 (55)	26 (62)	2 (10)	16 (41)
High impact	4 (13)	3 (7)	8 (40)	5 (13)
Serious	1 (3)	0 (0)	9 (45)	7 (18)
Causality assessment				
Consistent with causal association	30 (97)	21 (50)	2 (10)	16 (41)
Inconsistent with causal association	1 (3)	5 (12)	4 (20)	4 (10)
Indeterminate	0 (0)	16 (38)	13 (65)	18 (46)
Unknown	0 (0)	0 (0)	1 (5)	1 (3)

*Includes hypotonic-hyporesponsive episodes, persistent crying, high fever, thrombocytopenia and nonspecific symptoms.

†Includes single antigen *Haemophilus influenzae* type b conjugate, pandemic H1N1 influenza vaccine, tetanus-diphtheria, typhoid, typhoid-hepatitis A vaccine, yellow fever vaccine, hepatitis A, hepatitis B, hepatitis A and B, herpes zoster vaccine and multicomponent meningococcal serogroup B vaccine.

AEFI indicates adverse event following immunization; IQR, interquartile range; DTaP/Tdap diphtheria-tetanus-acellular pertussis containing vaccines; HPV, human papillomavirus vaccine; MenC, meningococcal conjugate vaccine (includes serogroup C vaccine and quadrivalent vaccine); MMRV, measles-mumps-rubella-varicella vaccine; PCV13, 13-valent pneumococcal conjugate vaccine.

serious in 2/3 patients who have not been reimmunized versus 2/14 patients who were reimmunized ($P = 0.1$). Six of 14 patients who were reimmunized (43%) experienced a recurrent ISR; five events occurred after TIV and one occurred after PCV13. All 6 patients reported that the AEFI was less severe than the initial occurrence and did not affect their daily activities.

Allergic-like Events

Among the 42 patients referred for ALE, 14 (33%) were diagnosed with immediate hypersensitivity without anaphylaxis, 8 (19%) with idiopathic urticaria/angioedema, 3 (7%) with anaphylaxis and 17 (40%) with other allergic events (eg, serum sickness, erythema multiforme). The median interval from immunization to onset of allergic symptoms was 2 hours (IQR 0.2–24 hours) (Table 2). As with ISR, most events were of low to moderate impact, with only 3 cases reported as high impact or serious. One or more vaccines were considered to be causally associated with the ALE in 50% of cases, most commonly DTaP/Tdap and pneumococcal conjugate vaccine (PCV; Table 3).

Allergy testing was conducted on 18/42 patients. Skin prick testing with the vaccine was performed on 17 patients, 13 of whom also underwent intradermal testing. One patient underwent intradermal testing to the vaccine without a prior skin prick test. Four of 18 patients also underwent skin prick testing to one or more vaccine excipients (eg, latex, formaldehyde) or other allergens (eg, egg protein). The results of allergy testing were negative in 16/18 patients. One patient with a positive skin prick test to influenza vaccine was reimmunized without recurrence. One patient had positive intradermal tests to influenza vaccine and latex. The patient was advised to receive influenza immunization in graded doses, but has not been reimmunized to date. Reimmunization was recommended to 16/18 patients who underwent skin prick or intradermal testing, of whom 11 have been reimmunized. One patient with a negative skin prick test experienced a mild recurrence of the AEFI, a pruritic erythematous rash at both injection sites, after reimmunization with hepatitis A and B and quadrivalent human papillomavirus vaccines. Among the 24 patients who did not undergo skin prick testing, 19 were offered reimmunization and 10 had been reimmunized at the time of the analysis (Table 4). One patient developed a recurrence of erythematous rash and edema of the hands and feet 12 hours after reimmunization with MMRV, which was coadministered with DTaP-IPV-Hib. Reimmunization was contraindicated for 2 patients: one patient developed erythema multiforme 15 days after MMR immunization and the other patient developed symptoms of serum sickness (rash with target-like lesions, fever, arthritis) with onset 2 days after DTaP-IPV. Although definitive evidence of a causal association with the vaccine was lacking in both cases, the risk of severe AEFI was determined to outweigh the benefit of

TABLE 3. The Vaccines Temporally and Causally Associated With Adverse Events Following Immunization

AEFI Type	DTaP/Tdap (N = 64)	PCV (N = 42)	Rotavirus (N = 13)	MMR/MMRV (N = 30)	Varicella* (N = 14)	MenC (N = 21)	HPV (N = 10)	Influenza (N = 33)	Other† (N = 20)
Local reactions N = 31									
Single vaccine	6	3	–	0	0	0	1	13	1
Causally associated	6	3	–	0	0	0	1	13	1‡
Coadministered§	5	3	–	4	1	1	0	2	0
Causally associated	4	3	–	3	1	1	0	2	0
Allergic-like events N = 42									
Single vaccine	4	0	1	1	0	0	0	8	2
Causally associated	3	0	0	0	0	0	0	4	0
Coadministered	15	14	3	13	8	7	4	3	8
Causally associated	11	8	2	7	4	3	0	2	4¶
Neurologic events N = 20									
Single vaccine	5	0	0	1	0	0	1	2	2
Causally associated	0	0	0	0	0	0	0	0	0
Coadministered	5	6	1	3	2	5	0	1	2
Causally associated	1	0	0	1	0	0	0	0	1‖
Other** N = 39									
Single vaccine	9	0	0	1	0	0	2	2	2
Causally associated	2	0	0	1	0	0	0	2	0
Coadministered	15	16	8	7	3	8	2	2	3
Causally associated	8	10	4	3	1	4	0	1	1††

*Includes MMRV.

†Includes *Haemophilus influenzae* type b, pandemic H1N1 influenza vaccine, tetanus-diphtheria, typhoid, typhoid-hepatitis A vaccine, yellow fever vaccine, hepatitis A, hepatitis B, hepatitis A and B, herpes zoster vaccine and multicomponent meningococcal serogroup B vaccine.

‡Herpes zoster vaccine.

§More than one vaccine given on same visit before onset of AEFI.

¶Includes pandemic H1N1 influenza vaccine, hepatitis A vaccine, hepatitis B vaccine, *Haemophilus influenzae* type b vaccine.

‖Patient received hepatitis A and B and yellow fever vaccines concurrently.

**Includes hypotonic-hyporesponsive episodes, persistent crying, high fever, thrombocytopenia and nonspecific symptoms.

††Multicomponent meningococcal serogroup B vaccine.

DTaP/Tdap indicates diphtheria-tetanus-acellular pertussis containing vaccines; HPV, human papillomavirus vaccine; MenC, meningococcal conjugate vaccine (includes serogroup C vaccine and quadrivalent vaccine); MMRV, measles-mumps-rubella-varicella vaccine; PCV13, 13-valent pneumococcal conjugate vaccine.

reimmunization. AEFI severity did not differ significantly between patients who were revaccinated and those were not revaccinated.

Neurologic Events

There were 20 patients seen with neurologic events that had their onset after immunization, including 4 with Guillain-Barré syndrome, 4 with encephalitis, myelitis or acute disseminated encephalomyelitis, 3 with febrile seizures, 1 with peripheral neuropathy and 8 with other neurologic symptoms. The median interval from immunization to onset of neurologic symptoms was 24 hours (IQR 12 hours–14 days) (Table 2). The majority of neurologic events were either serious (45%; 9/20) or high impact (40%; 8/20). However, the role of the vaccine in causing the adverse event was indeterminate in 13/20 cases. The vaccine was reported to be causally associated with the event in 2 cases: one patient developed febrile seizures after DTaP at 16 months and after MMR at 5 years of age, and the other patient developed Bell's palsy 4 days after hepatitis A and B and yellow fever vaccines.

Reimmunization was recommended in 13/20 cases (Table 4). Four patients have been reimmunized without recurrence. Four patients refused immunization, 2 were not due for immunization at the time of the analysis, and 3 were not vaccinated for other reasons or were lost to follow-up. AEFI severity and determination of causality did not differ between patients who were reimmunized and those who were eligible but remain unimmunized. Reimmunization with one or more vaccines was contraindicated in 3 patients. The patient with Bell's palsy mentioned above was advised not to receive yellow fever vaccine in the future. The second patient developed Guillain-Barré Syndrome <6 weeks after influenza, MMRV, PCV and meningococcal conjugate serogroup C (MenC-C) immunizations, and was advised against future influenza immunization. The third patient had a remote history of left-sided hemiparesis and possible encephalitis after MMR vaccine.

Other Systemic Events

Thirty-nine patients experienced a range of systemic symptoms after immunization: fever ≥40.5°C (8 patients), hypotonic-hyporesponsive episode (7), thrombocytopenia (5), persistent crying >3 hours (4), vasovagal or anxiety reactions (3), other systemic reactions (12) [nonspecific rash (5), pain, malaise, Kawasaki disease, gastrointestinal symptoms, aplastic anemia, glomerulonephritis, nephrotic syndrome]. Most of these events had a low to moderate impact on health and daily activities (Table 2). All 7 patients with hypotonic-hyporesponsive episodes had received a DTaP-containing vaccine and PCV. Three patients had also received rotavirus vaccine, 1 had received rotavirus and MenC-C, and 1 had received influenza and multicomponent meningococcal B vaccine. The 4 children with persistent crying had all received a DTaP-containing vaccine; 2 had also received PCV and a third had received PCV and rotavirus vaccine. In 16/39 cases, the vaccine was considered to be causally associated with the event and in 18 cases a causal association was indeterminate. DTaP and PCV were the vaccines most often reported to be causally associated with systemic events (Table 3). Reimmunization was recommended for 34 patients (87%) and was contraindicated in only 2 cases (Table 4). Of 21 patients who have been revaccinated to date, 3 experienced a recurrence of

TABLE 4. Reimmunization Status of Patients and Their Outcomes by Adverse Event Type

	Injection-site Reaction	Allergic-like Events	Neurologic Events	Others*
	n (%)	n (%)	n (%)	n (%)
Reimmunization recommendation	N = 31	N = 42	N = 20	N = 39
Recommended	27 (87)	35 (83)	13 (65)	34 (87)
Not recommended	0 (0)	2 (5)	3 (15)	2 (5)
No further doses required	3 (10)	1 (2)	1 (5)	2 (5)
Recommendation deferred	1 (3)	4 (10)	3 (15)	0 (0)
Unknown	0 (0)	0 (0)	0 (0)	1 (3)
Reimmunization status	N = 27	N = 35	N = 13	N = 34
Reimmunization refused	0 (0)	5 (14)	4 (31)	3 (9)
Dose not yet due	10 (37)	4 (11)	2 (15)	2 (6)
Revaccinated with ≥1 common antigen	14 (52)	21 (60)	4 (31)	21 (62)
Vaccinated with different antigen or status unknown	3 (11)	5 (14)	3 (23)	8 (24)
Reimmunization outcome	N = 14	N = 21	N = 4	N = 21
AEFI recurred	6 (43)	2 (10)	0 (0)	3 (14)
Different AEFI	0 (0)	1 (5)	1 (25)	2 (10)
No AEFI	8 (57)	18 (86)	3 (75)	16 (76)
Severity	Unaffected DA: 6/6	Unaffected DA: 1/2 Limited DA: 1/2	N/A	Unaffected DA: 1/3 Limited DA: 2/3
Severity relative to initial AEFI	Milder: 6/6	Milder: 1/2 Same severity: 1/2	N/A	Milder: 1/3 Same severity: 1/3, More severe: 1/3,

*Includes hypotonic-hyporesponsive episodes, persistent crying, high fever, thrombocytopenia and nonspecific symptoms.
AEFI indicates adverse event following immunization; DA, daily activities

the AEFI. The first patient developed a recurrence of fever, diarrhea and erythema at the injection site after TIV. The second patient developed fever, vomiting and nonspecific rash after reimmunization with DTaP-IPV-Hib coadministered with MenC-C and MMRV. The third patient, a child with periodic fever syndrome, developed recurrence of high fever after PCV13 coadministered with MenC-C and MMR; this recurrence was more severe than the first event.

Patients With Contraindications to Immunization

Nineteen patients were assessed for underlying conditions that may alter immunization recommendations; they ranged in age from 1.2 to 16.4 years. Ten patients were seen for pretransplant evaluation but had no immediate contraindication to immunization; no AEFI were subsequently reported from this group. The clinical characteristics of the 9 patients who were seen for possible contraindications to immunization are shown in Table 5. Seven patients were immunocompromised because of immunosuppressive medication or splenectomy. Two patients were assessed for fibrodysplasia ossificans progressiva, a rare genetic condition in which patients develop painful inflammatory soft tissue swellings that lead to heterotopic ossification at sites of trauma to muscle and connective tissue.[18] Both patients were advised against receiving any intramuscular injections. They tolerated varicella vaccine (administered subcutaneously) well. Practices varied between sites, with one site recommending deferral of all immunizations for a patient with vasculitis on prednisone (dose unknown), while another patient on sirolimus for lymphangiectasia was vaccinated with live and inactivated vaccines after immunologic assessment (all vaccines were well tolerated).

DISCUSSION

This report from the Canadian SICs Network demonstrates the breadth of referrals received for patients with AEFI and potential contraindications to immunization. ALEs after DTaP/Tdap and ISRs after influenza vaccines were the most common events seen in the clinics. Although most events were of low to moderate impact, 13% of events were serious and 15% were of high impact, indicating a need for urgent medical attention and/or >4 days of disability. Of 60 patients with AEFI who were revaccinated with at least one vaccine that was temporally associated with the primary event, 11 (18%) had a recurrence of the primary adverse event. However, the recurrence was of similar or lesser severity than the first event in 10/11 patients. The one patient for whom the recurrence was more severe than the first event had high fever in the setting of an underlying autoinflammatory syndrome. None of the recurrences were considered serious adverse events.

Patients with ISR had the highest risk of recurrence (43%). Previous studies have reported similar recurrence risks of 10%–72%.[19–22] These patients need to be counseled regarding the risk of recurrence, but the findings suggest that they can be reassured that such events are likely to be mild and not limit daily activities. None of the patients with ISR refused reimmunization despite their prior experiences, suggesting a high level of support for immunization in this group.

Most patients with ALE did not appear to have IgE-mediated reactions. Although skin testing was conducted in 18/42 patients, 14 of whom underwent intradermal testing, only 2 patients had a positive skin-prick or intradermal test suggestive of an IgE-mediated reaction to a vaccine or vaccine component. Therefore, it was not surprising that only 10% of patients who were reimmunized experienced a recurrence of their allergic symptoms. Furthermore, there were no cases of anaphylaxis after reimmunization. These findings are consistent with those of prior studies of ALE after immunization,[23–25] and provide further reassurance that among patients who present with symptoms of immediate hypersensitivity after immunization, the risk of a subsequent severe allergic reaction is low.

Neurologic events after immunization were the most serious type of AEFI seen in the SIC network, but they were also the events associated with the greatest degree of uncertainty regarding the causal role of the vaccine. Reimmunization of patients with neurologic events was contraindicated in 3 patients, while 4 patients refused reimmunization, perhaps reflecting the severity of the AEFIs and the uncertainty surrounding these events. In some cases, early referral after the AEFI or during the acute event might have permitted a more complete evaluation to confirm the diagnosis and

TABLE 5. Characteristics and Outcomes of Patients With Potential Contraindications to Immunization

Patient Age (y)	Underlying Condition	Immunosuppressed Y/N (Medication)	Vaccines Recommended	Recommendation Details	Immunized (y/n)	Vaccine(s) Received	Outcome
4.5	Fibrodysplasia ossificans progressiva	No	PPV23, Varicella	Administer vaccines subcutaneously, no intramuscular immunizations	Yes	Varicella	No AEFI
10.3	Fibrodyslasia ossificans progressiva	No	Influenza	Administer vaccines subcutaneously, no intramuscular immunizations	Yes	Varicella	No AEFI
1.2	Post heart-transplant	Yes (medication unknown)	DTaP, PCV13, PPV23, MenC-ACWY, MMR, Varicella	Delayed schedule, 2 vaccines at a time	Yes	DTaP-IPV-Hib-HepB, PCV13	No AEFI
4.6	Congenital systemic lymphangiectasia	Yes (sirolimus)	Varicella, Influenza, MMR	–	Yes	MMR, varicella	Varicella-like rash without fever on day 6. Seroconversion documented
3.8	Neuroblastoma in remission	Yes (dexamethasone)	Varicella, PCV13, MenC-C, DTaP-IPV-Hib, Influenza	Delayed schedule, 1 vaccine at a time. Varicella serology	Yes	Varicella, PCV13, MenC-C, DTaP-IPV-Hib	No AEFI
1.5	Denys-Drash syndrome	Yes (vincristine + dactinomycin)	PCV13, DTaP-IPV-Hib, HepB, MenC-ACWY, MMRV	Chemotherapy should be held for 4–6 weeks before immunization with live vaccines.	Unknown	-	Lost to follow-up
13.6	Anti-neutrophil cytoplasmic antibody-positive vasculitis	Yes (prednisone)		Immunization deferred. Live vaccines contraindicated and the patient would not respond to inactivated vaccines.	No	–	N/A
14.3	Myasthenia Gravis	Yes (prednisone)	DTaP, MenC-C, HPV		No	–	N/A
16.4	Splenectomy	Yes	4CMenB, PCV13, PPV23 and Hib		No	–	N/A

DTaP-IPV-Hib indicates diphtheria-tetanus-acellular pertussis-inactivated polio-*Haemophilus influenzae* type b conjugate vaccine; HepB, hepatitis B vaccine; HPV, human papillomavirus vaccine; 4CMenB, multicomponent meningococcal serogroup B vaccine; MenC-ACWY, meningococcal conjugate serogroup ACWY vaccine; MenC-C, meningococcal conjugate serogroup C vaccine; MMRV, measles-mumps-rubella-varicella vaccine; PCV13, 13-valent pneumococcal conjugate vaccine; PPV23, 23-valent pneumococcal polysaccharide vaccine.

search for other causes of the event (eg, infection). Such information might have informed the causality assessment and immunization recommendations.

Overall, reimmunization was recommended to over 80% of patients, of whom only 11% refused reimmunization. To date, 60 patients have been reimmunized without any serious AEFI occurring and only 3 patients experienced a recurrent AEFI severe enough to limit their daily activities or to lead them to seek medical attention. These findings are consistent with reports from specialized immunization services in Australia, Italy and the United Kingdom, in regards to the high acceptance of immunization among these patients and the safety of reimmunization.[7–10] Studies have found that the experience of an AEFI can negatively impact patient perceptions of vaccine safety, which could contribute to a reluctance to proceed with future immunizations.[26,27] SICs have a role to play in alleviating these concerns and promoting safe immunization practices for "high-risk" patients.

This study had limitations. Patients required a referral by a healthcare provider and there was likely referral bias related to the travel distance to the nearest SIC, differences in public health policy and capacity for managing patients with AEFI, and local awareness of the existence of the SIC. Recruitment rates differed by study site and province. Few adults were referred to SICs and those who were referred were more likely to decline participation than patients <18 years of age, limiting our ability to draw conclusions regarding their outcomes after reimmunization. The AEFI diagnosis was made retrospectively based on the SIC physician's assessment, which often occurred months to years after the initial AEFI. This may have contributed to uncertainty regarding the final diagnosis and assessment of causality. Finally, the number of patients with high impact or serious AEFI was low and overall, fewer than 50% of these patients have been reimmunized. Therefore, we have limited data on which to draw conclusions regarding the risk of recurrence of clinically significant AEFI.

CONCLUSIONS

Based on our findings, patients with low to moderate impact AEFI can be reassured that their risk of a recurrent adverse event that limits their daily activities is low. However, data concerning

the outcomes of patients with AEFI or with potential contraindications to immunization remain limited. Large numbers of patients are needed to determine the risk of recurrence of specific AEFI after specific immunizations and to identify which patients are at increased risk of recurrence. Specialized immunization clinics are an ideal platform for systematically evaluating patients and following them after reimmunization. Such clinics exist in several locales but few have published their data. Clinicians and public health officials should be encouraged to refer high-risk patients to specialized immunization clinics, where available, and physicians operating these clinics should be encouraged to systematically collect and publish their data on outcomes after reimmunization. Only by pooling data from multiple clinics, will sufficient data be collected to support the development of immunization guidelines for patients with prior AEFI and potential contraindications to immunization.

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