DESCRIPTION AND FACTORS OF REVACCINATION AMONG PATIENTS WITH PREVIOUS ADVERSE EVENTS FOLLOWING VACCINATION.

by

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Abstract

Background: The Special Immunization Clinic (SIC) Network manages revaccination in patients with prior adverse events following immunization (AEFI). We identified factors associated with physician recommendation for revaccination and patient intention for revaccination among patients with AEFIs.
Methods: This was a retrospective observational study of patients assessed at a SIC for prior AEFIs who required revaccination. Physicians performed standardized assessments and provided recommendations. Participant revaccination intentions were captured during the visit. Logistic regression analysis identified factors associated with physician recommendation for revaccination and patient intention for revaccination.
Results: From 2013-2019, 588 patients were assessed at a SIC for 627 prior AEFIs. Revaccination was recommended to 513/588 participants and 426/513 intended to be revaccinated. Physician recommendation for revaccination was associated with AEFI type and AEFI severity and participant intent for revaccination was associated with AEFI impact.
Conclusions: The results may improve patient counselling around revaccination and revaccination acceptance following an AEFI.

List of Abbreviations Used

AEFI- Adverse event following immunization

CI- Confidence interval

DTaP-Diphtheria-tetanus-acellular-pertussis

HPV- Human papillomavirus

Hib- Haemophilus influenzae type b

LASSO- Least absolute shrinkage and selection operator

MMR- Measles-mumps-rubella

OR- Odds ratio

PCP-primary care physician

PCV-pneumococcal conjugate vaccine

SIC- Special Immunization Clinic

WHO- World Health Organization

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1. Chapter 1: Introduction

Vaccines are biologics consisting of weakened or inactivated forms of a pathogen, a pathogen toxin, or proteins from a pathogen that interact with a host's immune system to build immunity or resistance to that pathogen. Live attenuated vaccines consist of weakened, though living pathogens, whereas inactivated vaccines consist of killed pathogens or purified pathogen-specific antigens. Subunit vaccines are a type of inactivated vaccine that contain portions of viruses or bacteria. Subunit vaccines include toxoid vaccines composed of inactivated toxins, recombinant vaccines composed of replicated yeast cells containing viral genes, polysaccharide vaccines composed of polysaccharide molecules from the outer membrane of bacteria, and conjugate vaccines composed of protein-linked polysaccharide molecules from bacteria.[1] Vaccines also contain excipients such as stabilizers which ensure the vaccine stays effective during transportation and storage, preservatives to prevent contamination of the vaccine during storage and use, antibiotics to prevent contamination of the vaccine during manufacturing and use, and adjuvants to enhance host immune response to the vaccine.[2]

Vaccination is one of the primary preventative healthcare practices that has led to significant reductions in deaths, infections, hospitalizations, and healthcare costs associated with infectious disease.[2–4] From 2010 to 2015, an estimated 10 million deaths were avoided due to vaccinations.[2] In Canada, vaccines have been targeted to over 20 infectious diseases including diphtheria, pertussis, measles, rotavirus, and hepatitis B virus.[2] The introduction of routine infant diphtheria vaccination in 1930 led to a reduction of diphtheria cases from 84.2 cases per 100 000 population, to only 0.006 cases per 100 000 population in 2007 to 2011.[2] Vaccines are essential for providing populations with long-term protection against infectious diseases.[2]

Vaccines are not only effective in protecting populations from vaccine-preventable diseases, they are also safe.[5–7] However, adverse events following immunization (AEFI) do occur. An AEFI is any untoward medical occurrence following vaccination, which is temporally, but not necessarily causally, linked to vaccination.[8–10] In establishing

immunity, the immune system-vaccine interaction may trigger symptoms of natural infection or inflammation, such as fever and malaise. Knowing a vaccine's components is necessary to estimate whether or not the interaction between the host's immune system and the vaccine could have caused an AEFI, as different types of vaccines and excipients may be associated with different AEFIs.[11,12] Clinical trials monitor and assess AEFIs prior to incorporation of vaccines into publicly funded vaccination programs, while surveillance systems monitor and assess AEFIs after incorporation of vaccines into publicly funded vaccination programs.[5–7] Safety evaluations have demonstrated that the most commonly occurring AEFIs are mild such as injection site reactions and malaise.[4] Additional safety evaluations have shown more severe AEFIs, such as seizure, occur less frequently following vaccination than from natural infection.[12,13] Vaccines provide significant benefits to individuals that outweigh the risk of AEFIs.

1.1. AEFI Safety Surveillance

All forms of AEFI safety surveillance capture AEFIs based on temporality.[13] Temporality does not mean that the vaccine caused the event, only that the event occurred following exposure to the vaccine.[15] Pre-clinical studies (i.e. in animal models) and clinical trials assess the efficacy and safety of vaccines before they are approved for use. Pre-clinical studies and clinical trials aim to identify common AEFIs (AEFIs, such as injection site reactions and fever, occurring in 1% to less than 10% of patients)[13] but are limited in their ability to detect rare AEFIs (AEFIs, such as seizures, occurring in 0.01% to less than 0.1% of patients)[13] due to their restricted sample size (100's to 10,000s). Surveillance of vaccine safety is needed to detect rare AEFIs after a vaccine has been authorized and introduced for use in a population.[14]

Post-market surveillance of vaccines is conducted after a vaccine is authorized and introduced for use in a population. The purpose of post-market vaccine surveillance is to detect new, rare, or unexpected AEFIs and estimate rates of AEFI occurrence.[14] Types of post-market vaccine safety surveillance can include passive, active, and sentinel surveillance.

Passive surveillance is the spontaneous reporting of AEFIs by vaccine manufacturers, healthcare providers, patients and others.[5–7,16] Passive surveillance provides information about the safety of a new vaccine or changes in the safety profile of an established vaccine. In Canada, this information is collected and used by federal, provincial, and territorial public health agencies to determine whether the benefit from a vaccine outweighs the risk of AEFIs. Passive surveillance systems are cost-effective but have limited specificity to detect expected and common AEFIs and produce imprecise risk estimates due to under-reporting and reporting bias.[5–7,14,16,17]

Active surveillance involves contacting healthcare providers and reviewing hospital records to collect information about pre-specified events, such as disease occurrence, vaccinations and AEFIs, real-time analysis of large linked healthcare databases, and patient-based self-reporting systems. Active surveillance reduces under-reporting of AEFIs, however it is costly to establish and maintain.[5–8,17–19] For those reasons, active surveillance is most often utilized for monitoring the safety of new vaccines or serious AEFIs (a life-threatening event or event that results in hospitalization, extended hospitalization of an already hospitalized patient, permanent disability, congenital abnormality, or a fatal outcome).[13]

Active sentinel surveillance is employed for rapid detection of emerging vaccine safety signals and to monitor changes in known AEFIs within defined reporting units. Reporting units, regions from which data are captured, are chosen based on their likelihood of identifying AEFIs and their access to resources for establishing and maintaining the sentinel surveillance system.[20] Data captured from sentinel surveillance systems is useful for establishing the number of cases of an event and providing descriptive data about the population who experienced the event of interest. Due to the focus on specific reporting units, sentinel surveillance systems result in high quality data capture. The focus on reporting units also limits the ability of sentinel surveillance systems to identify rare events that may only be captured at the population level and limits the generalizability of their surveillance.[20–22]

In Canada, the Canadian Adverse Event Following Immunization Surveillance System receives passive AEFI reports from provincial and territorial public health departments and sentinel surveillance reports from the Immunization Monitoring Program ACTive (IMPACT). IMPACT is an active, hospital-based sentinel surveillance system where nurses monitor hospital admission lists to capture conditions that could be AEFIs, then confirm if a vaccine was given within a specified timeframe relative to the event. IMPACT includes 12 pediatric hospitals and is managed by the Canadian Paediatrics Society and receives funding from the Public Health Agency of Canada.[23,24]

1.2. Assessing Causal Associations Between AEFIs and Vaccines

AEFIs may be assessed at an individual level to determine whether the AEFI was causally, and not just temporally related to an administered vaccine.[15] Causality is the process where an exposure, the vaccine, contributes to producing an outcome, the AEFI.[25] Koch's postulates, created by Koch and Loeffler in 1884, provide four criteria to determine whether a microbe causes disease: (1) the microbe must be found in an individual with the disease and not among individuals without the disease, (2) the microbe must be isolated from an individual and grown in a pure culture, (3) the cultured microbe must cause disease once introduced in a healthy individual, and (4) the microbe must be re-isolated from the diseased individual and identified as the same microbe as the one that caused the original disease.[26,27] In the context of AEFIs, the AEFI could be viewed as the disease and the vaccine as representing the microbe. Koch's postulates are not used to assess AEFI causality; however, they are useful for understanding the requirements to establish a causal association between an AEFI and vaccine.

AEFI causality can be determined by applying all available information about the patient, the AEFI, the vaccine(s) and the act of vaccination to the WHO's AEFI causality assessment tool. Though not the intention, the tool provides evidence that supports or refutes each of Koch's postulates in the context of vaccination and thus the presence of a causal association. Components of the WHO's AEFI causality assessment tool require

information about the AEFI to identify if there is evidence for or against a causal association with the vaccine and evidence for or against a cause other than the vaccine. Firstly, the assessor must confirm that the AEFI is eligible for assessment using the tool by confirming that there is available information to complete the assessment and that AEFI diagnosis meets an existing case definition (Figure 1).

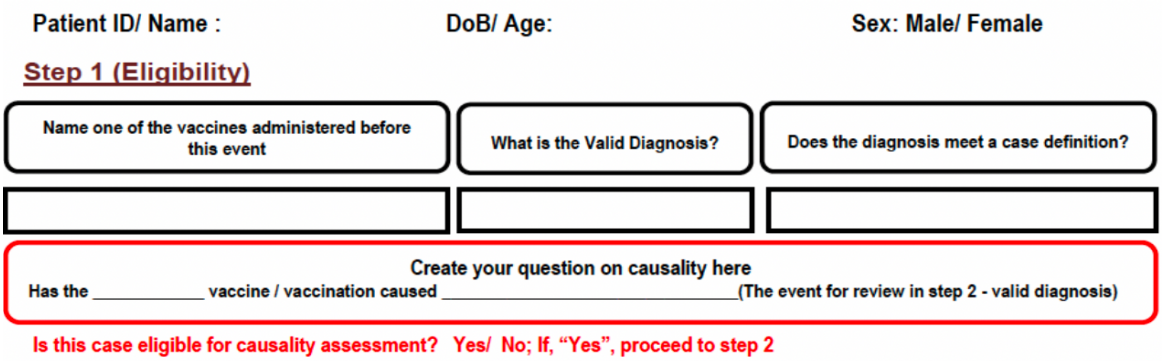

Figure 1. First step of WHO AEFI causality assessment tool: confirming that the AEFI is eligible for assessment using the tool

The assessor must then look for: 1) evidence for a cause other than the vaccine, (2) evidence from literature of a known causal association between the event and vaccine, (3) evidence from literature against a causal association with the vaccine, and (4) whether there are other factors that could have caused the event including the occurrence of another health condition or illness prior to the event, exposure to a toxin or risk factor, whether the event occurred following a previous dose of the same vaccine, and whether medications were taken prior to the event (Figure 2).

Step 2 (Event Checklist) ✓ (check) all boxes that apply

I. Is there strong evidence for other causes?	Y N UK NA	Remarks
1. In this patient, does the medical history, clinical examination and/ or investigations, **confirm** another cause for the event?	☐☐☐☐	
II. Is there a known causal association with the vaccine or vaccination?		
Vaccine product		
1. Is there evidence in published peer reviewed literature that this vaccine may cause such an event if administered correctly?	☐☐☐☐	
2. Is there a biological plausibility that this vaccine could cause such an event?	☐☐☐☐	
3. In this patient, did a specific test demonstrate the causal role of the vaccine ?	☐☐☐☐	
Vaccine quality		
4. Could the vaccine given to this patient have a quality defect or is substandard or falsified?	☐☐☐☐	
Immunization error		
5. In this patient, was there an error in prescribing or non-adherence to recommendations for use of the vaccine (e.g. use beyond the expiry date, wrong recipient etc.)?	☐☐☐☐	
6. In this patient, was the vaccine (or diluent) administered in an unsterile manner?	☐☐☐☐	
7. In this patient, was the vaccine's physical condition (e.g. colour, turbidity, presence of foreign substances etc.) abnormal when administered?	☐☐☐☐	
8. When this patient was vaccinated, was there an error in vaccine constitution/preparation by the vaccinator (e.g. wrong product, wrong diluent, improper mixing, improper syringe filling etc.)?	☐☐☐☐	
9. In this patient, was there an error in vaccine handling (e.g. a break in the cold chain during transport, storage and/or immunization session etc.)?	☐☐☐☐	
10. In this patient, was the vaccine administered incorrectly (e.g. wrong dose, site or route of administration; wrong needle size etc.)?	☐☐☐☐	
Immunization anxiety (Immunization Triggered Stress Response - ITSR)		
11. In this patient, could this event be a stress response triggered by immunization (e.g. acute stress response, vasovagal reaction, hyperventilation or anxiety)?	☐☐☐☐	
II (time). If "yes" to any question in II, was the event within the time window of increased risk?		
12. In this patient, did the event occur within a plausible time window after vaccine administration?	☐☐☐☐	
III. Is there strong evidence against a causal association?		
1. Is there a body of published evidence (systematic reviews, GACVS reviews, Cochrane reviews etc.) **against** a causal association between the vaccine and the event?	☐☐☐☐	
IV. Other qualifying factors for classification		
1. In this patient, did such an event occur in the past after administration of a similar vaccine?	☐☐☐☐	
2. In this patient did such an event occur in the past independent of vaccination?	☐☐☐☐	
3. Could the current event have occurred in this patient without vaccination (background rate)?	☐☐☐☐	
4. Did this patient have an illness, pre-existing condition or risk factor that could have contributed to the event?	☐☐☐☐	
5. Was this patient taking any medication prior to the vaccination?	☐☐☐☐	
6. Was this patient exposed to a potential factor (other than vaccine) prior to the event (e.g. allergen, drug, herbal product etc.)?	☐☐☐☐	

Y: Yes N: No UK: Unknown NA: Not applicable or Not available

Figure 2. WHO AEFI causality assessment tool event checklist.

The assessor uses evidence for or against a causal association to estimate the probability of a causal association (Figure 3) and classify the AEFI as being consistent or inconsistent with a causal association to the vaccine, or the causal association between the AEFI and vaccine being indeterminate (Figure 4). If information about the patient, vaccination or AEFI is lacking, the causality of an AEFI is defined as unclassifiable.[28–30]

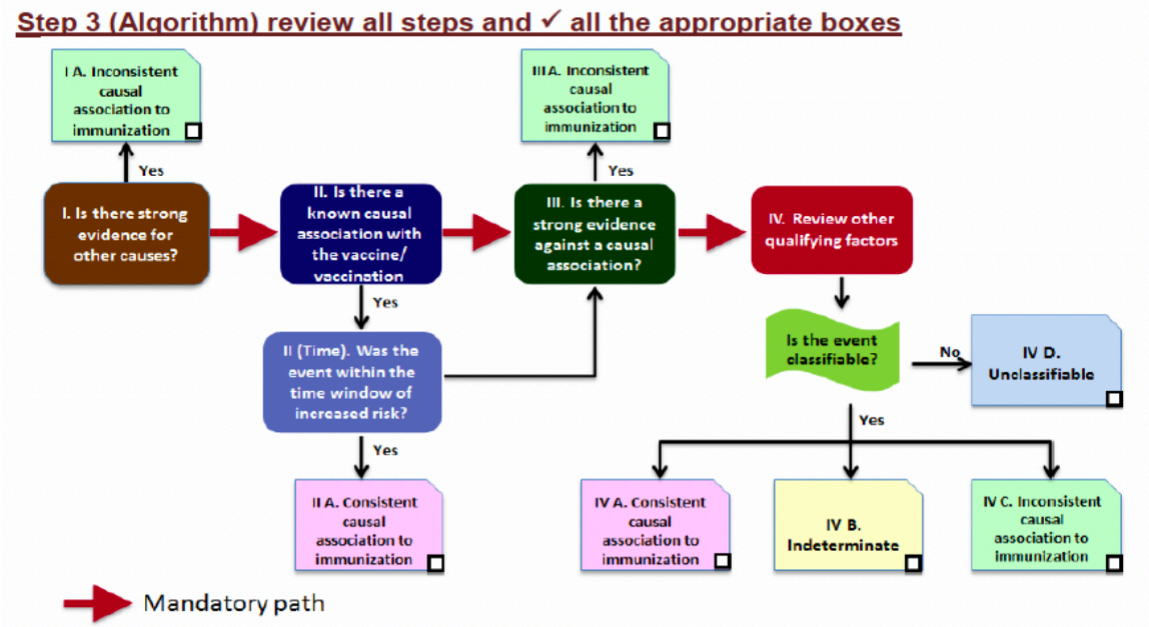

Figure 3. WHO AEFI causality algorithm.

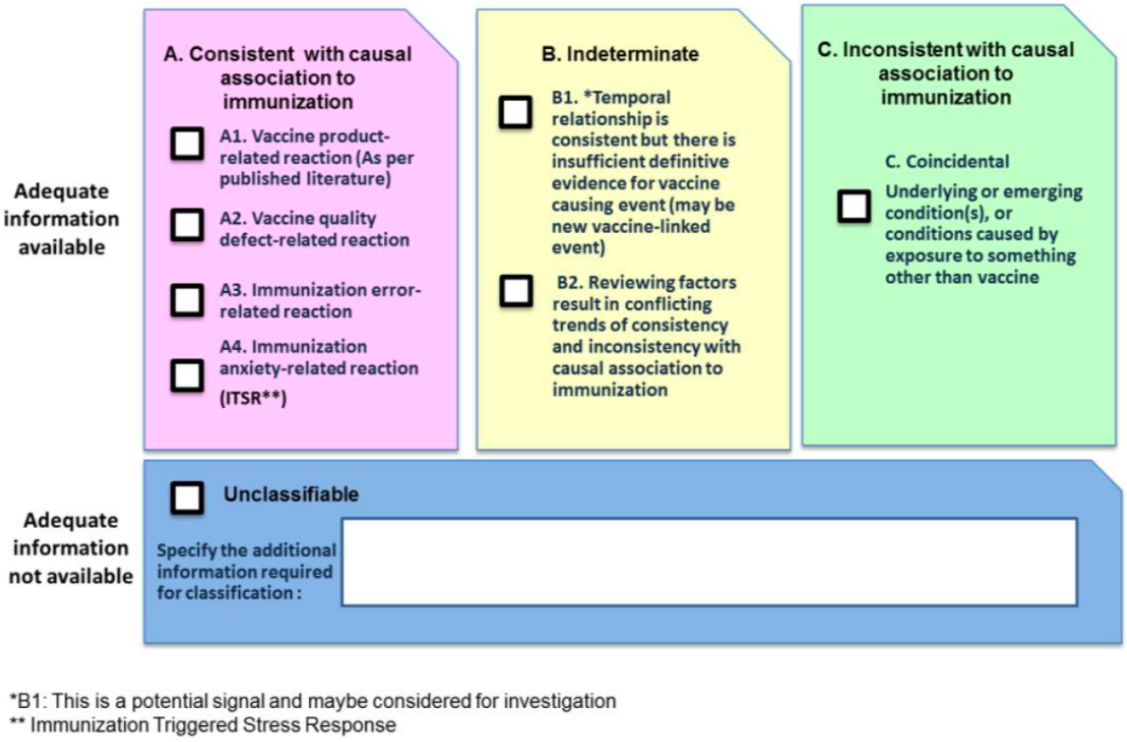

Figure 4. WHO AEFI causality classification.

An AEFI may be causally associated with a vaccine if the AEFI is a symptom of the interaction between the host's immune system and vaccine. For example, clinical trials have identified causal associations between diphtheria-tetanus-acellular pertussis (DTaP), influenza, and pneumococcal conjugate vaccines (PCV) and injection site reactions as well as certain systemic reactions (e.g. fever). Injection site reactions such as warmth, swelling, and redness at the injection site, have been reported in approximately 10% of DTaP vaccine recipients, between 10%-64% of inactivated influenza vaccine recipients, and 20% of PCV recipients.[31–38] Systemic reactions, such as fever, malaise, and myalgia, have been reported in 10%-25% of DTaP vaccine recipients, up to 12% of inactivated influenza vaccine recipients, and 30% of live attenuated influenza vaccine recipients.[31–33,38–42] Rash is associated with measles-containing vaccines, varicella vaccines, and zoster vaccine; it is a common symptom of infection by wild-type measles and varicella-zoster viruses and occurs within a similar temporal window of onset following vaccination as with natural infection.[43–45] Thrombocytopenia is a known though infrequent complication of wild-type measles infection and has been reported following vaccination with measles-containing vaccines.[46–52]

A causal association between an AEFI and a vaccine may occur with an allergic reaction to a vaccine component. In this instance, immunological mechanisms initiated through vaccination may interact with other biological processes occurring in a patient to produce an AEFI.[55,56] An allergic or hypersensitivity reaction is an over-reactive and unexpected response by the immune system to a foreign and harmless substance, allergen, that has been diagnosed by an allergist.[53,54] Allergic-like events are those events that involved signs and symptoms suggestive of a hypersensitivity reaction but have not been diagnosed by an allergists as allergic reactions.[57] Allergic-like events that have been causally linked to vaccination include anaphylaxis and non-anaphylaxis immediate hypersensitivity.[55,56] Hypersensitivity reactions to vaccine components such as latex, gelatin, and certain antibiotics have been reported in patients, though confirmed allergy to either a vaccine or its excipients is rare.[55,56] Identifying the cause of an AEFI facilitates assessment of the safety of current vaccines and improves vaccine safety in the future.

An AEFI is considered a coincidental event if it is related to an emerging or underlying condition or a condition caused by an exposure other than the vaccine.[6,58] Coincidental events may be pre-existing or emerging medical conditions not previously diagnosed, caused by an infection, an adverse reaction to medications, an allergic reaction to an allergen unrelated to a vaccine, or caused by injury from a traumatic event or exposure to environmental stimulus.[28] For example, the Canadian Immunization Monitoring Program ACTive (IMPACT) surveillance system identified 7 cases of encephalitis and encephalopathy occurring within 7 days of pertussis vaccination from 1993 to 2002. In each case, the encephalopathy was attributed to a cause other than the pertussis vaccine such as influenza or herpes simplex infection.[59,60] Though an adverse event may be only temporally related to a vaccine, coincidental AEFIs provide information about the background rate of non-related events that can be used to interpret emerging vaccine safety signals or increases in the frequency of an AEFI.

An AEFI is classified as having indeterminate causality under two circumstances. Firstly, AEFI causality may be estimated as indeterminate if there is evidence of a temporal relationship with the vaccine but a lack of evidence (e.g., from empirical studies) to support a causal association between the AEFI and vaccine. Secondly, AEFI causality may be indeterminate if there is conflicting evidence that supports both a consistent and inconsistent causal association between the AEFI and vaccine.[29] For example, retrospectively reviewed AEFIs reported to the Slovenian AEFI registry from 2009-2013 classified a migraine episode several hours after vaccination with a third dose of quadrivalent human papillomavirus (HPV) vaccine as having indeterminate causality. Though there was sufficient information about the event to assess causality, migraine was not listed as an expected AEFI for the quadrivalent HPV vaccine, nor was there biological evidence to support a link leading the authors to classify the event's causality as "indeterminate".[61] An AEFI with indeterminate causality to a vaccine may represent a new safety signal or a coincidental event. As such, it may provide limited information at the time of the causality assessment but may contribute to a better understanding of similar AEFIs in the future.

1.3. AEFI Recurrence

Revaccination is the administration of a vaccine with at least one of the same components as the vaccine associated with the initial AEFI.[4] Studies of AEFI recurrence provide information about possible associations between AEFIs and vaccines, and potential risk of AEFI recurrence among patients with prior AEFIs who require revaccinations.[9]

A systematic review summarized 29 studies which examined the risk of AEFI recurrence in pediatric and adult patients. Included in the review were 2 randomized-controlled trials, 1 of which collected data from physician and patient and/or parent reports, and the other which collected data from patient and/or parent reports only. The remaining 27 studies were observational cohort studies. Fourteen cohort studies prospectively collected data from physician reports (n=1), physician and patient and/or parent reports (n=3), patient and/or parent reports (n=9), and chart review or hospital records (n=1). Thirteen cohort studies retrospectively collected data from physician and patient and/or parent reports (n=3), patient and/or parent reports (n=2), chart review or hospital records (n=6), and passive surveillance systems (n=2). The vaccines that were studied included diphtheria-tetanus-pertussis containing vaccines, PCV, rotavirus, measles-mumps-rubella (MMR) ± varicella, influenza, meningococcal conjugate, and HPV vaccines. The pooled risk of fever recurrence following revaccination with diphtheria-tetanus-pertussis containing vaccines, PCV, MMR, and influenza vaccines was 33% (95% Confidence Interval (CI): 16%-53%). Among patients with prior injection site reactions the pooled risk estimate for patients with prior extensive limb swelling (swelling or erythema extending from joint-to-joint or crossing a joint) was 48% (95% CI: 18%-79%). AEFIs that recurred infrequently included seizure, anaphylaxis and hypotonic-hyporesponsive episodes, all of which had separate pooled estimates of risks of recurrence of 0% (seizure 95% CI: 0%-3%, anaphylaxis 95% CI: 0%-1%, hypotonic-hyporesponsive episodes 95% CI: 0%-0.1%) following revaccination with a similar vaccine.[4]

A cohort study using data from the AEFI passive surveillance system in Quebec, Canada measured AEFI recurrence in 1350 pediatric and adult patients from 1998 to 2016. Patients were revaccinated with a variety of vaccines including DTaP, PCV, rotavirus, MMR±varicella, hepatitis B±A, and HPV vaccines. Among patients with prior injection site reactions, 8% (1/12) of those with cellulitis and 48% (10/21) of those with sterile abscess/nodule experienced AEFI recurrence. Among those with prior fever, 15% (11/71) experienced recurrence. Allergic-like events recurred in 12% (76/659) of patients, though no patients with prior anaphylaxis experienced AEFI recurrence. Seizure recurred in 6% (3/49) of patients. Hypotonic-hyporesponsive episodes recurred in 2% (1/50) of revaccinated patients.[62] This is similar to the rate of recurrence reported in an observational study of patients assessed for prior hypotonic-hyporesponsive episodes at 2 Australian specialist immunization clinics.[63] Three percent (7/235) of patients with prior AEFI reported the recurrent AEFI.[63] The systematic review and Quebec cohort study both found that injection site reactions, fever, malaise, and myalgia recurred more commonly than seizure, anaphylaxis and hypotonic-hyporesponsive episodes following revaccination.[62,64]

Silcock et al. reported recurrence of nodule at the injection site following revaccination of any vaccine in a pediatric cohort using data from the passive surveillance system Surveillance of Adverse Events Following Vaccination in the Community (SAFEVIC) in Victoria, Australia from 2007 to 2016. The passive surveillance system received 41 reports of nodule at the injection site. Six cases of recurrent nodule following revaccination were reported, including 5 participants who had a history of a nodule following a previous vaccination that was not reported to SAFEVIC and 1 participant who reported recurrent nodule following a nodule previously reported to SAFEVIC.[65]

1.4. Special Immunization Clinics

Healthcare providers who encounter AEFIs, such as anaphylaxis, hypotonic-hyporesponsive episodes, and injection site reactions may be concerned about AEFI

recurrence following revaccination and therefore may choose to delay or withhold revaccination. There is limited literature to guide revaccination of patients with prior AEFI. As a result, physicians often turn to experts for managing revaccination of patients with prior AEFI.[28,29,66]

In 2013, Canadian pediatricians and subspecialist pediatricians demonstrated their interest in a special immunization service as a resource for managing patients with prior AEFI in a cross-sectional survey assessing their experience managing vaccination of patients with AEFIs and potential vaccine contraindications. Of the 2490 distributed surveys, 586 pediatricians responded; 26% (148/586) of whom had seen patients for either a vaccine contraindication or previous AEFI in the prior year. Less than 8% (37/438) of respondents felt dissatisfied with current resources for managing these patient populations. Still, 69% (404/583) responded that they were "Very/somewhat likely" to refer patients with vaccine contraindications or who had experienced an AEFI to a special immunization service if one existed.[9] These results suggested that Canadian physicians recognized the need for, and potential benefit of special immunization services for managing vaccination of patients with vaccine contraindications and prior AEFIs.

1.4.1. ***Special Immunization Clinic Network***

The Special Immunization Clinic (SIC) Network is part of the Canadian Immunization Research Network and was established in 2013. SIC sites exist across 6 provinces: Nova Scotia, Quebec, Ontario, Saskatchewan, Alberta, and British Columbia. The SIC Network involves public health physicians, infectious disease specialists, and allergists across Canada who assess and prospectively collect data from patients with prior AEFIs and/or potential contraindications to vaccination. The SIC Network was designed for two purposes: 1) to provide clinical consultation for patients with prior AEFIs and vaccine contraindications and 2) to act as a research platform for studying vaccine safety and revaccination of these patient populations. All SIC Network research studies have received Research Ethics Board approval at all SIC sites and are conducted

in accordance with Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans.

The SIC Network was modelled after special immunization services in the United Kingdom, Australia, and Italy. The SIC Network is a multi-centre network and uses standardized referral, data collection, patient assessment, and patient management procedures across all sites to study revaccination of patients with prior AEFI.[67–71]

Patients referred to a SIC by a healthcare provider are screened for eligibility for inclusion in the SIC Network research database. Patients with prior AEFI who are eligible based on the inclusion/exclusion criteria, such as patients referred to the SIC for a previous large local reaction >10cm, fever >40.5˚C, seizure, or previously unidentified AEFI, are recruited to participate in the SIC Network research study. To be enrolled in the SIC Network study, participants are required to consent for their data to be transferred to the SIC Network research database. Informed consent to participant in a SIC study is requested by SIC nurses. Participants are fully informed of the details of their consent, including what data is collected and used for research purposes, how data are de-identified, stored, secured, managed, presented, and with whom data could be shared. Once participants are enrolled in the SIC research database they are assigned a unique identifier to ensure participant data are de-nominalized.

All data are collected and recorded on standardized forms developed by SIC investigators (Appendix 3). De-nominalized data are collected by a nurse from the SIC physician and/or other consulting physicians and entered in the SIC Network electronic research database on the DACIMA platform by SIC nurses and/or research assistants at each site.[9,57,69]

After data are entered into DACIMA, the SIC Network data management team conducts quality checks to identify and query missing data, data that are inconsistent with other data entered in DACIMA for the same participant, and data that are inconsistent with information recorded in SIC Network source documents through comparison of data

entered into DACIMA and data recorded on source documents. Following corrections or updates to entered data, quality checks are repeated. Data that pass quality checks are locked to prevent changes. The database is only accessible to designated SIC Network personnel, including the data managers and data analysts, using a password-protected server.

1.4.2. ***Participant Experience from Vaccination to Follow-up***

To experience an AEFI patients, must first receive a vaccination. Vaccinations can be administered by family physicians, pediatricians, and public health physicians and nurses. An AEFI can occur in a healthcare setting immediately following vaccination or after a patient has returned home following receipt of a vaccination. Patients who experience an AEFI may discuss revaccination with their healthcare provider immediately following the AEFI or weeks to years after the AEFI occurred. Healthcare providers that know of the SIC Network as a service for referral of patients with prior AEFIs can check a patient's symptoms against the SIC Network's inclusion-exclusion criteria to decide whether they should be referred to a SIC. Healthcare providers, including family physicians, pediatricians, emergency physicians, and public health physicians and nurses, refer patients to a SIC by emailing or calling a SIC physician and nurse. Patients are contacted by a SIC nurse to be seen in the clinic.

During the visit, SIC physicians assess participants with previous AEFIs, vaccinate them when appropriate, and provide reports to the referring physician. Each site investigator works in collaboration with an allergist co-investigator who assesses participants with allergic-like events. Participants who are revaccinated are subsequently contacted by SIC staff via email or telephone to collect data on any AEFI recurrences.

1.4.3. ***Physician Recommendation for Revaccination***

For patients with prior AEFI, SIC physicians gather all available information about the events and previous vaccinations from patients, their healthcare providers, and

referring parties, conduct clinical assessments, determine the diagnosis, assess causality and risk-benefit of revaccination, and make a recommendation regarding revaccination. SIC physicians use the WHO's AEFI causality assessment algorithm to estimate whether an AEFI has a consistent, inconsistent, or indeterminate causal association with the vaccination (Figure 4).[57,69]

When there is evidence of a consistent causal association between the AEFI and the vaccine, the physician may be able to estimate the risk of recurrence. Physicians may recommend alternative revaccination practices such as the use of an alternative vaccine product, graded dosing or prophylactic medication, or provide increased monitoring of patients following revaccination. If there is evidence of an inconsistent causal association between the AEFI and the vaccine then the risk of recurrence should be similar to the risk of their initial AEFI. Indeterminate causal associations may be of concern as it is not clear whether or not the vaccine caused the AEFI. Therefore, estimating the risk of recurrence may be difficult for physicians and may require further assessments and advice from experts to estimate the potential risks of revaccination.[72,73] In addition to estimating the likelihood of a causal association, physicians conduct a risk assessment for the patient to determine whether the risks of revaccination outweigh the benefits of completing a vaccine series.

Risk of revaccination varies by risk of recurrence of the AEFI and the severity of the AEFI. For example, the risk of revaccination may be considered high in a patient who previously experienced a significant health event such as encephalitis following vaccination. Though the literature has demonstrated little evidence that encephalitis occurs following revaccination, a physician may feel that the risk of harm due to recurrence is too high to recommend revaccination. In contrast the risk of revaccination may be considered low in a patient who experienced an injection site reaction following vaccination. Though recurrence of injection site reactions following revaccination is frequent, the low severity and rapid resolution without treatment or long-term effects of the event may lead a physician to estimate a low risk of revaccination in this patient.[66,74]

In addition to establishing the risk of revaccination, the benefit of revaccination must also be determined. The benefit of revaccination to patients who require additional doses may vary based on the number of doses they have already received, their risk of disease without additional vaccine doses, and underlying medical conditions, such as immunosuppression. If there is no individual benefit of revaccination or the benefit is low, a physician may decide to recommend against revaccination.[66,74]

To improve patient management, the SIC Network has developed a standardized, evidence-based approach for making recommendations for revaccination, which can be beneficial to physicians managing patients with prior AEFIs.[9,29,67] The SIC Network's standardized approach to making recommendations for revaccination may help physicians understand how infectious disease specialists and allergists use the available guidelines as well as the information about a patient with prior AEFI to make recommendations for revaccinations.

SIC physicians make recommendations for revaccination based on best-practice and risk-benefit assessments in collaboration with the patient (Appendix 1). Guidelines for recommending revaccination were developed based on literature review and discussion among SIC investigators to ensure consistency in revaccination recommendations across all SIC sites. Recommendations for revaccination of complex cases are discussed informally between SIC investigators.

Clinical investigations by physicians use all relevant and available information about a patient and an AEFI to decide whether or not to recommend revaccination. Further research is needed to understand how SIC physicians use the SIC guideline to make revaccination recommendations and under what circumstances. The outcome of such research can be used to standardize physicians' revaccination recommendations for future patients with AEFI.

1.4.4. ***Revaccination Intention and Acceptance***

Patients are often concerned about the risk of AEFI recurrence when deciding whether or not to accept revaccination. An AEFI may reduce confidence in vaccine safety and willingness to accept revaccination.[75–78] Additionally, patients may feel that additional vaccine doses are not necessary. Though concerns about vaccine safety are a known barrier to vaccination uptake, few studies have measured the effect of vaccine safety concerns on revaccination intentions among patients with prior AEFI.[79,80] Cross-sectional surveys from Australia, the United States and Poland have compared revaccination intentions and perceptions of vaccine safety between parents of children with and without prior AEFI.[75–78,81] These studies have found increased general concerns about vaccine safety and pre-licensure safety testing among parents of children with prior AEFI when compared to parents of children without prior AEFI. Parents of children with prior AEFI are also more likely to report missed vaccinations and to expect minor reactions with future vaccinations than parents of children without prior AEFI.[75–78,81] These findings suggest increased general vaccine safety concerns and knowledge among parents of children with prior AEFI.

Studies of patients with prior AEFI who require revaccinations can provide insight about patients who accept and do not accept revaccination after physician counseling. A prospective cohort study of 132 Canadian patients with prior AEFI assessed at the SIC Network found varying patient refusal of revaccination by AEFI type. No patients with prior injection site reactions refused revaccination, but 14% (5/35) of patients with prior allergic-like events, 31% (4/13) of patients with neurologic AEFIs, and 9% (3/34) of patients with prior systemic AEFIs (e.g., hypotonic-hyporesponsive episodes, persistent crying, high fever, and thrombocytopenia) refused revaccination after physician recommendation for revaccination. Revaccination acceptance may also differ by the impact of an AEFI on daily activities. Patients with prior neurologic AEFIs most frequently reported their AEFIs as being serious or having high impact and were the most likely group to refuse revaccination suggesting a possible influence of AEFI impact on revaccination acceptance.[69] A prospective cohort study from Australia used data from the vaccination records of 83 children who reported an AEFI following a 2016/2017 seasonal influenza vaccination and data from parental questionnaires to identify an association

between prior AEFI and intention to be revaccinated and revaccination with a 2017/2018 seasonal influenza vaccine. Parents who perceived their child's AEFI to be "very severe" were significantly less likely to intend to revaccinate and to be revaccinated during the 2017/2018 influenza season compared to parents who perceived their child's AEFI to be "very mild".[82,83] Physicians counselling and recommendation for revaccination may improve revaccination acceptance.

Though the studies presented here have assessed revaccination intent and revaccination among patients with prior AEFI, gaps still exist in our understanding of revaccination among patients with prior AEFI. A limited number of studies compare how AEFIs affect revaccination acceptance among patients with prior AEFI. It is important for physicians assessing patients with prior AEFIs to understand what factors influence revaccination acceptance. Physician can use this information to increase counselling following an AEFI and tailor their counselling around specific factors that may be of concern to patients. This may improve willingness to revaccinate after physician recommendation.

1.5. Study Rationale

There are gaps in the literature regarding what information physicians use when deciding whether or not to recommend revaccination to patients with prior AEFI and the factors which influence patients' decision to be revaccinated. Few studies of patients with prior AEFIs describe and compare patients who are recommended and not recommended for revaccination, and who intend versus do not intend to be revaccinated. Studies of revaccination in patients with prior AEFI are subject to certain limitations such as restriction of study populations by patient population, AEFI type, or vaccine. This limits sample sizes, leading to over or under estimations of true effects, and limits the generalizability of study findings.

Our study described the demographic and clinic characteristics of patients assessed in the SIC Network for a prior AEFI. Our study also identified factors associated with

physician recommendation for revaccination and patient intent to be revaccinated among patients with prior AEFI. The findings of our study have the potential to inform future research and clinical assessments of patients with prior AEFI. The intention of our analysis was to improve our understanding of the information SIC physicians use to make recommendations for revaccination. An additional intent of our study was to identify what factors about a patient and their AEFI may influence revaccination intentions. The findings from our study can be used to harmonize and improve physician recommendation practices for revaccination in patients with prior AEFI. The goal of this study was to improve patient care by informing best practices for revaccination of patients after an AEFI and ensure that patients were optimally protected against vaccine-preventable diseases.

2. Chapter 2: Specific Aims and Objectives

The aim of this study was to describe and identify factors associated with physician recommendation for revaccination and participants' intention to be revaccinated among participants with a prior AEFI. These aims were achieved through the following objectives:

1) To describe the demographic and clinical characteristics of participants assessed in the SIC Network for a prior AEFI.

2) To identify factors associated with a physician recommendation for revaccination among participants who were assessed in the SIC Network for a prior AEFI.

3) To identify factors associated with participant intention to be revaccinated among participants who were assessed in the SIC Network for a prior AEFI and who received a recommendation from a SIC physician for revaccination.

3. Chapter 3: Methods

3.1. Study Design

The study was a multi-centre, retrospective analysis of data from participants enrolled in the SIC Network research database for evaluation following a suspected AEFI, from June 2013 to September 2019. Participants were included in our analysis if they were included in the SIC Network research database due to assessment at the SIC Network for at least one of the AEFIs listed in Table 1, and were due for additional doses of the vaccine associated with the AEFI they were assessed for at the SIC Network.

3.1.1. ***Objective 1***

This was a retrospective, observational study. A retrospective, observational study design was advantageous as we were able to conduct a descriptive analysis of our participant population and measure associations between exposures and outcomes during a pre-specified time period. Data about participants, participant's prior AEFIs, revaccination recommendations, and revaccination intentions were collected during SIC consultations. Data about revaccination and AEFI recurrence were collected during follow-up visits and/or phone calls. In the descriptive analysis we were able to describe the demographic and clinical characteristics of participants with a number of outcomes (i.e. physician recommendation for revaccination, physician recommendation against revaccination, deferral of recommendation for further assessment, participant intention to be revaccinated, participant intention not to be revaccinated, participant revaccination, AEFI recurrence).

3.1.2. ***Objectives 2 and 3***

Objectives 2 and 3 were accomplished using a cross-sectional study design. A cross-sectional design allowed us to measure whether associations existed between certain clinical characteristics and physician recommendation for revaccination and patient

intention to be revaccinated. Physician recommendation for revaccination and patient intention to be revaccinated were captured at a single point in time. Unfortunately, causality cannot be inferred from the findings of a cross-sectional study due to exposure data and outcome data being collected during the same time period.

3.2. Study Population

Our study population included participants referred to the SIC Network from June 2013 to December 2018 for assessment for a prior AEFI who were enrolled and assessed by September 2019. Participants included male and female children (<18 years of age) and adults from 13 SIC sites in Nova Scotia, Quebec, Ontario, Saskatchewan, Alberta, and British Columbia. All SIC sites were based in urban areas and 11 of the 13 sites were located at tertiary pediatric care centers.

3.2.1. ***Objective 1***

Objective 1 described the demographic and clinical characteristics of all participants included in our study (Figure 5). Participants not yet due for revaccination during the study period were not included in the descriptive analysis of revaccination intentions and uptake. Participants who were eligible for revaccination during the study period but chose to delay or refuse their revaccinations were included in the descriptive analysis of revaccination intentions and uptake.

3.2.2. ***Objective 2***

Our analysis for objective 2 included those participants from objective 1 without missing age, AEFI type, or AEFI impact, who received a physician recommendation for or against revaccination or received a deferred recommendation pending further assessment following SIC assessment for a prior AEFI (Figure 5). Participants who received a recommendation of "Other" were not included in the analysis. Thirty participants had multiple prior AEFIs for which they were assessed at a SIC:

1. For 27/30 participants all AEFI forms had data on the dates (at a minimum month and year) of vaccination, therefore the most recent prior AEFI was included in the analysis.
2. For 1/30 participants only some AEFI forms had data on the date (at a minimum month and year) of vaccination, therefore the most recent prior AEFI with date of vaccination was included.
3. For 2/30 participants no AEFI forms had data on the dates of vaccination and all prior AEFIs had the same recorded impact, therefore the first prior AEFI form was accepted.

Note: For all but one participant, the most recent prior AEFI had the same or highest impact of all prior AEFIs.

The outcome of objective 2 was physician recommendation for revaccination, recommendation against revaccination or a deferred recommendation for further assessment. We identified whether participant age, AEFI type, and AEFI impact were associated with our outcome groups: 1) participants who received a recommended for revaccination and (2) participants who received a recommendation against revaccination or received a deferred recommendation for further assessment. Against and deferred recommendations were combined into a single group.

3.2.3. ***Objective 3***

The analysis for objective 3 included those participants in objective 2 who were recommended for revaccination and provided an intention regarding revaccination (Figure 5) without missing age, AEFI type, AEFI impact, or vaccine antigen. Participants not yet due for revaccination during the study period were excluded from the objective 3 analysis. Participants were excluded from the analysis if they experienced an AEFI type contraindicated for revaccination (Table 2) based on SIC Network, provincial, and national revaccination guidelines.[84–89] The outcome was participant intention to be revaccinated. We identified whether participant age, AEFI type, AEFI impact, and

vaccine antigen were associated with our outcome groups: 1) participants who intended to be revaccinated and (2) participants did not intend to be revaccinated.

3.3. Data Extraction

We extracted data on participant gender, age at vaccination, study site, interval of time between vaccination and onset of symptoms of the AEFI, vaccine antigen(s), impact of initial AEFI, final diagnosis of AEFI, outcome of causality assessment, outcome of skin prick testing to a suspected vaccine, outcome of intradermal testing to a suspected vaccine, revaccination uptake, recurrence of the AEFI, vaccine antigen(s) administered prior to AEFI recurrence, and severity of recurrent AEFI relative to initial AEFI.

3.4. Data Sources

Data was extracted from the SIC Network's electronic DACIMA database (https://www.dacimasoftware.com/).

3.5. Descriptive Analysis

We conducted a descriptive analysis using, SAS Version 9.4., to complete objective 1:

To describe the demographic and clinical characteristics of participants assessed in the SIC Network and requiring additional doses(s) of the same vaccine.

3.5.1. Variables

1. **Physician recommendation** made by SIC physicians for participants with prior AEFI assessed at a SIC. SIC nurses collected physician recommendations from SIC physicians using a standardized SIC questionnaire (Appendix 3) and entered the recommendation in the SIC Network electronic research database. Recommendation was collected as a categorical variable

with 4 values (Revaccination not recommended, revaccination recommended, recommendation deferred, other). We described recommendation for revaccination as a categorical variable with 3 values:

1. Revaccination not recommended
2. Revaccination recommended
3. Recommendation deferred pending further assessment

2. **Revaccination intention** of participants with prior AEFI assessed at a SIC and who were recommended for revaccination by a SIC physician. SIC nurses collected participants' intentions from participants using a standardized SIC questionnaire (Appendix 3) and entered the intention in the SIC Network electronic research database. Participant intention to be revaccinated was collected as a categorical variable with 6 values: participant was revaccinated at the SIC, participant was/will be revaccinated by a primary care physician or public health department, participant will return to the SIC for revaccination, participant opted to defer revaccination, participant refused revaccination, and dose not yet due. Participant intention captured some revaccination behaviour. However, we chose to define participant intention solely by intention with the understanding that certain responses demonstrated an intention and a behaviour. Participant intention was defined as the provided intention regarding revaccination with the vaccine antigen(s) associated with the prior AEFI of interest. Participant intention to be revaccinated was described as a categorical variable with 5 values:
    1. Participant was revaccinated at SIC
    2. Participant was/will be revaccinated by a primary care physician or public health department
    3. Participant will return to SIC for revaccination
    4. Participant delayed revaccination
    5. Participant refused revaccination

3. **Revaccination status** of a participant with prior AEFI assessed in a SIC and recommended for revaccination by a SIC physician. Revaccination status was collected using a standardized SIC questionnaire (Appendix 3) and entered in the SIC Network electronic research database. Revaccination status was captured by the presence of a completed Vaccination form. Revaccination was defined as the first record of vaccination for the same vaccine antigen(s) as administered in the included AEFI of interest and for which the participant received a recommendation for revaccination. Revaccination status was a binary variable:
    1. Record of revaccination
    2. No record of revaccination

4. **AEFI recurrence** among participants with prior AEFI who were revaccinated following a recommendation for revaccination by a SIC physician. SIC nurses collected AEFI recurrence data from participants using a standardized SIC questionnaire (Appendix 3) and entered the recurrence data in the SIC Network electronic research database. AEFI recurrences were collected in the research database as an immediate recurrence <30 minutes following revaccination (No AEFI reported, AEFI reported), recurrence within 7 days post revaccination (No AEFI reported, AEFI reported), or recurrence >7 days post revaccination (No AEFI reported, AEFI reported). One participant with a record of revaccination but unknown recurrence data was not included in our descriptive analysis of participants with AEFI recurrence. AEFI recurrence was described as a binary variable with the values:
    1. No AEFI recurrence
    2. AEFI recurrence

5. **Participant age** at time of vaccination prior to the AEFI for which the participant was assessed at the SIC. SIC nurses collected birth month, birth year, and date of prior vaccination from participants using a standardized SIC questionnaire (Appendix 3) and entered the values in the SIC Network

electronic research database. Birth month was collected as a value from 1 to 12 or unknown. Birth year was collected as a value from 1900 to 2018 or unknown. Date of vaccination was collected as a date. Birth month, birth year, and date of vaccination were used to calculate participant age, in years, at the time of vaccination. Participant age at vaccination was described as a 4-level categorical variable. The following categories were chosen due to their use by the Public Health Agency of Canada:

1. <2 years of age
2. 2-6 years of age
3. 7-17 years of age
4. ≥18 years of age

6. **Participant gender** was collected by SIC nurses from participants using a standardized SIC questionnaire (Appendix 3) and captured in the SIC Network electronic research database as a binary variable. Participant gender was collected as a dichotomous variable and therefore may miss participants non-binary gender identities. Participant gender was collected and described as a single binary variable with the values:
    1. Male
    2. Female

7. **SIC site** where participants with a prior AEFI were enrolled. SIC site was captured by SIC nurses as part of participants' unique identifier and described as a categorical variable with 13 values:
    1. ACC
    2. AMR
    3. CCV
    4. CHE
    5. CHL
    6. ECH
    7. HSJ

8. MCH
9. MMC
10. RUH
11. SHE
12. SKH
13. WCH

8. **Province** of SIC site where participants with a prior AEFI were enrolled. Province was captured by reporting the province of SIC site at which participants were enrolled. Province was described as a categorical variable with 6 values:
    1. Nova Scotia
    2. Quebec
    3. Ontario
    4. Saskatchewan
    5. Alberta
    6. British Columbia

9. **AEFI type** was based on the SIC physician's final diagnosis. The diagnosis was determined by the SIC physician by applying information provided by participants, their primary care physician (PCP), and/or the referring party to standardized case definitions. When standardized case definitions did not exist or could not be applied (e.g., due to missing information) the diagnosis was based on the SIC physician's assessment. SIC nurses collected AEFI type from SIC physicians using a standardized SIC questionnaire (Appendix 3) and entered the value in the SIC Network electronic research database as a categorical variable with 32 values. Appendix 2 presents the AEFI type definitions. We described AEFI type as a categorical variable with 32 values. AEFI types diagnosed as "Other" events in which the SIC physician provided text describing the event were reviewed with a SIC physician and categorized into 1 of the 32 values:

1. Large local reactions ≥10cm in diameter
2. Cellulitis, infectious
3. Abscess, infectious
4. Abscess, sterile
5. Nodule
6. Other injection site reactions
7. Anaphylaxis
8. Type I immediate hypersensitivity
9. Type I delayed hypersensitivity
10. Type III/IV delayed hypersensitivity
11. Oculo-respiratory syndrome
12. Other allergic-like events
13. Seizure
14. Anaesthesia/paraesthesia
15. Peripheral neuropathy
16. Encephalitis
17. Myelitis
18. Acute disseminated encephalomyelitis
19. Meningitis
20. Guillain-Barré/Fisher-Miller Syndrome
21. Other neurologic AEFIs
22. Fever
23. Hypotonic-hyporesponsive episode
24. Persistent crying
25. Arthralgia/arthritis
26. Thrombocytopenia
27. Immunization stress related response
28. Gastrointestinal symptoms
29. Non-urticarial rash
30. General symptoms
31. Autoimmune disease

32. Other systemic AEFIs

10. **AEFI impact** was categorized by SIC physicians/nurses by applying information from participants, their PCP, and/or referring party to Public Health Agency of Canada AEFI impact categories.[90] SIC nurses collected AEFI impact using a standardized SIC questionnaire (Appendix 3) and entered the value in the SIC Network electronic research database as a categorical variable with 4 values. AEFI impact on daily activities was described as a categorical variable with 4 values:
    1. Low: AEFI treated by onsite clinic staff without or medical telephone advice or self-medication, disabled <24 hours
    2. Moderate: Unscheduled medical visit to an emergency department, clinic or emergency department services called to vaccine clinic without further care needed, drug prescription required or increased prescription dose, disabled 1-3 days
    3. High: ≥3 physician assessments, medical supervision required outside of hospital, >3 days disability or ≤24 hours hospitalization
    4. Serious: Hospitalization required for >24 hours, fatal or life-threatening outcome, congenital abnormality, ongoing disability

11. **Interval of time between vaccination and onset of AEFI symptoms** was collected by SIC nurses from participants, their PCP, and/or referring party using a standardized SIC questionnaire (Appendix 3) and entered in the SIC Network electronic research database as a text value. The unit of time, minutes, hours and days was captured as a list field. We analyzed interval of time between vaccination and onset of AEFI symptoms as a continuous variable measured in hours.

12. **Vaccine antigens received prior to AEFI** was collected by SIC nurses from participants, their PCP, and/or referring party using a standardized SIC questionnaire (Appendix 3) and entered in the SIC Network electronic

research database as a categorical variable. Participants may have received more than one vaccine during clinic visits. Vaccine antigen was described as a categorical variable with 13 levels:

1. Diphtheria toxoid- tetanus toxoid-reduced acellular pertussis (DTaP)/ Tetanus toxoid-reduced diphtheria toxoid-reduced acellular pertussis (Tdap) containing vaccines
2. Pneumococcal conjugate vaccine (PCV)
3. Rotavirus
4. Measles-mumps-rubella (MMR)/ Measles-mumps-rubella-varicella (MMRV)
5. Varicella
6. Meningococcal C (MenC-C)/ Meningococcal C ACYW (MenC-ACWY)
7. Meningococcal B (Men-B)
8. Human papillomavirus (HPV)
9. Influenza
10. Hepatitis B/AB
11. Haemophilus influenzae type b (Hib)
12. Herpes-zoster
13. Travel vaccines (i.e. IPV, OPV, hepatitis A, other meningococcal vaccines, pneu-P-23, BCG, cholera-ETEC, JE, rabies, oral typhoid, injectable typhoid, yellow fever)

13. **AEFI causality** was estimated by SIC physicians who applied all available information from participants, their PCP, and/or referring party to the WHO AEFI causality assessment tool. AEFI causality classification was collected from SIC physicians by SIC nurses using a standardized SIC questionnaire (Appendix 3) and entered in the SIC Network electronic research database as a categorical variable with 4 values. AEFI causality was described as a categorical variable with 4 values:

1. Consistent: AEFI demonstrates consistent causal association to vaccination (Adequate information available)
2. Inconsistent: AEFI demonstrates inconsistent causal association to vaccination (Adequate information available)
3. Indeterminate: Indeterminate causal association of AEFI and vaccination (Adequate information available)
4. Unclassifiable: Unclassifiable causal association of AEFI and vaccination (Adequate information not available).

14. **Allergy skin testing to vaccine antigen received prior to AEFI** was conducted by allergists working in collaboration with the SIC Network. A subset of the participants included in this study underwent allergy skin testing following recommendation by a SIC physician. Receipt of allergy skin testing, either skin prick test and/or intradermal test, was collected by SIC nurses using a standardized SIC questionnaire (Appendix 3) and captured in the SIC Network electronic research database at the presence of an allergy skin testing form. We described whether allergy skin testing with a vaccine was performed as a binary variable with the following outcomes:
    1. Allergy skin testing performed
    2. No allergy skin testing performed

15. **Result of allergy skin testing to vaccine antigen received prior to AEFI** was determined by allergists co-investigators in the SIC Network. Result of allergy skin testing was collected by SIC nurses using a standardized SIC questionnaire (Appendix 3) and captured in the SIC Network electronic research database as a categorical variable with 3 values (positive, negative, and indeterminate). A positive control test with histamine and negative control test with saline were administered during allergy skin testing. A positive response to a skin prick test and/or intradermal test was defined as a flare and/or erythema surrounding a wheal at least 3mm larger than the saline control.[91] A negative response was defined as a flare and/or erythema

surrounding a wheal less than 3mm with a positive control response.[92] An indeterminate response was defined as a response that was <3mm, had erythema surrounding the prick but no wheal, when the positive control was negative and thus the test result could not be interpreted, or when there was dermatographism at the negative control causing it to appear to be positive and thus the test result again could not be interpreted. The result of allergy testing was described as a binary variable:

1. Any positive allergy skin test result to a vaccine antigen of at least 1 vaccine associated with the prior AEFI
2. All negative or indeterminate allergy skin test results to the vaccine antigen(s) of the vaccine(s) associated with the prior AEFI.

16. **Severity of recurrent AEFI relative to initial AEFI** was collected by SIC nurses based on participant reported severity of recurrent AEFI relative to initial AEFI using a standardized SIC questionnaire (Appendix 3). Severity of recurrent AEFI relative to initial AEFI was entered in the SIC Network electronic research database as a categorical variable with 4 values (milder, same severity, more severe, unknown). Severity of recurrent AEFI relative to initial AEFI was described as a categorical variable with 4 values:
    1. Milder
    2. Same severity
    3. More severe
    4. Unknown

*3.5.2. **Statistical Analysis Plan***

The demographic and clinical characteristics of participants were summarized in the descriptive analysis. Firstly, we estimated the frequency of SIC physician recommendations for revaccination, participants' intention to receive revaccination, and revaccination status among participants who were assessed in the SIC Network for a prior AEFI. Participant demographic (age, gender, SIC site, and province) and clinical

characteristics (AEFI type, AEFI impact, vaccine antigen received, AEFI causality, and allergy skin testing to a vaccine antigen) were reported by physician recommendation (recommendation for revaccination, recommendation against revaccination, recommendation deferred pending further assessment), by intent to be revaccinated (participant revaccinated at SIC, participant revaccinated by GP/PH, participant will return to SIC for revaccination, participant delayed revaccination, participant refused revaccination), and by revaccination status (record of revaccination, no record of revaccination). The results of the descriptive analysis provided prevalence estimates of the outcome and exposure variables included in the multivariable analyses.

Lastly, we estimated the frequency of AEFI recurrence following revaccination among participants included in our analysis. Participant demographic (age, gender, SIC site, and province) and clinical characteristics (AEFI type, severity of recurrent AEFI relative to initial AEFI, vaccine antigen received, and allergy skin testing to a vaccine antigen) were reported by AEFI recurrence (recurrence, no recurrence).

3.6. Multivariable Analysis

The multivariable analysis was conducted using, SAS Version 9.4., as part of our second and third objectives:

3.6.1. ***Objective 2- Physician Recommendation for Revaccination***

To identify factors associated with a physician recommendation for revaccination among participants who were assessed in the SIC Network for a previous AEFI.

3.6.1.1. ***Variables***

3.6.1.1.1. Outcome Variable

SIC physician recommendation for revaccination among participants who were assessed at a SIC for a prior AEFI and required additional doses of the vaccine associated with their prior AEFI. Physician recommendation was collected and captured in the SIC Network electronic research database as described in section 3.5.1.1. SIC physician recommendation was described as a binary variable: 1) physician recommendation for revaccination and (2) physician recommendation against revaccination or recommendation deferred pending further assessment.

3.6.1.1.2. Exposure Variables

Our review of the literature and advice from experts led us to explore the association between physician recommendation and three exposures: participant age, AEFI type, and AEFI impact. As described in section 1.4.1 there is evidence of an association between AEFI type and AEFI impact and physicians' decisions to recommend or not recommend revaccination. An association between recommendation and participant age was also explored as increasing age may be associated with physician recommendation for revaccination.

Participant age was collected and captured in the SIC Network electronic research database as described in section 3.5.1.5.

AEFI type-3 was collected and captured in the SIC Network electronic research database as described in section 3.5.1.9. We described AEFI type-3 as a categorical variable with 3 levels: AEFIs not contraindicated for revaccination based on SIC Network, provincial, and national AEFI management guidelines, AEFIs contraindicated for revaccination based on SIC Network, provincial, and national AEFI management guidelines, and AEFIs with variable revaccination management guidelines (Table 2).[57,84–89] We requested the advice of the SIC investigators as how to collapse AEFI type in a meaningful way. The SIC investigators suggested collapsing AEFI type as a 3-level variable using AEFI management guidelines. The SIC Network, provincial (only those provinces with SIC sites), and national AEFI management guidelines were reviewed to

determine which AEFI types were not contraindicated for revaccination, contraindicated for revaccination, and had variable management guidelines.[57,84–89] The SIC Network investigators were contacted after collapsing AEFI type as a 3-level for their review and approval of the new description.

1. AEFIs contraindicated for revaccination based on SIC Network, provincial, and national AEFI management guidelines: anaphylaxis with positive skin allergy test result, type III/IV delayed hypersensitivity reaction, Guillain-Barré/Miller-Fisher syndrome
2. AEFIs not contraindicated for revaccination based on SIC Network, provincial, and national AEFI management guidelines: large local reaction, cellulitis, abscess (infectious), abscess (sterile), nodule, other injection site reaction, non-anaphylactic immediate hypersensitivity reaction with negative skin allergy test result, delayed onset type I hypersensitivity reaction with negative skin allergy test result, other allergic-like event with negative skin allergy test result, oculo-respiratory syndrome, seizure, fever, hypotonic-hyporesponsive episode, persistent crying, arthritis/arthralgia, immunization stress related response, gastrointestinal symptoms, non-urticarial rash, general symptoms, other systemic AEFIs
3. AEFIs with variable SIC Network, provincial, and national AEFI management guidelines: anaphylaxis with missing skin allergy test result or no allergy testing, non-anaphylactic immediate hypersensitivity reaction with positive skin allergy test result, non-anaphylactic immediate hypersensitivity reaction with missing skin allergy test result or no allergy testing, delayed onset type I hypersensitivity reaction, other allergic-like event with positive skin allergy test result, anaesthesia, peripheral neuropathy, encephalitis, myelitis, acute disseminated encephalomyelitis, meningitis, other neurologic AEFIs, autoimmune, thrombocytopenia

AEFI type-8 was collected and captured in the SIC Network electronic research database as described in section 3.5.1.9. In addition to creating AEFI type-3, the SIC investigators suggested creating AEFI type-8 by collapsing the 32 levels of AEFI type into 8 common AEFI type levels. A secondary analysis was conducted to compare the findings of the primary analysis (AEFI type-3) to an analysis using AEFI type-8. AEFI type-8 had the following levels (Table 2):

1. Large local reaction
2. Other injection site reaction: cellulitis, abscess (infectious), abscess (sterile), nodule, other injection site reaction
3. Immediate hypersensitivity reaction: anaphylaxis, non-anaphylactic immediate hypersensitivity reaction
4. Delayed hypersensitivity reaction: delayed onset type I hypersensitivity reaction, type III/IV delayed hypersensitivity reaction, other allergic-like events
5. Seizure
6. Other neurologic AEFIs: Guillain-Barré syndrome, anaesthesia, peripheral neuropathy, encephalitis, myelitis, acute disseminated encephalomyelitis, meningitis, other neurologic AEFIs
7. Autoimmune disease: autoimmune diseases, thrombocytopenia
8. Other systemic AEFIs: fever, hypotonic-hyporesponsive episode, persistent crying, arthritis/arthralgia, immunization stress related response, gastrointestinal symptoms, non-urticarial rash, general symptoms, other systemic AEFIs

AEFI impact was categorized, collected, and captured in the SIC Network electronic research database as described in section 3.5.1.10.

3.6.1.1.3. Covariates

SIC province of SIC site at which a participant was enrolled for a prior AEFI was included in our multivariable analysis as a confounder. SIC province was collected and

captured in the SIC Network electronic research database as described in section 3.5.1.8. SIC province was described as a categorical variable with 5 levels: Nova Scotia, Quebec, Ontario, Saskatchewan/ Alberta, and British Columbia. We chose to use province of SIC site instead of SIC site due to the variation in enrollment between SIC sites and sample sizes at some sites being very small. Additionally, the sample size of the analysis would not support a 13-level variable in the model thus we chose to collapse SIC site by province resulting in the 6-level variable.

The presence of a non-random effect due to SIC province on the relationship between the outcome and exposure variables was assessed using mixed-effect modelling. A significant effect of SIC province was not identified therefore we proceeded to produce logistic regression models instead of mixed-effect models. However, we conducted a sensitivity analysis to identify whether differences existed in the relationships between physician recommendation for revaccination and participant and clinical characteristics between SIC sites with high (i.e. >10%) enrollment of participants with prior AEFIs and SIC sites with low (i.e. ≤10%) enrollment of participants with prior AEFIs. A sensitivity analysis was conducted to compare the results of our primary and secondary analyses to the results of the sensitivity analysis. In the sensitivity analysis, SIC site enrollment was described as a binary variable with the following levels: high enrolling SIC site (>10% enrollment of participants with prior AEFIs) and low enrolling SIC site (≤10% enrollment of participants with prior AEFIs).

*3.6.1.2.**Statistical Analysis Plan***

We conducted simple logistic regression and expressed our results in odds ratio (ORs) with 95% confidence interval (CIs) and p-values to test whether there was an unadjusted association between physician recommendation and 1) participant age, (2) AEFI type, and (3) AEFI impact. Multiple logistic regression was conducted to identify whether an association existed between physician recommendation for revaccination and 1) participant age, (2) AEFI type, and (3) AEFI impact while controlling for SIC province. The findings were presented as adjusted ORs (aORs) with 95% CIs.

3.6.2. ***Objective 3 –Participant Intention to be Revaccinated***

To identify factors associated with participant intention to be revaccinated among participants who were assessed in the SIC Network for a prior AEFI and who received a recommendation from a SIC physician for revaccination.

3.6.2.1. ***Variables***

3.6.2.1.1. Outcome Variable

Participant intention to be revaccinated among participants assessed at the SIC for a prior AEFI and who received a recommendation for revaccination from a SIC physician. Participants' revaccination intentions were collected and captured in the SIC electronic research database as described in section 3.5.1.2.

Participant intention to be revaccinated was a binary variable: intention to be revaccinated and intention not to be revaccinated. Participant intention to be revaccinated included participants who were revaccinated at the SIC, intended to be revaccinated by their primary care physician or public health department, and who intended to return to the SIC for revaccination. Participant intention not to be revaccinated included participants who refused revaccination and participants who delayed revaccination and did not have a record of revaccination in the database at the time of data extraction. Participant intention captures certain revaccination behaviours; however, we defined the revaccination behaviours as intentions to ensure all responses of participant intention were consistently defined as intentions.

3.6.2.1.2. Exposure Variable

Evidence from our literature review and advice from experts led us to explore potential associations between participant intention to be revaccinated and 1) participant

age, (2) AEFI type, (3) AEFI impact, and (4) vaccine antigen administered prior to AEFI onset. Section 1.4.2 provides evidence from studies of participants with prior AEFI that revaccination uptake may differ by AEFI type and AEFI impact which led us to explore whether AEFI type and AEFI impact were associated with revaccination intentions. We included vaccine antigen and participant age in our analysis as revaccination uptake has been reported to vary by vaccine antigen and participant age.[62]

AEFI type-3 followed the same methods of collection, capture, and description as described in section 3.6.1.1.2. and are presented in Table 2.

AEFI type-8 followed the same methods of collection, capture, and description as described in section 3.6.1.1.2. and are presented in Table 2.

AEFI impact and **participant age** followed the same methods of collection, capture, and description as described in section 3.6.1.1.2.

Vaccine antigen administered prior to AEFI was collected and captured in the SIC Network electronic research database as described in section 3.5.1.12. For the analysis of participant intention to be revaccinated vaccine antigen was described as a binary variable with the following levels: influenza vaccine and non-influenza vaccine.

3.6.2.1.3. Covariates

SIC province of SIC site at which a participant with a prior AEFI was enrolled was included in our multivariable analysis as a confounder. SIC province was collected and captured in the SIC Network electronic research database as described in section 3.5.1.1.3. SIC province was described as a categorical variable with 5 levels: Nova Scotia, Quebec, Ontario, Saskatchewan/Alberta, and British Columbia.

The presence of a non-random effect on the relationship between the outcome and exposure variables was assessed using mixed effect modelling. A significant effect of SIC province was not identified.

3.6.2.2. ***Statistical Analysis Plan***

We conducted simple logistic regression and expressed our results in odds ratio (ORs) with 95% confidence interval (CIs) and p-values to test whether there was an unadjusted association between participant intention for revaccination and 1) participant age, (2) AEFI type, (3) AEFI impact, and (4) vaccine antigen. Multiple logistic regression was conducted to identify whether an association existed between participant intention for revaccination and 1) participant age, (2) AEFI type, (3) AEFI impact, and (4) vaccine antigen while controlling for SIC province. The findings were presented as adjusted ORs (aORs) with 95% CIs.

3.6.3. ***Model Selection***

We assessed multicollinearity between exposure variables prior to model development and selection. Multicollinearity is the linear dependence between two variables. Multicollinearity can lead to large standard errors of regression coefficients which may lead to the unnecessary removal of exposure variables and inaccurate interpretations of results. We used the Variance Inflation Factors to assess multicollinearity. Variance Inflation Factors were calculated for each variable in the regression models to measure the degree of collinearity between variables and amount of inflation as a result of the collinearity. No variables demonstrated a VIF greater than 1.20, therefore no variables were excluded from the final models due to multicollinearity.[93]

We used Least Absolute Shrinkage and Selection Operator (LASSO) regression for variable selection. LASSO regression for model selection is useful for improving the accuracy and stability of a model compared to forward, backward, or stepwise selection. Additionally, LASSO is useful for developing a model that contains a large number of variables when only a small number are strongly associated with the outcome. Finally, LASSO regression was used as opposed to stepwise selection as it does not select

variables for inclusion in a model solely based on their p-values. LASSO regression considers both the significance of an association and the strength of the association between variables in the model.[94]

Following our assessment of multicollinearity and LASSO methods we produced logistic models using the LASSO selected variables to report the ORs and 95% CIs estimates of the fully adjusted model and assess each model's Goodness of Fit (GOF). We produced fully adjusted models and reported on the GOF of each model for the primary, secondary, and sensitivity analyses. The Receiver Operating Curve (ROC) c-statistic was used to assess model fit. The ROC measured the models' accuracy in estimating the outcomes by plotting the models' sensitivity against their specificity at various thresholds. Sensitivity is the proportion of true positive predictions of an outcome among all participants with that outcome. Specificity is the proportion of true negative predictions of the alternative outcome among all participants with the alternative outcome. The area under the ROC provides a single value for the accuracy of the model's ability to predict an outcome at each threshold.[95]

3.6.4. **Missing Data**

Data can be missing completely at random, missing at random, missing not at random, and structurally missing. Missing completely at random occurs when the pattern of missingness is not related to any observable variables or the variable itself. Missing at random occurs when the pattern of missingness is related to another observable variable but not the variable itself. Missing not at random occurs when the pattern of missingness is related to the variable in question.[96] Finally, structurally missing data occurs when an event did not occur and therefore no data about the event could be captured.

Data that was missing at random was encountered in the descriptive analysis. Data was missing as a result of the AEFI happening prior to participants' assessments at a SIC for their prior AEFI and being unable to recall the information about the event. In the multivariable analysis missing data was identified for the following exposure variables:

AEFI type, AEFI impact, age at vaccination, and vaccine antigen administered prior to vaccination. Participant study records were reviewed to identify data that was reported as missing in our analysis. When AEFI type was missing, the physician notes and symptoms reported in the participant study records were used to complete missing AEFI type and categorize it under one of the categorical levels of AEFI type in section 3.5.1.9. A SIC physician was consulted to confirm the updated AEFI types were appropriate given the data reported. When AEFI impact was missing, participant records were reviewed for data regarding level of medical care required and duration of disability following the AEFI to complete the missing observation. If day of vaccination was missing, we assumed the participant was vaccinated on the 1st day of the month. If month of vaccination was missing, we assumed the participant was vaccinated on the 6th month of the year. If vaccine antigen was missing, the AEFI description was reviewed for a written statement of the vaccine administered prior to the AEFI. When missing data was unable to be identified directly from participant records using the aforementioned methods, the participant was excluded from the multivariable analysis. Structurally missing data was identified for participants who did not have a record of revaccination. Data about possible revaccinations could not be captured if we did not have a record of the revaccination.

3.7. Ethics

Research Ethics Board (REB) approval was granted to CM by the IWK REB to conduct this study. The study was approved by the REBs of all participating centres.

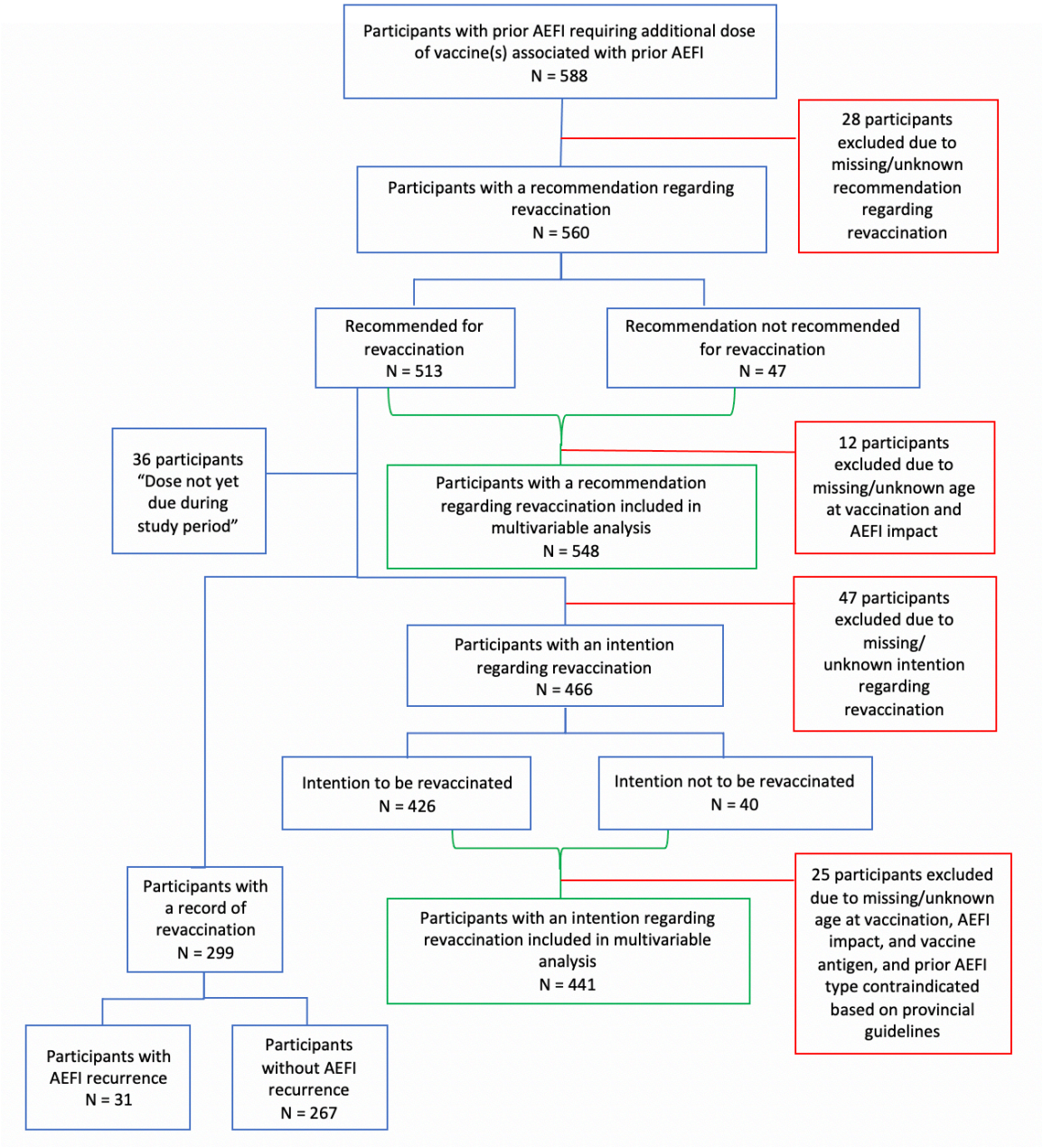

Figure 5. Flow diagram describing the participants included in the descriptive analyses (blue), multivariable analyses (green), and those excluded (red) from the analyses and the reason for exclusion.

Table 1. SIC research database inclusion-exclusion criteria

Inclusion criteria
Patients were included in the SIC Network research database if they provided consent for inclusion and were referred to the SIC Network for at least one of the following AEFIs: 1. Fever of ≥ 40.5°C (105°F) within 72 hours after a dose of inactivated vaccines or 5-10 days after a dose of live vaccine 2. Local reaction ≥ 10cm 3. Cellulitis, abscess or nodule at the injection site following a previous vaccination 4. Arthus reaction following a previous vaccination 5. Persistent, inconsolable crying lasting for at least 3 hours occurring within 48 hours of a dose in infants and children. 6. Seizure within 72 hours after a dose of inactivated vaccine or 5-10 days after a dose if live vaccine 7. Hypotonic-hyporesponsive episode occurring within 48 hours of a dose in children 8. Arthralgia/arthritis occurring within 30 days of a dose 9. Allergic-like symptoms (Anaphylaxis, Oculo-respiratory syndrome (bilateral red eyes, with ≥ 1 respiratory symptoms including coughing, wheezing, chest tightness, difficulty breathing, difficulty swallowing, hoarseness, or sore throat, within 24 hours following vaccination, with or without facial oedema[90]), other allergic symptoms) occurring within 24 hours of a dose 10. Unexpected AEFI of concern as an emerging vaccine safety signal. Previously unidentified AEFI or previously identified AEFIs occurring at a greater frequency.
Exclusion criteria
Patients who did not consent to inclusion in the SIC research database or who received consultation at the SIC Network for at least one of the conditions listed below but have no history of AEFI were excluded from the SIC Network research database: 1. Egg-allergic patients without history of AEFI 2. Personal history of allergic disease/atopy not related to vaccine 3. Personal history of headache/Migraine 4. Personal history of adverse drug reaction (except antibiotics included in vaccines) 5. Personal history of preterm birth/perinatal/neonatal problems 6. Family history of seizures 7. Family history of vaccine reaction 8. Family history of pre-existing medical condition 9. Vaccines concerns/needle phobia

Table 2. AEFI types categorized as AEFI type-3 and AEFI type-8.

AEFI type	AEFI type-3	AEFI type-8
Anaphylaxis with positive skin allergy test result	Contraindicated for revaccination	Immediate hypersensitivity reaction
Type III/IV delayed hypersensitivity reaction		Delayed hypersensitivity reaction and other allergic-like events
Guillain-Barré/Fisher-Miller syndrome		Other neurologic AEFI
Large local reaction	No contraindicated for revaccination	Large local reaction
Cellulitis		Other injection site reaction
Abscess, infectious		
Abscess, sterile		
Nodule		
Other injection site reaction		
Non-anaphylactic immediate hypersensitivity reaction with negative skin allergy test result		Immediate hypersensitivity reaction
Delayed onset type I hypersensitivity reaction with negative skin allergy test result		Delayed hypersensitivity reaction and other allergic-like events
Other allergic-like event with negative skin allergy test result		
Oculo-respiratory syndrome		
Seizure		Seizure
Fever		Other systemic AEFIs
Hypotonic-hyporesponsive episode		
Persistent crying		
Arthritis/arthralgia		
Immunization stress related response		
Gastrointestinal symptoms		
Non-urticarial rash		
General symptoms		
Other systemic AEFIs		
Anaphylaxis with missing skin allergy test result or no allergy testing	Variable revaccination management	Immediate hypersensitivity reaction
Non-anaphylactic immediate hypersensitivity reaction with positive skin allergy test result		
Non-anaphylactic immediate hypersensitivity reaction with missing skin allergy test result or no allergy testing		
Delayed onset type I hypersensitivity reaction with positive skin allergy test result		Delayed hypersensitivity reaction and other allergic-like events
Delayed onset type I hypersensitivity reaction with missing skin allergy test result or no allergy testing		
Other allergic-like event with positive skin allergy test result		
Other allergic-like event with missing skin allergy test result or no allergy testing		
Anaesthesia		Other neurologic AEFI
Peripheral Neuropathy		
Encephalitis		
Myelitis		Other neurologic AEFI
Acute disseminated encephalomyelitis		
Meningitis		
Other neurologic AEFIs		
Autoimmune disease		Autoimmune disease
Thrombocytopenia		

4. Chapter 4: Results

4.1. Descriptive Analysis

4.1.1. Total Prior AEFIs

From 2013 to 2019 the SIC Network assessed 588 participants who required additional doses of the vaccine(s) associated with their prior AEFIs with 627 prior AEFIs (Table 3). Among the 627 AEFIs, 306 (49%) were reported in males, 570 (91%) were reported in participants < 18 years of age at vaccination, and 43 (7%) were reported in participants ≥ 18 years of age at vaccination.

Injection site reactions accounted for 140 (22%) prior AEFIs (Table 3). Large local reactions accounted for 107 (77%) injection site reactions, followed by 16 (11%) sterile abscess events, 5 (4%) nodule events, and 12 (8%) other injection site reactions. Five (4%) serious (i.e. hospitalization required for >24 hours, life-threatening outcome, ongoing disability) injection site reactions were reported, of which 4 were large local reactions and 1 was an infectious abscess (Table 4). A consistent causal association between large local reactions and vaccination was reported in 96/107 (90%) cases, of which 51/96 (53%) cases were causally associated with influenza vaccinations and 37/96 (38%) case were causally associated with DTaP/Tdap vaccinations.

Among the 627 AEFIs, 220 (35%) were allergic-like events (Table 3), of which 89 (40%) were delayed onset (>4h post-vaccination) type I hypersensitivity reactions, 87 (40%) were non-anaphylactic immediate hypersensitivity reactions, 38 (17%) were anaphylactic events, 4 (2%) were delayed type III/IV hypersensitivity reactions, and 2 (1%) were non-specific allergic-like events. Two allergic-like events were serious AEFIs both of which were anaphylaxis following DTaP/Tdap vaccinations (Table 4). Ten (5%) allergic-like events were of high impact (i.e. ≥3 physician assessments, medical supervision required outside of hospital, >3 days disability or ≤24 hours hospitalization):

5 anaphylactic events, 3 delayed onset type I hypersensitivity reactions, and 2 non-anaphylactic immediate hypersensitivity reactions. A total of 98/220 (45%) had allergy skin testing (i.e. skin prick and/or intradermal testing). Allergy skin test (i.e. skin prick and/or intradermal testing) results were positive in 15/25 (60%) participants with prior anaphylaxis who had allergy skin testing, 9/48 (18%) participants with prior non-anaphylactic immediate hypersensitivity reactions who had allergy skin testing, and 4/25 (16%) participants with delayed onset type I hypersensitivity reactions who had allergy skin testing.

Neurologic AEFIs accounted for 60 (10%) prior AEFIs, of which 26 (43%) were seizure, 5 (8%) were Guillain-Barré Syndrome/Fisher Miller Syndrome, and 29 (48%) were other neurologic AEFIs, including myelitis, encephalitis, anaesthesia/paranesthesia, developmental regression, rapid eye blinking, stroke, optic neuritis, Bell's palsy, and cerebellitis (Table 3). Eleven (42%) of 26 prior seizure cases were reported as serious AEFIs and 13/26 (50%) prior seizures were febrile. Five of the 26 (19%) prior seizures were estimated as having consistent causal association with DTaP/Tdap, PCV, MMR, varicella, and meningococcal B vaccinations, respectively.

Other systemic AEFIs accounted for 199 (32%) AEFIs (Table 3). These included 51/199 (26%) cases of non-urticarial rash, 22/199 (11%) cases of hypotonic-hyporesponsive episode, 18/199 (9%) cases of fever, 17/199 (9%) cases of immunization stress related response, 13/199 (7%) cases of persistent crying, and 11/199 (6%) cases of thrombocytopenia. Twenty-four of 199 (12%) other systemic AEFIs were defined as "Other" events which included unilateral eye swelling, chronic urticaria, glossitis, breath holding spells, aplastic anemia, concomitant illness, neutropenia, stiff neck, osteoma cutis, acute pancreatitis, and petechiae. Fourteen of 22 (64%) cases of hypotonic-hyporesponsive episodes were reported following DTaP/Tdap and PCV vaccinations, 13/14 (93%) of which were estimated as having a consistent causal association with those vaccinations. Eight of 13 (62%) cases of persistent crying were reported following DTaP/Tdap and PCV vaccinations, of which 4/8 (50%) were estimated as having a consistent causal association with the vaccinations. Seven of 11 (64%) cases of

thrombocytopenia were estimated as having a consistent causal association with MMR vaccinations, 4/7 (57%) of which were serious AEFIs.

4.1.2. **Revaccination and AEFI Recurrence**

Revaccination was recommended to 92% (513/588) of participants assessed at a SIC, recommended against to 4% (24/588) of participants, and the recommendation was deferred pending further assessment for 4% (23/588) of participants (Table 5). Among the 513 participants recommended for revaccination, 36 (7%) were not yet due for revaccination during the study period, 426 (83%) intended to be revaccinated, and 299 (58%) had a record of revaccination (Table 6). Specifically, 59% (305/513) of participants intended to be revaccinated at a SIC, 85% (260/305) of which were due for revaccination during the study period and had a record of revaccination.

Thirty-one participants reported an AEFI recurrence following revaccination (Table 8); of these participants 4/31 (13%) had an event more severe than the initial event and none were serious. AEFI recurrence was more frequent in females compared to males; however, the difference was non-significant (68% vs. 32%, p-value: 0.08). Twenty-one of 31 (68%) participants with AEFI recurrence experienced an initial AEFI reported as causally associated with the vaccination.

4.1.2.1.***Injection Site Reactions***

Among the 119 participants with injection site reactions who received a recommendation, 114/119 (96%) were recommended for revaccination, 3/119 (3%) were recommended against revaccination, and in 2/119 (1%) participants the recommendation was deferred pending further assessment (Table 5). Among the 114 participants recommended for revaccination, 18 (16%) were not yet due for revaccination during the study period, 87/114 (76%) intended to be revaccinated, and 59/114 (52%) had a record of revaccination (Tables 6 and 7). Sixteen of the 59 (27%) participants who were

revaccinated experienced AEFI recurrence, of which 2 participants reported the recurrent injection site reactions as more severe than the initial event (Table 8).

A recommendation for revaccination was given to 89 participants with large local reaction (Table 5). Large local reactions were reported as causally associated with vaccination in 79/89 (89%) participants recommended for revaccination. Two of the 89 (2%) participants had an AEFI that was considered serious. Among the 87 non-serious large local reactions reported, 27/87 (31%) were of low impact, 58/87 (66%) were of moderate impact, and 3/87 (3%) were of high impact.

Revaccination was not recommended in 2 participants with large local reaction. Both events were considered causally associated with vaccination. One event occurred following quadrivalent inactivated influenza vaccination and was a serious AEFI. The participant was admitted to hospital for >24 hours. The second participant had a large local reaction following DTaP-IPV-Hib and MMR vaccinations that was a non-serious AEFI of low impact. However, the participant had a positive intradermal allergy test to a DTaP-IPV-Hib vaccine. Revaccination was not recommended in a participant with nodule following DTaP-IPV-Hib and MMR vaccinations who had a positive intradermal test result to DTaP-HB-IPV-Hib and monovalent Hib conjugate vaccines. The AEFI was reported as being causally associated with the vaccinations and was of low impact.

A recommendation was deferred pending further assessment in a participant with large local reaction following DTaP-IPV-Hib vaccination as the physician was waiting to receive the participant's immunization history and was considering referring the participant for allergy skin testing. A recommendation was deferred pending further assessment in a second participant with large local reaction following DTaP-IPV and MMR vaccinations as the participant was to undergo allergy skin testing before being given a recommendation regarding revaccination.

Seventy of the 89 (79%) participants with prior large local reactions who were recommended for revaccination intended to be revaccinated and 48/89 (54%) had a

record of revaccination (Tables 6 and 7). Three participants who were recommended for revaccination with positive intradermal test results to DTaP-IPV and influenza vaccines intended to be revaccinated and 1 had a record of revaccination. Two of the 89 (2%) participants with large local reaction who were recommended for revaccination refused revaccination; both events followed influenza vaccinations and were of moderate impact. Three of 89 (3%) participants with large local reaction who were recommended for revaccination delayed their revaccinations: 1 case followed varicella vaccination and was of high impact, 1 case followed Tdap and MMR vaccinations and was of moderate impact, and 1 case followed DTaP-IPV vaccination and was of moderate impact.

Fourteen of 48 participants with prior large local reactions and a record of revaccination experienced AEFI recurrence (Table 8). The risk of recurrence of large local reaction was 29% (95% CI: 16%-42%). Among the 14 participants with recurrent large local reactions, 13 (92%) participants were revaccinated with influenza and/or DTaP/Tdap vaccinations. Two of the 14 (14%) participants reported the recurrent events as more severe than the initial events. Two participants experienced recurrent other injection site reactions (risk of recurrence: 22% [95% CI: 0%-49%]) which were less severe than the initial events.

4.1.2.2.***Allergic-like Events***

A recommendation was given to 207 participants with prior allergic-like events, of whom 183/207 (88%) were recommended for revaccination, 10/207 (5%) were not recommended for revaccination, and in 14 of 207(7%) the recommendation was deferred pending further assessment (Table 5). Among the 183 participants recommended for revaccination 4 (2%) were not yet due for revaccination during the study period, 165 (90%) intended to be revaccinated, and 127 (69%) had a record of revaccination (Tables 6 and 7). Allergic-like event recurrences were reported in 10 participants following revaccination, of which 1 event was more severe than the initial event (Table 8).

Revaccination was recommended to 21/35 (60%) participants with anaphylaxis, of which 2 were serious AEFIs. Both participants with serious anaphylaxis had positive intradermal test results to Tdap and DTaP-IPV-Hib vaccines. Seventy-eight of 84 (93%) participants with prior non-anaphylactic immediate hypersensitivity reaction were recommended for revaccination. Revaccination was recommended to 78/82 (95%) participants with delayed onset (>4 hours) type I hypersensitivity reaction. Finally, revaccination was recommended to 4 participants with delayed type III or IV hypersensitivity reactions all of which were non-serious AEFIs. One participant had a type IV hypersensitivity reaction that was considered causally associated with DTaP-HB-IPV-Hib vaccination, 1 participant had a serum sickness-like reaction that was considered causally associated with DTaP-HB-IPV-Hib, PCV, meningococcal C, MMR, and rotavirus vaccinations, 1 participant had erythema multiforme with indeterminate causal association to PCV13, meningococcal C, trivalent influenza, and MMRV vaccinations, and 1 participant had erythema multiforme with indeterminate causal association to a DTaP-HB-IPV-Hib vaccination.

A recommendation against revaccination was given to 8/35 (23%) participants with anaphylaxis, 6 of whom had reactions of moderate impact and 2 of whom had reactions of high impact. Seven of these participants underwent allergy skin testing and 4/7 (57%) participants had positive allergy skin test results to the vaccine(s) of interest. One participant who experienced a non-anaphylactic immediate hypersensitivity reaction following influenza vaccination was recommended against revaccination. The participant had a positive skin prick test response to an influenza vaccine. A recommendation against revaccination was given to 1 participant with delayed onset (>4 hours) type I hypersensitivity reaction following meningococcal C vaccination. The AEFI was considered as having inconsistent causal association with the vaccination; that participant was advised to undergo allergy skin testing but did not have a record of allergy skin testing.

A recommendation was deferred pending further assessment for 6/35 (17%) participants with anaphylaxis, of which 5 were of moderate impact and 1 was of high

impact. Two of these participants underwent intradermal testing and tested positive to Tdap vaccines; however, further allergy skin testing was requested before making recommendations regarding revaccination in these participants. A recommendation was deferred pending further assessment for 5 participants with non-anaphylactic immediate hypersensitivity reaction, of which 1 was to be reassessed before their next vaccination and 4 were referred for allergy skin testing. Two participants referred for allergy skin testing had positive allergy skin testing results.

Eighteen of 21 (86%) participants with anaphylaxis intended to be revaccinated, all of whom had previously experienced non-serious anaphylactic reactions. Eleven of 21 (52%) participants had a record of revaccination. Seventy-one of 78 participants (91%) with prior non-anaphylactic immediate hypersensitivity reaction intended to be revaccinated and 57/78 (73%) had a record of revaccination. Seventy-two of 82 (92%) participants with prior delayed onset (>4 hours) type I hypersensitivity reaction intended to be revaccinated and 55/82 (71%) had a record of revaccination. Three of 4 (75%) participants with prior delayed type III or IV hypersensitivity reactions intended to be revaccinated and 2/4 (50%) participants had a record of revaccination.

Two of 21 (10%) participants with anaphylaxis did not intend to be revaccinated. Both participants delayed their revaccination. In 1 participant who delayed their revaccination, the anaphylactic event followed a DTaP-IPV-Hib vaccination and was a serious AEFI. In the second participant who delayed their revaccination, the anaphylactic event followed DTaP-IPV-Hib and MMR vaccinations and was of moderate impact. Six of 78 (8%) participants with non-anaphylactic immediate hypersensitivity reaction did not intend to be revaccinated, of which 2 participants had prior reactions of low impact and 4 had prior reactions of moderate impact. Four of 82 (5%) participants with prior delayed onset (>4 hours) type I hypersensitivity reaction did not intend to be revaccinated; 1 had a prior reaction of low impact and 3 had prior reactions of moderate impact.

One of 11 participants with anaphylaxis experienced a recurrence resulting in a risk of recurrence of 9% (95% CI: 0%-26%). The initial anaphylactic event followed a DTaP-IPV-Hib vaccination. The participant had a positive skin prick allergy test to a Td vaccine and had a record of Td revaccination. The recurrent event was reported as more severe than the initial event, which was of moderate impact. Four of 57 participants with prior non-anaphylactic immediate hypersensitivity reaction and a record of revaccination experienced AEFI recurrence resulting in a risk of recurrence of non-anaphylactic immediate hypersensitivity reaction of 7% (95% CI: 0%-14%). Among the participants with recurrent non-anaphylactic immediate hypersensitivity events, 3/4 had a positive allergy skin test to the vaccine of interest. Three of the recurrent reactions were milder than the initial events and 1 reaction was of the same severity. Five of 55 participants with prior delayed onset (>4 hours) type I hypersensitivity reaction experienced a recurrent AEFI (risk of recurrence: 9% [95% CI: 0%-17%]). In 1 participant, the initial AEFI was considered causally associated with varicella and HPV vaccinations. Four of the recurrent events were milder than the initial reactions and 1 was the same severity at the initial reaction.

4.1.2.3. ***Neurologic AEFIs***

Among the 53 participants with neurologic AEFIs who received a recommendation, 44/53 (83%) were recommended for revaccination, 6/53 (11%) were recommended not to be revaccinated, and in 3/53 (6%) participants the recommendation was deferred pending further assessments (Table 5). Serious AEFIs were reported in 15/44 (34%) participants recommended for revaccination, 3/6 (50%) participants recommended against revaccination, and 1/15 (33%) participant with a deferred recommendation. Among the 44 participants recommended for revaccination 2/44 (5%) were not yet due for revaccination during the study period, 31/44 (70%) intended to be revaccinated, and 21/44 (48%) had a record of revaccination (Tables 6 and 7). One of 21 (5%) participants who were revaccinated experienced a recurrence (Table 8). The recurrent event was a seizure and the risk of recurrence was 8% (95% CI: 0%-22%).

Of 22 participants with seizure, 21 (95%) were recommended for revaccination. Revaccination was recommended in 2/4 (50%) participants with GBS and 21/27 (78%) participants with other neurologic AEFIs including participants with myelitis, encephalitis, peripheral neuropathy, Bell's palsy, hypotonia, and developmental regression.

Revaccination was not recommended for 1/22 participant with seizure. The seizure had reported indeterminate causal association with DTaP-IPV-Hib, PCV, and rotavirus vaccinations and was a serious AEFI. Two participants with prior Guillain-Barré syndrome were not recommended for revaccination; both Guillain-Barré syndrome events had indeterminate causal associations with vaccinations and were serious events. In both cases, influenza was administered prior to symptom onset (one participant also received PCV, meningococcal C, MMR, and varicella vaccinations). Revaccination was not recommended for a participant with peripheral neuropathy and a participant with optic neuritis pending referral to a neurologist. Finally, revaccination was not recommended to a participant with prior ADEM following DTaP/Tdap vaccination who was beginning immunosuppressive treatment.

Seventeen of 21 (81%) participants with prior seizure intended to be revaccinated, 6/17 (35%) of which had prior serious AEFIs. Thirteen of 21 (62%) participants with prior seizure recommended for revaccination had a record of revaccination. The two participants with Guillain-Barré syndrome who were recommended for revaccination intended to be revaccinated and 1 participant had a record of revaccination, without recurrence of the event. Among the 21 participants with other neurologic AEFIs who were recommended for revaccination 12/21 (57%) participants intended to be revaccinated and 7/21 (33%) had a record of revaccination without event recurrence.

Revaccination was refused by 2/21 (10%) participants with seizure: 1 seizure followed DTaP-IPV-Hib, PCV, and rotavirus vaccinations and was a serious AEFI and 1 seizure followed DTaP-Hib vaccination and was a non-serious AEFI of high impact.

4.1.2.4. *Other Systemic AEFIs*

Overall, 181 participants with prior other systemic AEFIs received a physician recommendation, of which 172/181 (95%) were recommended for revaccination, 5/181 (3%) were not recommended for revaccination, and in 4/181 (2%) participants the recommendation was deferred pending further assessments (Table 5). Serious AEFIs were reported in 22/172 (13%) participants recommended for revaccination, 2/5 (40%) participants not recommended for revaccination, and 1/4 (25%) participant in which the recommendation was deferred pending further assessments. Among the 172 participants recommended for revaccination, 12/172 (7%) were not yet due for revaccination during the study period, 143/172 (84%) intended to be revaccinated, and 92/172 (53%) participants had a record of revaccination (Tables 6 and 7). Four of 92 (4%) participants experienced AEFI recurrence, none of which reported the recurrent events as more severe than the initial events (Table 8).

Revaccination was recommended to 49 participants with prior non-urticarial rash including 2 participants with positive allergy skin tests (to a Tdap vaccine and a DTaP-HB-IPV-Hib respectively). Revaccination was recommended to 20 (100%) participants with prior hypotonic-hyporesponsive episodes, 15 (94%) participants with prior fever, and 12 (100%) participants with prior persistent crying.

Among the 5 participants with prior other systemic AEFIs who received a recommendation against revaccination, 2 cases were serious AEFIs: 1 participant experienced aplastic anemia with indeterminate causal association to hepatitis B and HPV vaccinations and 1 participant experienced thrombocytopenia with consistent causal association with MMR vaccination. Among the participants with non-serious AEFIs who were recommended against revaccination 1 patient had fever of moderate impact following PCV, meningococcal C, and MMR vaccinations and had a positive intradermal allergy test to PCV and meningococcal C vaccines, 1 patient had Henoch Schonlein purpura of moderate impact with reported indeterminate causal association with DTaP-IPV vaccination, and 1 patient with urticaria, fever, persistent crying and arthritis of high

impact had reported indeterminate causal association with DTaP-IPV and varicella vaccinations.

A recommendation was deferred pending further assessment for 4 participants with other systemic AEFIs, 3 of which were serious AEFIs: 1 participant experienced general symptoms with indeterminate causal association to influenza vaccination, 1 participant developed an autoimmune disease considered causally associated with DTaP-HB-IPV-Hib, PCV, and rotavirus vaccinations, and 2 participants experienced thrombocytopenia considered causally associated with vaccinations (PCV+ meningococcal C + and MMR and DTaP/Tdap + PCV + meningococcal C vaccinations, respectively).

Forty-five of 49 (92%) participants with prior non-urticarial rash intended to be revaccinated and 32/49 (65%) participants had a record of revaccination. Ten of 15 (67%) participants with prior fever who received a recommendation for revaccination intended to be revaccinated, one of whom had experienced a prior serious AEFI following DTaP-IPV-Hib and PCV vaccinations. Seven of 15 (47%) participants with prior fever were revaccinated. Eighteen of 20 (90%) participants with prior hypotonic-hyporesponsive episodes intended to be revaccinated and 14/20 (70%) had a record of revaccination. Ten of 12 (83%) participants with prior persistent crying intended to be revaccinated and 4/12 (33%) participants had a record of revaccination.

One participant with prior hypotonic-hyporesponsive episode of moderate impact following DTaP-HB-IPV-Hib and PCV vaccinations and 1 participant with prior persistent crying of low impact following DTaP-IPV-Hib and PCV vaccinations intended to delay their revaccinations. Revaccination was refused by 2 (10%) participants with non-specific other systemic symptoms. One participant experienced abdominal pain and glossitis and 1 participant experienced chronic urticaria. Both events followed influenza vaccination and were of moderate impact.

Three of 32 (9%) participants experienced recurrent non-urticarial rash following revaccination. The risk of recurrence of non-urticarial rash was 9% [95% CI: 0%-19%]. The three cases of recurrent non-urticarial rash followed DTaP/Tdap revaccinations. Two of the recurrent events of non-urticarial rash were milder than the initial events and 1 event had the same severity. A participant with fever causally associated with influenza vaccination experienced a recurrence reported as more severe than the initial event. Risk of recurrence of fever was 14% (95% CI: 0%-40%).

4.2. Multivariable Analysis

4.2.1. Physician Recommendation for Revaccination

We included 548 participants with a physician recommendation in the analysis to identify participant demographic and clinical characteristics associated with physician recommendation for revaccination. Overall, 501 participants received a recommendation for revaccination and 47 participants were not recommended for revaccination (24 recommended against revaccination and 23 participants with a deferred recommendation for further assessment) at the time of data collection.

4.2.1.1. ***Primary Analysis***

Table 9 presents demographic and clinical characteristics associated with a physician recommendation for revaccination. Physician recommendation for revaccination was significantly associated with AEFI impact and AEFI type-3 in crude models and after adjusting for SIC province ($p < 0.05$). Participants with AEFIs of moderate impact (aOR: 0.21 [95% CI: 0.07-0.65]), AEFIs of high impact (aOR: 0.08 [95% CI: 0.02-0.30]), and serious AEFIs (aOR: 0.11 [95% CI: 0.03-0.37]) had lower odds of physician recommendation for revaccination than participants with AEFIs of low impact.

Participants with AEFIs generally contraindicated for revaccination (e.g. GBS, anaphylaxis with a positive allergy skin test result) (aOR: 0.05 [95% CI: 0.02-0.14]) and participants with AEFIs with variable revaccination guidelines (e.g. non-anaphylactic immediate hypersensitivity reactions with a positive allergy skin test result, thrombocytopenia, neurologic AEFIs excluding GBS and seizure) (aOR: 0.20 [95% CI: 0.10-0.42]) had lower odds of physician recommendation for revaccination than participants with AEFIs not contraindicated for revaccination (e.g. large local reactions, non-anaphylactic immediate hypersensitivity reactions with a negative allergy skin test result, seizure, hypotonic-hyporesponsive episode).

*4.2.1.2.**Secondary Analysis***

A secondary analysis measured the crude and adjusted associations between physician recommendation for revaccination and AEFI type-8 (Table 10). Participants with prior immediate hypersensitivity reaction (aOR: 0.23 [95% CI: 0.07-0.71]), prior other neurologic AEFI (aOR: 0.12 [95% CI: 0.03-0.44]), and prior autoimmune disease (aOR: 0.16 [95% CI: 0.04-0.69]) had significantly decreased odds of physician recommendation for revaccination compared to participants with large local reactions.

*4.2.1.3.**Model Selection***

LASSO regression was employed to build a model that would predict physician recommendation for revaccination. In the primary analysis (AEFI type-3), LASSO regression selected a model that included AEFI type-3 and AEFI impact as the model that best fit the data (Table 9). AEFI type-3 and AEFI impact were significantly associated with a physician recommendation for revaccination while controlling for SIC province ($p < 0.05$).

For the secondary analysis (AEFI type-8), LASSO regression again selected a model containing AEFI type-8 and AEFI impact as the model that best fit the data (Table 10). All levels of AEFI impact were significantly associated with physician

recommendation for revaccination, while of the 8 AEFI types in AEFI type-8, only immediate hypersensitivity and other neurologic AEFI were significantly associated with recommendation for revaccination while controlling for SIC province ($p < 0.05$).

The models selected using LASSO regression for the primary and secondary analyses produced the same AIC statistic of 273.31 and 284.25 (Tables 9 and 10). The c-statistic measuring the AUROC curve was slightly higher in the secondary analysis LASSO model compared to the primary analysis LASSO model (0.83 vs. 0.82) (Figure 6). The model fit statistics indicated that both models fit the data well.

*4.2.1.4.**Sensitivity Analysis***

A sensitivity analysis was conducted to measure the associations between physician recommendation for revaccination and participant demographic and clinical characteristics while controlling for SIC site enrollment. As in the primary (AEFI type-3) and secondary (AEFI type-8) analyses 501 participants received a recommendation for revaccination and 47 participants did not receive a recommendation for revaccination (24 recommended against revaccination and 23 participants with a deferred recommendation for further assessment). LASSO regression was used to select the model with best fit to the data while analyzing AEFI type-3 and AEFI type-8.

As in the primary analysis (AEFI type-3), LASSO regression selected AEFI type-3 and AEFI impact for inclusion in the model with best fit (Table 11). Participants with prior AEFIs generally considered a contraindication for revaccination and participants with prior AEFIs with variable revaccination guidelines had significantly decreased odds of physician recommendation for revaccination compared to participants with prior AEFIs not contraindicated for revaccination while controlling for SIC site enrollment. Participants with prior AEFIs of moderate impact, high impact, and serious AEFIs had significantly decreased odds of physician recommendation for revaccination compared to participants with prior AEFIs of low impact while controlling for SIC site enrollment.

When conducting the secondary analysis (AEFI type-8), the LASSO regression selected AEFI impact for inclusion in the model (Table 12). Participants with AEFIs of moderate impact, high impact, and serious AEFIs had significantly decreased odds of physician recommendation for revaccination compared to participants with AEFIs of low impact while controlling for SIC site enrollment.

4.2.2. Participant Intention for Revaccination

We analyzed 441 participants with an intention regarding revaccination following a physician recommendation for revaccination to identify participant and clinical characteristics associated with participant intention to be revaccinated. Four-hundred and three participants intended to be revaccinated and 38 participants did not intend to be revaccinated at the time of data collection.

4.2.2.1.***Primary Analysis***

Table 13 presents the crude and adjusted OR and 95% CI estimates for participant intention for revaccination by age at vaccination, AEFI type-3, AEFI impact, and vaccine antigen. AEFI impact was the only characteristic significantly associated with participant intention for revaccination. Participants with AEFIs of high impact were significantly less likely to intend to be revaccinated (aOR 0.12 (95% CI: 0.04-0.42) compared to participants with AEFIs of low impact. Age at vaccination, AEFI type-3, and vaccine type were not significantly associated with intent to be revaccinated (Table 13).

4.2.2.2.***Secondary Analysis***

The secondary analysis measured the association between intention to be revaccinated and AEFI type-8 (Table 14). Only “other neurologic AEFI” type was significantly associated with intention to be revaccinated. Participants with other neurologic AEFI were significantly less likely to intend to be revaccinated (aOR: 0.16 [95% CI: 0.04-0.74]) compared to participants with large local reactions.

4.2.2.3. ***Model Selection***

LASSO regression was applied to select the model predicting participant intention to be revaccinated that best fit the data. The primary LASSO regression (AEFI type-3) selected the model including AEFI impact (Table 13). Only AEFI of high impact was significantly associated with participant intention to be revaccinated. Participants with AEFIs of high impact (OR: 0.12 [95% CI: 0.04-0.42]) were significantly less likely to intend to be revaccinated compared to participants with AEFIs of low impact while controlling for SIC province.

The model produced from LASSO regression in the secondary analysis (AEFI type-8) included AEFI impact and vaccine antigen (Table 14). Participants with AEFIs of high impact (OR: 0.12 [95% CI: 0.04-0.41]) significantly were less likely to intend to be revaccinated compared to participants with AEFIs of low impact while controlling for SIC province. Participants vaccinated with a non-influenza vaccine antigen prior to their AEFI were more likely to intend to be revaccinated compared to participants vaccinated with an influenza vaccine while controlling for SIC province (OR: 1.67 [95% CI: 0.71-3.91]).

The model fit statistics suggested similar fit between the LASSO models in the primary and secondary analysis. The primary model produced an AIC of 251.61 and a c-statistic of 0.71 and the secondary model produced an AIC of 252.28 and a c-statistic of 0.72, respectively. Based on the model fit statistics it can be concluded that both models fit the data equally well (Figure 7).

4.2.3. **Assumptions**

The assumption of independent observations was met by ensuring a single prior AEFI and single record of physician recommendation and participant revaccination intention was included in our multivariable analyses. The independent observation

assumption may have been violated if participants were related to each other; however due to the nature of data collection and information captured on participants we were unable to identify and account for familial relations. The inclusion of non-independent observations in our analyses may have led to type I error and the conclusion that we identified an association between the outcome and exposure variables when a true association did not exist.

Multicollinearity was assessed between the covariates to ensure a linear relationship did not exist between variables. The presence of multicollinearity was assessed using tables, VIFs, and tests for linear associations. The tests indicated a possible presence of relationship between age at vaccination and province, and AEFI type and AEFI impact. Both relationships were not surprising. Age at vaccination and province may have been related as certain SIC sites only enrolled pediatric participants while other sites enrolled both pediatric and adult (≥ 18 years of age) participants. AEFI type and AEFI impact could have been related as certain AEFI types, such as neurologic AEFIs and anaphylaxis, may more frequently be reported as AEFIs of high impact or serious AEFIs. The strength of the relationships was assessed using Pearson correlation coefficients which did not indicate a strong presence of multicollinearity.

The 1 in 10 rule was violated in the objective 2 secondary analysis LASSO regression model due to the low number of responses of the outcome *no recommendation for revaccination* and objective 3 multivariable and LASSO regression models due to the low number of responses of the outcome *participant intention against revaccination*. Given the data, we did not have 10 observations per outcome for each variable included in these final multivariable and LASSO regression models. As a result of this violation, we were limited in our ability to identify significant associations between the outcomes and exposure variables.

4.3. Figures and Tables

Table 3. Characteristics of the AEFIs for which participants who required an additional dose of a vaccination associated with the AEFI were assessed at a SIC (N = 627).

	Prior AEFIs N = 627 n (%)
Male gender	306 (49)
Age at vaccination	
<2 years	337 (54)
2-6 years	135 (21)
7-17 years	98 (16)
≥18 years	43 (7)
Missing age	14 (2)
Province	
Nova Scotia	117 (19)
Quebec	182 (29)
Ontario	181 (29)
Saskatchewan	23 (4)
Alberta	48 (8)
British Columbia	76 (12)
Injection site reaction	**140 (22)**
Large local reaction	107 (17)
Cellulitis, infectious	3 (0.4)
Abscess, infectious	1 (0.2)
Abscess, sterile	16 (3)
Nodule	5 (1)
Other *	8 (1)
Allergic-like events	**220 (35)**
Anaphylaxis	38 (6)
Non-anaphylactic immediate hypersensitivity	87 (14)
Delayed onset type I hypersensitivity	89 (14)
Type III/IV hypersensitivity	4 (0.5)
Other †	2 (0.2)
Neurologic AEFIs	**60 (10)**
Seizure	26 (4)
Anaesthesia/Paresthesia	1 (0.1)
Peripheral Neuropathy	2 (0.2)
Encephalitis	1 (0.1)
Myelitis	2 (0.2)
Acute disseminated encephalomyelitis	1 (0.1)
Guillain-Barré Syndrome/ Fisher Miller Syndrome	5 (1)
Other ¶	22 (4)
Other systemic AEFIs	**199 (32)**
Fever	19 (2)
Hypotonic-hyporesponsive episode	22 (4)
Persistent crying	13 (2)
Arthritis/arthralgia	6 (1)
Thrombocytopenia	11 (2)
Immunization-stress related response	17 (3)
Gastrointestinal symptoms	14 (2)
Non-urticarial rash	51 (8)
General symptoms	13 (3)

	Prior AEFIs N = 627 n (%)
Autoimmune disease	10 (1)
Other ‡	23 (4)
Missing	8 (1)
AEFI impact	
Low	201 (32)
Moderate	313 (50)
High	52 (8)
Serious	57 (9)
Missing	4 (1)
AEFI causal association with vaccination	
Consistent	298 (47)
Inconsistent	92 (15)
Indeterminate	205 (33)
Unclassifiable	4 (1)
Missing	28 (4)
Vaccine antigen administered prior to AEFI	
DTaP/Tdap	334 (53)
Hepatitis B	41 (7)
Herpes-Zoster	1 (1)
Hib	0 (0)
HPV	39 (6)
Influenza	126 (20)
Men-B	14 (2)
Men-C	102 (16)
MMR	134 (21)
PCV	198 (32)
Rotavirus	85 (14)
Travel and other°	40 (6)
Varicella	89 (14)

*Non-infectious cellulitis, myositis, granuloma, pustule, small local reaction, non-allergic pruritis
† Papular eruption, severe cutaneous reaction
¶ Developmental regression, rapid eye blinking, stroke, abnormal neuromuscular tonus, optic neuritis, Bell's palsy, paroxysmal tonic upgazing, cerebellitis, hypotonia
‡ unilateral eye swelling, chronic urticaria, improper vaccine administration, glossitis, breath holding spells, aplastic anemia, concomitant illness, neutropenia, stiff neck, osteoma cutis, acute pancreatitis, petechiae
° Includes IPV, OPV, hepatitis A, other meningococcal vaccines, pneu-P-23, BCG, cholera-ETEC, JE, rabies, oral typhoid, injectable typhoid, yellow fever
DTaP/Tdap, diphtheria tetanus acellular pertussis
Hib, Haemophilus influenzae type B
HPV, Human papillomavirus vaccine
Men, Meningococcal
MMR, Measles, mumps, rubella
PCV, pneumococcal vaccine

Table 4. Characteristics of prior AEFIs for which participants, who required an additional dose of a vaccination associated with the prior AEFI, were assessed at a SIC by AEFI category (N = 619) *.

	Injection site reaction N = 140 n (%)	**Allergic like event** N = 220 n (%)	**Neurologic AEFIs** N = 60 n (%)	**Other systemic AEFIs** N = 199 n (%)
Male gender	74 (53)	107 (49)	29 (48)	90 (45)
Age at vaccination				
<2 years	50 (35)	116 (53)	44 (74)	122 (62)
2-6 years	59 (41)	42 (19)	5 (8)	29 (15)
7-17 years	25 (18)	35 (16)	8 (13)	30 (15)
≥18 years	6 (4)	23 (10)	2 (3)	9 (4)
Missing age	0 (0)	4 (2)	1 (2)	9 (4)
Interval of time between vaccination and AEFI onset, median hours (IQR)	15 (8-24)	2 (0.17-12)	24 (6-168)	7 (1-36)
AEFI impact				
Low	36 (26)	86 (39)	6 (10)	73 (37)
Moderate	87 (62)	122 (55)	18 (30)	80 (40)
High	11 (8)	10 (5)	14 (23)	16 (8)
Serious	5 (3)	2 (1)	22 (37)	28 (14)
Missing	1 (1)	0 (0)	0 (0)	2 (1)
AEFI causal association with vaccination	118 (85)	96 (44)	9 (15)	72 (37)
Consistent	9 (6)	33 (15)	16 (27)	33 (16)
Inconsistent	9 (6)	84 (38)	31 (52)	81 (41)
Indeterminate	1 (1)	0 (0)	2 (3)	1 (1)
Unclassifiable	3 (2)	7 (3)	2 (3)	11 (5)
Missing				
Vaccine antigen administered prior to AEFI				
DTaP/Tdap	61 (43)	114 (52)	38 (63)	117 (59)
Hepatitis B	6 (4)	15 (7)	5 (8)	15 (8)
Herpes-Zoster	0 (0)	0 (0)	0 (0)	0 (0)
Hib	0 (0)	0 (0)	0 (0)	0 (0)
HPV	7 (5)	17 (8)	1 (2)	14 (7)
Influenza	53 (38)	45 (20)	6 (10)	21 (10)
Men-B	0 (0)	3 (1)	2 (3)	9 (5)
Men-C	10 (7)	41 (19)	9 (15)	41 (21)
MMR	22 (16)	57 (26)	13 (22)	41 (21)
PCV	17 (12)	61 (28)	26 (43)	92 (46)
Rotavirus	5 (4)	29 (13)	8 (13)	41 (21)
Travel and other°	9 (6)	11 (5)	0 (0)	0 (0)
Varicella	13 (9)	36 (16)	11 (18)	28 (14)
Allergy skin testing	N = 13	N = 98	N = 0	N = 36
Any positive test	5 (38)	28 (29)		3 (8)
Negative test	8 (62)	70 (71)		33 (92)

*8 AEFI occurrences with missing AEFI types not included

° Includes IPV, OPV, hepatitis A, other meningococcal vaccines, pneu-P-23, BCG, cholera-ETEC, JE, rabies, oral typhoid, injectable typhoid, yellow fever
DTaP/Tdap, diphtheria tetanus acellular pertussis
Hib, Haemophilus influenzae type B
HPV, Human papillomavirus vaccine
Men, Meningococcal
MMR, Measles, mumps, rubella
PCV, pneumococcal vaccine

Table 5. Characteristics of participants with a prior AEFI who required an additional dose of the same vaccine and received a recommendation regarding revaccination (N = 560)*.

	Recommended for revaccination	Not recommended for revaccination	
	Vaccination recommended N = 513 (%)	**Vaccination not recommended** N = 24 (%)	**Recommend-ation deferred** N = 23 (%)
Gender			
Female	270 (53)	9 (38)	11 (48)
Male	243 (47)	15 (63)	12 (52)
Age at vaccination			
< 2 years	280 (55)	9 (38)	12 (52)
2-6 years	107 (21)	9 (38)	6 (26)
7-17 years	82 (16)	5 (21)	4 (17)
≥ 18 years	32 (6)	1 (4)	1 (4)
Missing	12 (2)	0 (0)	0 (0)
Province			
Nova Scotia	100 (20)	2 (8)	1 (4)
Quebec	154 (30)	7 (29)	3 (13)
Ontario	151 (29)	7 (29)	8 (35)
Saskatchewan	22 (4)	0 (0)	0 (0)
Alberta	27 (5)	6 (25)	4 (17)
British Columbia	59 (12)	2 (8)	7 (30)
AEFI Type-3‡			
AEFIs not contraindicated for revaccination	332 (65)	7 (29)	4 (17)
AEFIs contraindicated for revaccination	14 (3)	7 (29)	2 (9)
AEFIs with variable revaccination guidelines	167 (33)	10 (42)	17 (74)
AEFI Type-8¢			
Large local reactions	89 (17)	2 (8)	2 (9)
Other injection site reactions	24 (5)	1 (4)	0 (0)
Immediate HS reactions	100 (19)	9 (36)	11 (48)
Delayed HS reactions and other allergic-like events	84 (16)	1 (4)	3 (13)
Seizure	21 (4)	1 (4)	0 (0)
Other neurologic AEFIs	23 (4)	5 (21)	3 (13)
Autoimmune diseases	15 (3)	2 (8)	3 (13)
Other systemic events	157 (31)	3 (3)	1 (4)
AEFI impact			
Low	178 (35)	2 (8)	2 (9)
Moderate	254 (49)	10 (42)	15 (65)
High	38 (7)	6 (25)	3 (13)
Serious	42 (8)	6 (25)	3 (13)
Missing	1 (1)	0 (0)	0 (0)
AEFI causal association with vaccination			

	Vaccination recommended N = 513 (%)	Vaccination not recommended N = 24 (%)	Recommend-ation deferred N = 23 (%)
Consistent	232 (45)	13 (54)	17 (74)
Inconsistent	80 (16)	2 (8)	1 (4)
Indeterminate	182 (36)	8 (33)	3 (13)
Unclassifiable	3 (1)	1 (4)	0 (0)
Missing	16 (3)	0 (0)	2 (9)
Vaccine antigen administered prior to AEFI			
DTaP/Tdap	275 (54)	11 (46)	13 (57)
Hepatitis B	35 (7)	2 (8)	2 (9)
Herpes-Zoster	0 (0)	0 (0)	0 (0)
Hib	0 (0)	0 (0)	0 (0)
HPV	35 (7)	1 (4)	2 (9)
Influenza	100 (20)	7 (29)	4 (17)
Men-B	14 (3)	0 (0)	0 (0)
Men-C	83 (17)	6 (25)	5 (22)
MMR	105 (21)	7 (29)	8 (35)
PCV	166 (33)	5 (21)	7 (30)
Rotavirus	74 (15)	1 (4)	1 (4)
Travel and other°	31 (6)	1 (4)	1 (4)
Varicella	70 (13)	4 (17)	5 (22)
Allergy skin testing			
Tests	N = 126	N = 10	N = 8
Any positive result	22 (17)	9 (90)	4 (50)
All negative results	104 (83)	1 (10)	4 (50)

*The sample includes participants with a recommendation after one AEFI. For participants with multiple AEFIs only one AEFI was included in table per section 3.2. The same AEFI was included in the multivariable analysis.

° Includes IPV, OPV, hepatitis A, other meningococcal vaccines, pneu-P-23, BCG, cholera-ETEC, JE, rabies, oral typhoid, injectable typhoid, yellow fever

‡AEFI type-3, 32 levels of AEFI type categorized into 3 levels based on SIC Network, provincial, and national revaccination management guidelines.

ᵠAEFI type-8, 32 levels of AEFI type categorized into 8 levels of common AEFI types.

HS, hypersensitivity

DTaP/Tdap, diphtheria tetanus acellular pertussis

Hib, Haemophilus influenzae type B

HPV, Human papillomavirus vaccine

Men, Meningococcal

MMR, Measles, mumps, rubella

PCV, pneumococcal vaccine

Table 6. Characteristics of participants recommended for revaccination who provided an intention regarding revaccination (N = 466)*.

	Participant intended to be revaccinated following recommendation for revaccination			Participant did not intend to be revaccinated following recommendation for revaccination	
	Intended to be revaccinated at SIC N = 305 (%)	**Intended to be revaccinated by GP/PH** N = 106 (%)	**Intended to return to SIC for revaccination** N = 15 (%)	**Intended to delay revaccin-ation** N = 29 (%)	**Intended to refuse revaccin-ation** N = 11 (%)
Gender					
Female	158 (52)	55 (52)	8 (53)	20 (69)	6 (55)
Male	147 (48)	51 (48)	7 (47)	9 (31)	5 (45)
Age at vaccination					
<2 years	180 (59)	53 (50)	7 (47)	13 (45)	6 (55)
2-6 years	54 (17)	25 (23)	2 (13)	7 (24)	1 (9)
7-17 years	45 (15)	19 (18)	4 (27)	6 (21)	3 (27)
≥18 years	24 (8)	3 (3)	2 (13)	2 (7)	1 (9)
Missing	2 (1)	6 (5)	0 (0)	1 (3)	0 (0)
Province					
Nova Scotia	50 (16)	29 (27)	4 (27)	2 (7)	7 (64)
Quebec	126 (41)	16 (15)	0 (0)	6 (21)	1 (9)
Ontario	61 (20)	42 (40)	9 (61)	15 (52)	3 (27)
Saskatchewan	18 (6)	3 (3)	0 (0)	0 (0)	0 (0)
Alberta	9 (3)	13 (12)	1 (6)	1 (3)	0 (0)
British Columbia	41 (13)	3 (3)	1 (6)	5 (17)	0 (0)
AEFI Type-3‡					
AEFIs not contraindicated for revaccination	193 (63)	80 (75)	3 (20)	15 (52)	7 (64)
AEFIs contraindicated for revaccination	8 (3)	2 (2)	1 (7)	1 (3)	0 (0)
AEFIs with variable revaccination guidelines	104 (34)	24 (23)	11 (73)	3 (45)	4 (36)
AEFI Type-8¢					
Large local reactions	44 (14)	25 (24)	1 (7)	3 (10)	2 (18)
Other injection site reactions	10 (3)	7 (7)	0 (0)	1 (3)	0 (0)
Immediate HS reactions	78 (26)	7 (7)	4 (27)	7 (24)	1 (9)
Delayed HS reactions and other allergic-like events	55 (18)	14 (13)	7 (47)	3 (10)	1 (9)
Seizure	10 (3)	7 (7)	0 (0)	1 (11)	2 (18)
Other neurologic AEFIs	9 (3)	4 (4)	1 (7)	2 (7)	2 (18)
Autoimmune diseases	6 (2)	4 (4)	1 (7)	3 (10)	0 (0)
Other systemic events	93 (31)	38 (36)	1 (7)	9 (31)	3 (27)

	Intended to be revaccinated at SIC N = 305 (%)	Intended to be revaccinated by GP/PH N = 106 (%)	Intended to return to SIC for revaccination N = 15 (%)	Intended to delay revaccin-ation N = 29 (%)	Intended to refuse revaccin-ation N = 11 (%)
AEFI impact					
Low	122 (40)	33 (31)	2 (13)	7 (21)	0 (0)
Moderate	145 (47)	52 (49)	10 (67)	14 (50)	7 (64)
High	16 (5)	9 (9)	2 (13)	5 (18)	3 (27)
Serious	22 (7)	11 (10)	1 (6)	3 (11)	1 (9)
Missing	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
AEFI causal association with vaccination					
Consistent	131 (42)	51 (49)	5 (33)	15 (52)	3 (27)
Inconsistent	41 (14)	19 (17)	2 (13)	6 (21)	3 (27)
Indeterminate	122 (40)	31 (29)	8 (54)	5 (17)	5 (45)
Unclassifiable	2 (1)	1 (1)	0 (0)	0 (0)	0 (0)
Missing	9 (3)	4 (4)	0 (0)	3 (10)	0 (0)
Vaccine antigen administered prior to AEFI					
DTaP/Tdap	168 (55)	48 (45)	9 (60)	17 (59)	4 (36)
Hepatitis B	23 (8)	6 (6)	2 (13)	0 (0)	1 (9)
Herpes-Zoster	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Hib	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
HPV	20 (7)	7 (7)	4 (27)	2 (7)	0 (0)
Influenza	59 (19)	21 (20)	2 (13)	4 (14)	5 (45)
Men-B	6 (2)	5 (5)	0 (0)	1 (3)	0 (0)
Men-C	56 (18)	18 (17)	1 (7)	1 (3)	1 (9)
MMR	63 (21)	25 (24)	0 (0)	5 (17)	1 (9)
PCV	108 (35)	38 (36)	3 (20)	7 (24)	4 (36)
Rotavirus	59 (19)	12 (11)	1 (7)	0 (0)	1 (9)
Travel and other°	19 (6)	5 (5)	0 (0)	4 (14)	0 (0)
Varicella	37 (12)	19 (18)	0 (0)	2 (7)	1 (9)
Allergy skin testing	N = 97	N = 10	N = 4	N = 6	N = 2
Any positive result	19 (20)	0 (0)	0 (0)	2 (33)	0 (0)
All negative results	78 (80)	10 (100)	4 (100)	4 (66)	2 (100)

*The sample includes 466 participants with an intention per one AEFI. For participants with multiple AEFIs only one was included in table per section 3.2. The same AEFI was included in the multivariable analysis.
‡AEFI type-3, 32 levels of AEFI type categorized into 3 levels based on SIC Network, provincial, and national revaccination management guidelines.
ᵋAEFI type-8, 32 levels of AEFI type categorized into 8 levels of common AEFI types.
° Includes IPV, OPV, hepatitis A, other meningococcal vaccines, pneu-P-23, BCG, cholera-ETEC, JE, rabies, oral typhoid, injectable typhoid, yellow fever
HS, hypersensitivity
DTaP/Tdap, diphtheria tetanus acellular pertussis
Hib, Haemophilus influenzae type B
HPV, Human papillomavirus vaccine
Men, Meningococcal

MMR, Measles, mumps, rubella
PCV, pneumococcal vaccine

Table 7. Characteristics of participants with and without a record of revaccination due for revaccination during the study period (N = 477).

	Record of revaccination N = 299 (%)	**No record of revaccination** N = 178 (%)
Gender		
Female	153 (51)	99 (56)
Male	146 (49)	79 (44)
Age at vaccination		
< 2 years	178 (60)	89 (50)
2-6 years	51 (17)	40 (22)
7-17 years	47 (16)	30 (17)
≥ 18 years	21 (7)	11 (6)
Missing	2 (1)	8 (5)
Province		
Nova Scotia	62 (21)	31 (17)
Quebec	119 (40)	31 (17)
Ontario	50 (17)	86 (48)
Saskatchewan	19 (6)	2 (1)
Alberta	15 (5)	12 (7)
British Columbia	34 (11)	16 (9)
AEFI Type		
Injection site reactions	**58 (20)**	**37 (20)**
Large local reaction	48 (16)	28 (16)
Cellulitis, infectious	0 (0)	1 (1)
Abscess, infectious	1 (1)	0 (0)
Abscess, sterile	6 (2)	3 (2)
Nodule	0 (0)	3 (2)
Other*	3 (1)	2 (1)
Allergic-like events	**127 (42)**	**51 (29)**
Anaphylaxis	11 (4)	9 (5)
Non-anaphylactic immediate HS	57 (19)	19 (11)
Delayed onset type I HS	55 (18)	21 (12)
Type III or IV HS	2 (1)	2 (1)
Other†	2 (1)	0 (0)
Neurologic AEFIs	**21 (7)**	**21 (12)**
Seizure	13 (4)	8 (5)
Peripheral Neuropathy	0 (0)	1 (1)
Encephalitis	0 (0)	1 (1)
Myelitis	1 (1)	1 (1)
GBS/FMS	1 (1)	1 (1)
Other¶	6 (2)	9 (5)
Other systemic AEFIs	**93 (31)**	**69 (39)**
Fever	7 (2)	7 (4)
HHE	14 (5)	6 (3)
Persistent crying	4 (1)	8 (5)
Arthritis/arthralgia	1 (1)	5 (3)
Thrombocytopenia	4 (1)	2 (2)
ISRR	10 (3)	6 (3)
Gastrointestinal symptoms	4 (1)	4 (3)
Non-urticarial rash	32 (11)	14 (8)
General symptoms	3 (1)	5 (3)
Autoimmune disorder	3 (1)	5 (3)
Other‡	11 (4)	7 (4)
AEFI impact		

	Record of revaccination N = 299 (%)	No record of revaccination N = 178 (%)
Low	123 (41)	45 (25)
Moderate	138 (46)	94 (53)
High	18 (6)	18 (10)
Serious	19 (6)	21 (12)
Missing	1 (1)	0 (0)
AEFI causal association with vaccination		
Consistent	130 (43)	80 (45)
Inconsistent	45 (15)	28 (16)
Indeterminate	114 (38)	61 (34)
Unclassifiable	2 (1)	1 (1)
Missing	8 (3)	8 (5)
Vaccine antigen administered prior to AEFI		
DTaP/Tdap	166 (56)	89 (50)
Hepatitis B	27 (9)	6 (3)
Herpes-Zoster	0 (0)	0 (0)
Hib	0 (0)	0 (0)
HPV	25 (8)	8 (5)
Influenza	64 (21)	29 (16)
Men-B	7 (2)	5 (3)
Men-C	55 (18)	23 (13)
MMR	61 (20)	34 (19)
PCV	119 (40)	43 (24)
Rotavirus	61 (20)	13 (7)
Travel and other°	11 (4)	18 (10)
Varicella	35 (12)	26 (15)
Allergy skin testing		
	N = 90	N = 29
Any positive result	15 (17)	6 (21)
All negative results	75 (83)	23 (79)

[*]Myositis, granuloma, small local reaction, non-allergic pruritis

[†] Papular eruption

[¶] Developmental regression, abnormal neuromuscular tonus, Bell's palsy, paroxysmal tonic upgazing, hypotonia

[‡] Eye swelling, chronic urticaria, glossitis, breath holding spells, concomitant illness, neutropenia, stiff neck, osteoma cutis, petechiae, viral infection

[ø] One participant with a prior other allergic-like event did not provide an intention despite receiving a recommendation for revaccination and having a record of revaccination.

° Includes IPV, OPV, hepatitis A, other meningococcal vaccines, pneu-P-23, BCG, cholera-ETEC, JE, rabies, oral typhoid, injectable typhoid, yellow fever

HS, hypersensitivity

ADEM, acute disseminated encephalomyelitis

GBS/FMS, Guillain-Barré Syndrome/Fisher Miller Syndrome

HHE, hypotonic-hyporesponsive episode

ISRR, immunization-stress related response

DTaP/Tdap, diphtheria tetanus acellular pertussis

Hib, Haemophilus influenzae type B

HPV, Human papillomavirus vaccine

Men, Meningococcal

MMR, Measles, mumps, rubella

PCV, pneumococcal vaccine

Table 8. Characteristics of participants with and without AEFI recurrence after revaccination (N = 298).[œ]

	AEFI recurrence N = 31 (%)	**No AEFI recurrence**[Ω] N = 267 (%)
Gender		
Female	21 (68)	132 (49)
Male	10 (32)	135 (51)
Age at vaccination		
<2 years	12 (39)	165 (61)
2-6 years	8 (26)	43 (16)
7-17 years	8 (26)	39 (15)
≥18 years	3 (9)	18 (7)
Missing	0 (0)	2 (1)
SIC province		
Nova Scotia	8 (26)	54 (20)
Quebec	14 (45)	105 (39)
Ontario	5 (17)	44 (17)
Saskatchewan	1 (3)	18 (7)
Alberta	1 (3)	14 (5)
British Columbia	2 (6)	32 (12)
AEFI Type		
Injection site reactions	**16 (52)**	**42 (16)**
Large local reaction	14 (45)	34 (13)
Cellulitis, infectious	0 (0)	0 (0)
Abscess, infectious	0 (0)	1 (0.4)
Abscess, sterile	1 (3)	5 (2)
Nodule	0 (0)	0 (0)
Other[*]	1 (3)	2 (1)
Allergic-like events	**10 (32)**	**117 (44)**
Anaphylaxis	1 (3)	10 (4)
Non-anaphylactic immediate HS	4 (12)	53 (19)
Delayed onset type I HS	5 (16)	50 (18)
Type III or IV delayed HS	0 (0)	2 (1)
Other[†]	0 (0)	2 (1)
Neurologic AEFI	**1 (3)**	**20 (7)**
Seizure	1 (3)	12 (5)
Anaesthesia/ Paranesthesia	0 (0)	0 (0)
Peripheral Neuropathy	0 (0)	0 (0)
Encephalitis	0 (0)	0 (0)
Myelitis	0 (0)	1 (0.4)
ADEM	0 (0)	0 (0)
GBS/FMS	0 (0)	1 (0.4)
Other[¶]	0 (0)	6 (2)
Other systemic AEFI	**4 (13)**	**88 (33)**
Fever	1 (3)	6 (2)
HHE	0 (0)	14 (5)
Persistent crying	0 (0)	3 (1)
Arthritis/arthralgia	0 (0)	1 (0.4)
Thrombocytopenia	0 (0)	4 (1)
ISRR	0 (0)	10 (4)
Gastrointestinal symptoms	0 (0)	4 (1)
Non-urticarial rash	3 (10)	29 (11)
General symptoms	0 (0)	3 (1)
Autoimmune disorder	0 (0)	3 (1)

	AEFI recurrence N = 31 (%)	No AEFI recurrence[Ω] N = 267 (%)
Other[‡]	0 (0)	11 (4)
Severity relative to prior AEFI		
Less severe	22 (71)	---
Same severity	4 (13)	---
More severe	4 (13)	---
Missing	1 (3)	
AEFI causal association with vaccination		
Consistent	21 (68)	109 (40)
Inconsistent	4 (13)	40 (15)
Indeterminate	4 (13)	110 (42)
Unclassifiable	0 (0)	2 (1)
Missing	2 (6)	6 (2)
Vaccine antigen administered prior to AEFI		
DTaP/Tdap	10 (32)	155 (58)
Hepatitis B	4 (13)	23 (8)
Herpes-Zoster	0 (0)	0 (0)
Hib	0 (0)	0 (0)
HPV	5 (16)	20 (7)
Influenza	13 (42)	51 (19)
Men-B	0 (0)	7 (3)
Men-C	5 (16)	50 (18)
MMR	6 (19)	55 (20)
PCV	6 (19)	112 (42)
Rotavirus	1 (3)	59 (22)
Travel and other°	1 (3)	10 (4)
Varicella	3 (10)	32 (12)
Allergy skin testing	**8**	**82**
Any positive result	5 (63)	10 (12)
All negative results	3 (27)	72 (88)

[œ]One participant with a record of revaccination was excluded from the recurrence analysis as they did not have data on AEFI recurrence.

[Ω] No AEFI recurrence reported among participants with a record of revaccination and data on AEFI recurrence

[*]Myositis, granuloma, non-allergic pruritis

[¶] Abnormal neuromuscular tonus, paroxysmal tonic upgazing, hypotonia

[‡] Unilateral eye swelling, breath holding spells, concomitant illness, stiff neck, osteoma cutis, petechiae

° Includes IPV, OPV, hepatitis A, other meningococcal vaccines, pneu-P-23, BCG, cholera-ETEC, JE, rabies, oral typhoid, injectable typhoid, yellow fever

HS, hypersensitivity

ADEM, acute disseminated encephalomyelitis

GBS/FMS, Guillain-Barré Syndrome/Fisher Miller Syndrome

HHE, hypotonic-hyporesponsive episode

ISRR, immunization-stress related response

DTaP/Tdap, diphtheria tetanus acellular pertussis

Hib, Haemophilus influenzae type B

HPV, Human papillomavirus vaccine

Men, Meningococcal

MMR, Measles, mumps, rubella

PCV, pneumococcal vaccine

Table 9. Crude, adjusted, and LASSO adjusted ORs and 95% CI of recommendation for revaccination by age at vaccination, AEFI impact, and AEFI type-3 among 548 participants with a recommendation regarding revaccination following assessment at a SIC for a prior AEFI.

	Crude OR (95% CI)	**SIC province adjusted OR† (95% CI)**	**LASSO adjusted OR° (95% CI)**
Age at vaccination			
<2 years	Reference	Reference	---
2-6 years	0.53 (0.26-1.07)	0.49 (0.24-1.01)	---
7-17 years	0.68 (0.30-1.55)	0.71 (0.31-1.64)	---
≥18 years	1.20 (0.27-5.36)	0.83 (0.18-3.91)	---
AEFI impact			
Low	Reference	Reference	Reference
Moderate	0.24 (0.08-0.69) *	0.21 (0.07-0.65) *	0.28 (0.09-0.86) *
High	0.10 (0.03-0.33) *	0.08 (0.02-0.30) *	0.10 (0.03-0.36) *
Serious	0.11 (0.03-0.37) *	0.11 (0.03-0.37) *	0.13 (0.04-0.50) *
AEFI type-3			
AEFIs not contraindicated for revaccination	Reference	Reference	Reference
AEFIs contraindicated for revaccination	0.05 (0.02-0.15) *	0.05 (0.02-0.14) *	0.06 (0.02-0.17) *
AEFIs with variable revaccination guidelines	0.21 (0.10-0.42) *	0.20 (0.10-0.42) *	0.21 (0.10-0.50) *
C-statistic	---	---	0.82
AIC	---	---	273.31

* Values are statistically significant ($p < 0.05$).

†Adjusted ORs and 95% CIs controlling for SIC province

° Variables selected as having the best fit to predict recommendation for revaccination through LASSO regression while adjusting for SIC province.

Table 10. Crude, adjusted, and LASSO adjusted ORs and 95% CI of recommendation for revaccination by age at vaccination, AEFI impact, and AEFI type-8 among 548 participants with a recommendation regarding revaccination following assessment at a SIC for a prior AEFI.

	Crude OR (95% CI)	**SIC province adjusted OR[†] (95% CI)**	**LASSO Adjusted OR° (95% CI)**
Age at vaccination			
<2 years	Reference	Reference	---
2-6 years	0.53 (0.26-1.07)	0.49 (0.24-1.01)	---
7-17 years	0.68 (0.30-1.55)	0.71 (0.31-1.64)	---
≥18 years	1.20 (0.27-5.36)	0.83 (0.18-3.91)	---
AEFI type-8			
Large local reaction	Reference	Reference	Reference
Other injection site reaction	1.07 (0.11-9.99)	1.39 (0.15-13.13)	1.92 (0.19-19.21)
Immediate hypersensitivity	0.22 (0.07-0.66) *	0.23 (0.07-0.71) *	0.21 (0.07-0.67) *
Delayed hypersensitivity reactions	0.92 (0.22-3.81)	1.01 (0.24-4.32)	0.95 (0.22-4.09)
Seizure	0.93 (0.10-8.79)	1.09 (0.11-10.48)	2.36 (0.22-25.08)
Other neurologic AEFI	0.13 (0.04-0.46) *	0.12 (0.03-0.44) *	0.22 (0.05-0.94) *
Autoimmune disease	0.13 (0.03-0.55) *	0.16 (0.04-0.69) *	0.34 (0.07-1.75)
Other systemic AEFI	1.64 (0.40-6.74)	1.69 (0.41-7.00)	1.90 (0.44-8.16)
AEFI impact			
Low	Reference	Reference	Reference
Moderate	0.24 (0.08-0.69) *	0.21 (0.07-0.65) *	0.21 (0.07-0.63) *
High	0.10 (0.03-0.33) *	0.08 (0.02-0.30) *	0.08 (0.02-0.33) *
Serious	0.11 (0.03-0.37) *	0.11 (0.03-0.37) *	0.09 (0.02-0.40) *
C-statistic	---	---	0.83
AIC	---	---	284.25

* Values are statistically significant ($p < 0.05$).

[†]Adjusted ORs and 95% CIs controlling for SIC province.

° Variables selected as having the best fit to predict recommendation for revaccination through LASSO regression while adjusting for SIC province.

Table 11. LASSO adjusted ORs and 95% CI of recommendation for revaccination by age at vaccination (not selected for model inclusion), AEFI impact, and AEFI type-3 controlling for SIC site enrollment among 548 participants with a recommendation regarding revaccination following assessment at a SIC for a prior AEFI.

	LASSO adjusted OR (95% CI)°
AEFI type-3	
AEFIs not contraindicated for revaccination	Reference
AEFIs contraindicated for revaccination	0.06 (0.02-0.18) *
AEFIs with variable revaccination guidelines	0.20 (0.09-0.43) *
AEFI impact	
Low	Reference
Moderate	0.26 (0.08- 0.78) *
High	0.11 (0.03- 0.40) *
Serious	0.11 (0.03- 0.42) *
C-statistic	0.84
AIC	259.96

* Values are statistically significant ($p < 0.05$).
° Variables selected as having the best fit to predict recommendation for revaccination through LASSO regression while adjusting for SIC site enrollment.

Table 12. LASSO adjusted ORs and 95% CI of recommendation for revaccination by age at vaccination (not selected for model inclusion), AEFI impact, and AEFI type-8 (not selected for model inclusion) controlling for SIC site enrollment among 548 participants with a recommendation regarding revaccination following assessment at a SIC for a prior AEFI.

	LASSO adjusted OR (95% CI)°
AEFI impact	
Low	Reference
Moderate	0.22 (0.07-0.64) *
High	0.09 (0.03-0.30) *
Serious	0.10 (0.03-0.35) *
C-statistic	0.75
AIC	288.93

* Values are statistically significant ($p < 0.05$).
° Variables selected as having the best fit to predict recommendation for revaccination through LASSO regression while adjusting for SIC site enrollment.

Table 13. Crude, adjusted, and LASSO adjusted ORs and 95% CI of intention to be revaccinated by age at vaccination, AEFI impact, AEFI type-3, and vaccine antigen among 441 participants with a recommendation regarding revaccination following assessment at a SIC for a prior AEFI.

	Crude OR (95% CI)	SIC province adjusted OR (95% CI)[†]	LASSO adjusted OR° (95% CI)
Age at vaccination			
<2 years	Reference	Reference	---
2-6 years	0.93 (0.38-2.30)	1.12 (0.45-2.82)	---
7-17 years	0.61 (0.26-1.40)	0.67 (0.28-1.60)	---
≥18 years	0.74 (0.21-2.67)	0.55 (0.14-2.11)	---
AEFI impact			
Low	Reference	Reference	Reference
Moderate	0.36 (0.14-0.92) *	0.43 (0.16-1.12)	0.43 (0.16-1.12)
High	0.12 (0.04-0.39) *	0.12 (0.04-0.42) *	0.12 (0.04-0.42) *
Serious	0.43 (0.10-1.83)	0.57 (0.13-2.47)	0.56 (0.13-2.47)
AEFI type-3			
AEFIs not contraindicated for revaccination	Reference	Reference	---
AEFIs with variable revaccination guidelines	0.62 (0.32-1.22)	0.55 (0.28-1.10)	---
Vaccine antigen			
Influenza vaccines	Reference	Reference	---
Non-influenza vaccines	1.61 (0.73-3.56)	1.52 (0.67-3.47)	---
C-statistic	---	---	0.71
AIC	---	---	251.60

[*] Values are statistically significant ($p < 0.05$).

[†]Adjusted ORs and 95% CIs controlling for SIC province.

° Variables selected as having the best fit to predict recommendation for revaccination through LASSO regression while adjusting for SIC province.

Table 14. Crude, adjusted, and LASSO adjusted ORs and 95% CI of intention to be revaccinated by age at vaccination, AEFI impact, AEFI type-8, and vaccine antigen among 441 participants with a recommendation regarding revaccination following assessment at a SIC for a prior AEFI.

	Crude OR (95% CI)	SIC province adjusted OR (95% CI)[†]	LASSO adjusted OR° (95% CI)
Age at vaccination			
<2 years	Reference	Reference	---
2-6 years	0.93 (0.38-2.30)	1.12 (0.45-2.82)	---
7-17 years	0.61 (0.26-1.40)	0.67 (0.28-1.60)	---
≥18 years	0.74 (0.21-2.67)	0.55 (0.14-2.11)	---
AEFI impact			
Low	Reference	Reference	Reference
Moderate	0.36 (0.14-0.92) *	0.43 (0.16-1.12)	0.43 (0.16-1.13)
High	0.12 (0.04-0.39) *	0.12 (0.04-0.42) *	0.12 (0.04-0.41) *
Serious	0.43 (0.10-1.83)	0.57 (0.13-2.47)	0.55 (0.13-2.42)
AEFI type-8			
Large local reactions	Reference	Reference	---
Other injection site reactions	1.20 (0.13-10.62)	1.12 (0.12-10.53)	---
Immediate hypersensitivity reactions	0.83 (0.25-2.73)	0.66 (0.20-2.22)	---
Delayed hypersensitivity reactions	1.30 (0.34-5.10)	0.91 (0.23-3.66)	---
Seizure	0.41 (0.09-1.90)	0.39 (0.08-1.86)	---
Other neurologic AEFIs	0.22 (0.05-0.93) *	0.16 (0.04-0.74) *	---
Autoimmune diseases	0.27 (0.06-1.27)	0.21 (0.04-1.06)	---
Other systemic events	0.83 (0.2782.49)	0.71 (0.23-2.20)	---
Vaccine antigen			
Influenza vaccines	Reference	Reference	Reference
Non-influenza vaccines	1.61 (0.73-3.56)	1.52 (0.67-3.47)	1.67 (0.71-3.91)
C-statistic	---	---	0.72
AIC	---	---	252.28

* Values are statistically significant ($p < 0.05$).

[†]Adjusted ORs and 95% CIs controlling for SIC province.

° Variables selected as having the best fit to predict recommendation for revaccination through LASSO regression while adjusting for SIC province.

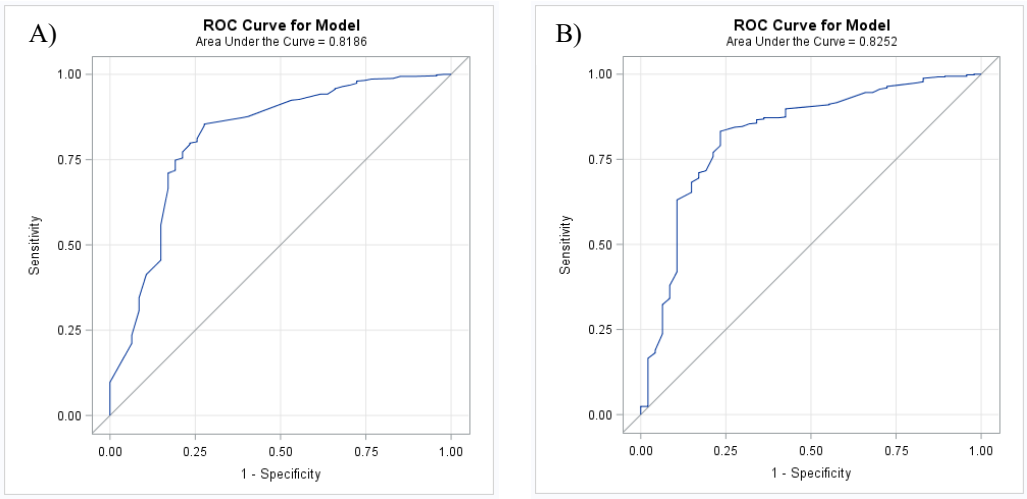

Figure 6. Receiver operating characteristics curve and area under the receiver operating characteristics curve of primary (A) (AEFI type-3) and secondary (B) (AEFI type-8) analysis LASSO selected models to predict recommendation for revaccination.

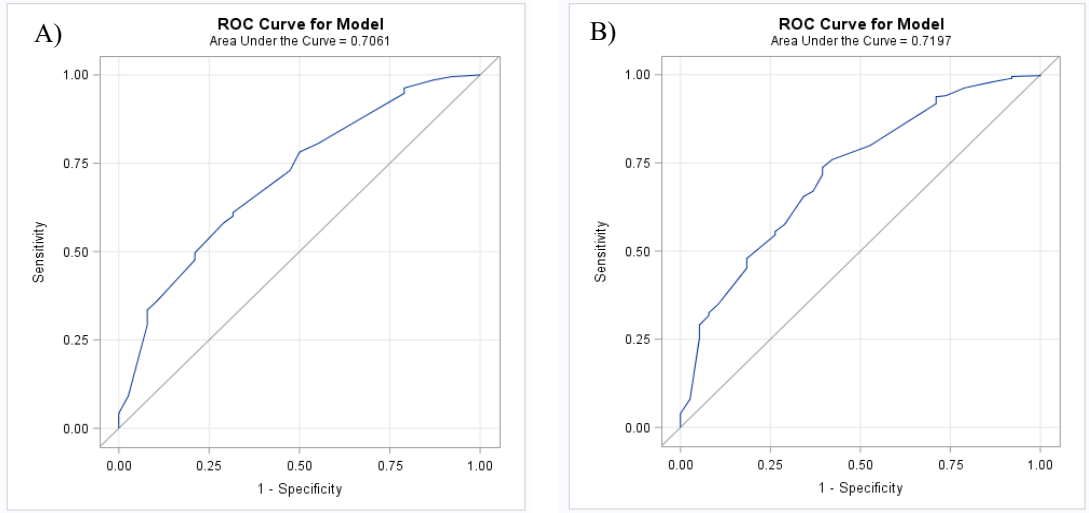

Figure 7. Receiver operating characteristics curve and area under the receiver operating characteristics curve of primary (A) (AEFI type-3) and secondary (B) (AEFI type-8) analysis LASSO selected models to predict participant intention to be revaccinated.

5. Chapter 5: Discussion

5.1. Summary of Results

This analysis described and identified factors associated with physician recommendation for revaccination and with participants' intention to be revaccinated among participants assessed in the SIC Network for an AEFI from 2013 to 2019. We described the demographic and clinical characteristics of 588 participants assessed for AEFIs in the SIC Network who required revaccination. The most common AEFIs reported were large local reactions, non-anaphylactic immediate hypersensitivity reactions, and delayed onset type I hypersensitivity reactions. Most AEFIs were of low or moderate impact though 8% were of high impact and 9% were serious AEFIs. The vaccines most frequently administered prior to AEFI onset were DTaP/Tdap, PCV, MMR and influenza vaccines. Revaccination was recommended in 92% of participants, not recommended in 4% of participants, and the recommendation was deferred pending further assessment in 4% of participants. We identified an association between physician recommendation for revaccination and both AEFI type and AEFI impact on daily activities and need for medical care. Among participants recommended for revaccination, 7% were not yet due for revaccination during the study period, 83% intended to be revaccinated and 8% intended not to be revaccinated. Patient intention for revaccination was only associated with AEFI impact, specifically having an AEFI of high impact versus a low impact AEFI. Among the 477 participants recommended for revaccination and due for revaccination during the study period, 299 (63%) had a record of revaccination. Of these 299 participants, 31 (10%) participants experienced AEFI recurrence.

5.2. Physician Recommendation for Revaccination

The results suggest physicians may have used information about AEFI type and AEFI impact when making revaccination recommendations. SIC physicians were less likely to recommend revaccination with AEFI types contraindicated for revaccination based on

SIC Network, provincial, and national guidelines[57,84–89] (e.g., anaphylaxis, Guillain-Barré syndrome), and those AEFI types with variable revaccination guidelines[57,84–89] (e.g., autoimmune disorders, non-anaphylactic hypersensitivity reactions). However, a small number of participants did receive recommendations not consistent with SIC Network, provincial, and national guidelines as revaccination was recommended to a few participants with anaphylaxis and positive allergy skin test results and a recommendation against revaccination was given to a few participants with prior large local reactions and fever. Studies from special immunization clinics in Italy, the UK, and Australia also reported recommending revaccination to some patients with prior anaphylaxis and neurologic AEFIs, though most patients with such AEFIs were advised against revaccination.[67,68,71,97]

SIC physicians were also less likely to recommend revaccination to participants with AEFIs of moderate impact, high impact, or serious AEFIs. These findings are consistent with those of the 2016 SIC Network report.[69] Special immunization clinic physicians in Italy, the UK, and Australia were also less likely to report revaccination to patients with serious AEFIs compared to non-serious AEFIs.[67,68,71,97,98] Further comparisons of revaccination management by AEFI impact between special immunization clinics is limited due to the low number of serious AEFIs seen and paucity of information on the impact of non-serious AEFIs reported in non-Canadian studies. By identifying an association between AEFI impact and recommendation for revaccination, future researchers may be motivated to provide more detail on revaccination advice in patients with varying AEFI impact levels.

The findings demonstrate that in most cases, SIC physicians followed SIC Network, provincial, and national revaccination guidelines in recommending revaccination to their patients. Furthermore, SIC physician recommendations, including those that deviated from revaccination guidelines, were consistent with recommendations by physicians working in special immunization clinics in other high-income countries. Most patients assessed in a SIC were recommended for revaccination.

5.3. Participant Intention to be Revaccinated

Participant intention for revaccination was negatively associated with having an AEFI of high impact (e.g. ≥3 physician assessments, medical supervision required outside of hospital, >3 days disability or ≤24 hours hospitalization). Our findings are consistent with those of a prospective cohort study which found that parents of children with prior AEFI following a influenza vaccination who perceived their AEFI to be "more severe" were significantly less likely to intend to receive an influenza vaccination the following year ($p < 0.05$) and to have a record of influenza vaccination ($p < 0.05$) compared to those who perceived the AEFI to be "very mild", after adjusting for personal characteristics of patients and their parents.[82,83] Additionally, a cohort study from the AEFI passive surveillance system in Quebec, Canada also reported that increased AEFI severity was associated with decreased revaccination uptake.[99] Though this study reported on revaccination uptake as opposed to intentions, their findings support the association we identified which suggests that patients may be using AEFI impact when considering whether to accept revaccination following an AEFI.

We hypothesized that there would be significant associations between AEFI type and intention for revaccination, as well as between vaccine antigen and intention. However, we did not find such associations in the logistic and LASSO regression models. The results suggest participant intention for revaccination is not influenced by AEFI type. Future studies with larger sample sizes may be able to identify associations between AEFI type and intention to be revaccinated if they do exist. In regards to vaccine antigen, a cross-sectional study from Australia reported significantly lower intention to be revaccinated among patients who experienced an AEFI following an influenza vaccination compared to those who experienced an AEFI following a routine (non-influenza) vaccination.[77] However, this study was conducted following the suspension of the 2010 influenza vaccination program in children <5 years of age due to the emergence of a vaccine safety signal. We did not identify such an association between participant intent for revaccination and influenza versus non-influenza vaccine antigens suggesting

vaccine antigen does not influence participant intention to be revaccinated following an AEFI under normal circumstances.

We have demonstrated that patients may be concerned about revaccination if the impact of the AEFI is high (e.g. emergency medical services were accessed, patients were hospitalized) regardless of the type of AEFI experienced. Higher general negative attitudes and beliefs about vaccination have been reported among participants requiring medical attention for an AEFI compared to participants able to treat their AEFIs at home.[75] SIC consultations allow physicians to explore patients' AEFI experiences and concerns, and tailor their discussions to those concerns, which may improve revaccination uptake and general attitudes towards vaccination in patients with AEFI. Physicians should make every attempt to explore and discuss the factors influencing revaccination in their patients to promote revaccination uptake following an AEFI.

5.4. Revaccination Uptake

Among participants recommended for revaccination, intention to be revaccinated was consistently higher than uptake of revaccination, indicating patients' revaccination intentions were not necessarily predictive of their behaviour. A prospective cohort study of parents of children with an AEFI following an influenza vaccination did not find an association between parental intention for revaccination at the following influenza season and revaccination uptake during the following influenza season, supporting our finding that revaccination intention is not necessarily predictive of revaccination behaviour following an AEFI.[82,83] Intention to be revaccinated and revaccination uptake may differ as a result of participants deciding against revaccination after leaving a SIC due to the passage of time between assessment at a SIC and vaccination due date or due to participants forgetting to make follow-up visits. Revaccination uptake may be lower than intention if a record of revaccination was not captured, especially if participants intended to be revaccinated outside of a SIC. Among participants who were due for revaccination during the study period, only 32% (32/106) of participants who intended to be revaccinated outside of a SIC had a record of revaccination while 85% (260/305) of

participants who intended to be revaccinated at a SIC had a record of revaccination. Standardized methods to capture revaccination uptake have been developed by the SIC Network and are diligently carried out by SIC nurses, yet revaccination uptake may be missed in participants once they have left a SIC if they forget to follow-up with SIC nurses. Our findings suggest the need to review the SIC Network's data capture quality and update or implement additional methods for improving data capture and data quality checks particularly for those participants intending to be vaccinated outside of the network. Capture of revaccination status would be improved if SIC nurses were able to contact primary care physicians/Public Health departments directly or had access to provincial immunization registries rather than relying on participant contact.[65] Additionally, data capture could be improved through the use of online surveys sent to participants by email or automated emails reminding participants that they are due for vaccination and to contact SIC nurses to report follow-up data.

We reported a record of revaccination for 63% of participants due for revaccination during the study period which is consistent with previous studies that have reported revaccination uptake in 55%-90% of participants with AEFIs due for revaccination.[63,67,69,97,100] We identified that participants with certain AEFI types including anaphylaxis, neurologic AEFIs, and autoimmune disease had lower frequency of recorded revaccination compared to participants with non-anaphylactic immediate hypersensitivity, delayed onset type I hypersensitivity, hypotonic-hyporesponsive episodes, immunization stress related responses, and non-urticarial rash. This follows trends in the literature that have found revaccination uptake to be least frequent in patients with anaphylaxis and neurologic AEFIs, excluding seizure.[67,82,99] The SIC Network's 2016 publication reported the highest frequency of revaccination uptake among participants with other systemic AEFIs and allergic-like events, which was consistent with our findings of revaccination uptake by AEFI category.[69]

5.5. AEFI Recurrence

The overall risk of recurrence was 10% (95% CI: 7%-14%) in participants with a record of revaccination. Large local reaction was the most frequent event to recur with a risk of recurrence of 29% (95% CI: 16%-42%), which was similar to the risk of recurrence of large local reaction ranging from 9% to 74% reported in a systematic review and in Quebec's passive AEFI surveillance system.[4,69] Seizure recurred in 8% of participants, which is consistent with the risk of recurrence reported from Quebec's passive AEFI surveillance system.[99] Among all the recurrent events, we reported recurrences most frequently following revaccination with influenza and DTaP/Tdap-containing vaccines. The Quebec study also reported that most recurrent events followed DTaP/Tdap-containing vaccinations.[99] That study did not capture AEFI recurrences after influenza vaccination. Our findings and those reported in the literature were not surprising given that the vaccines administered most frequently to patients undergoing revaccination were DTaP/Tdap-containing vaccines and influenza vaccines.[99]

Our findings demonstrated that AEFI recurrences following SIC physician recommended revaccination were common and generally mild. These findings suggest that in most cases SIC physicians made safe recommendations to participants for whom the risk of revaccination is low. Given that most SIC physician recommendations were consistent with SIC Network, provincial, and national revaccination guidelines, physicians following SIC Network revaccination guidelines should feel confident in the recommendations they provide to their patients with prior AEFI.

Finally, we reported recurrences as being non-serious AEFIs and the majority of recurrent events as having the same or milder severity relative to the initial AEFIs. Previous studies from the SIC Network and Quebec's passive AEFI surveillance system have also reported that the large majority of recurrent events are of similar or lesser severity than the initial events.[69,99] This finding is important for physicians discussing revaccination with their patients. Patients may be reassured that most recurrent events are of milder or the same severity as the initial events. This could improve revaccination uptake and positive attitudes towards revaccination among patients with AEFIs.

5.6. Strengths and Limitations

The first strength of this study was the SIC Network's standardized approach to data collection and data quality assessment. The SIC Network has developed standardized data collection forms and methods, as described in section 1.4, to ensure data were consistently and accurately collected by SIC staff across all sites. Another strength was the large number of patients with prior AEFI included in the analysis. We were able to analyze 588 participant records to describe the population and identify factors associated with revaccination recommendations and intentions in the multivariable analyses. Additionally, because the SIC Network is a multi-centre network, we were able to capture data on patients with prior AEFI from across Canada. Due to the wide range of AEFIs captured in SIC data, we had the benefit of studying revaccination recommendations and revaccination intentions by AEFI type, by vaccine administered prior to the AEFI, and by the impact of the AEFI. Our results are representative of experiences and outcomes among patients who undergo specialized assessment following a prior AEFI, increasing the generalizability of our study findings compared to previous literature on patients with prior AEFIs.

Although we are able to increase generalizability of our results through the multi-center design of the SIC Network, there are still limits to how far our results extend. SICs receive referrals for select patients, some of whom do not accept the referral, continue to be vaccinated by their primary care physician/Public Health nurses, or choose not to be revaccinated. Therefore, we introduced selection bias into our study by knowingly selecting patients who visited SICs for assessment of their AEFIs and who consented to participate in our study. Our study findings may not apply to patients who (1) were not referred to a SIC for their AEFI, (2) were referred but were not seen at a SIC for their AEFI, and (3) chose not to participate in the study. The findings from our study are only generalizable to patients with AEFI who are assessed for their event at a clinic with specialized infectious disease physicians and/or allergists. The results of our analysis of AEFI recurrence extend only to patients with AEFI who accept a physician recommendation for revaccination. We recognize that the population of patients with

AEFI who are assessed in the SIC and who intend to be revaccinated may be biased towards patients who are more willing to accept revaccinations.

A limitation of this study was its reliance on patient recall. The data on patient characteristics and AEFIs were primarily collected through patient interviews during clinical assessments, while vaccination data (vaccine, vaccination date) were collected from public health or primary care providers. Some data were captured through referral forms and health records. In some cases, the AEFI occurred a number of years prior to assessment. Patients may have reported data incorrectly, over or under-estimated the severity of their event, or forgotten event details. As a result of our reliance on patient recall we encountered missing data in the outcome and exposure variables for the multivariable analyses. Both patient recall and missing data are sources of measurement bias in our study that could have led to inaccurate results. Specifically, in the multivariable analyses patient recall and missing data could have resulted in underestimated effects of the exposure variables on the outcome variables.

Another limitation of this study was the small number of patients who were ≥ 18 years of age, had rare AEFI types such as delayed type III/IV hypersensitivity reactions, Guillain-Barré syndrome, neurologic AEFIs excluding seizure, and arthritis, or were from Alberta and Saskatchewan. This limited the conclusions we were able to make on the recommendations for revaccination, revaccination intentions and uptake, and AEFI recurrences among these patient groups.

In the multivariable analyses, the sample sizes were limited due to missing data which led us to collapse the levels of AEFI type into groups of AEFIs that may not have been managed similarly. In grouping AEFI types we may have lost out on identifying or accurately describing associations between the outcomes and various AEFI types. We were also unable to include additional covariates that may have had a role in physician recommendations for revaccinations and participant intention for revaccination such as outcome of allergy skin tests, interval of time between initial vaccination and AEFI onset, dose number of the vaccination associated with the prior AEFI, and AEFI symptoms.

Due to small sample sizes, specifically in the multivariable LASSO regression models, we were not able to meet the 1 in 10 rule. As a result, the LASSO models may not have produced valid and reliable findings and the findings should therefore be interpreted with caution.

Secondly, we were only able to identify associations between our covariates and intention to be revaccinated as opposed to uptake of revaccination. This was due to only having revaccination data on participants who had a record of revaccination. We could not assume those who intended not to be revaccinated were never revaccinated and those who intended to be revaccinated but for whom we did not have a record of revaccination were revaccinated. Making this assumption would bias the results to suggest participants' intentions were predictive of their actions. It should also be noted that though we identified factors associated with patient revaccination intention, we did not assess the level of vaccine hesitancy within our patient population. Based on the data available to us, we were unable to directly assess patients' attitudes and beliefs toward vaccination.

Finally, the multi-centre design of the SIC had the potential to introduce non-random error in the multivariable analyses due to vaccination schedules differing by provinces, variation in data collection, clinical assessments, site volume, revaccination management between SIC sites, and a lack of algorithms for managing and assessing participants with all AEFI types. This was supported by the findings which indicated that SIC site, included in the models both as SIC province and SIC site enrollment, influenced the relationships between physician recommendation for revaccination and participant demographic and clinical characteristics.

5.7. Conclusions

Our study explored the associations between physician revaccination recommendations and patient and AEFI characteristics. As well, we explored the associations between patient revaccination intentions and patient and AEFI characteristics in patients assessed in a SIC. Our findings suggest SIC physicians use

information about the AEFI type and impact to make revaccination recommendations. We found that SIC physician recommendations are generally consistent with SIC Network, provincial, and national revaccination guidelines. Additionally, we found the risk of AEFI recurrence was low following revaccination, suggesting that SIC Network revaccination guidelines appropriately indicate when the risk of revaccination is low and when the risk of revaccination is high. Finally, we identified that patients use information about the impact of their AEFI in deciding whether to accept revaccination recommendations. During patient counseling, physicians should emphasize that most recurrent AEFIs are milder or of the same severity as initial AEFIs to increase intentions for revaccinations and potentially revaccination uptake. The SIC Network has the potential to improve revaccination practices in patients with prior AEFI and ensure that patients are receiving all vaccines needed to be protected against infectious diseases.

References

1. Buonaguro L, Pulendran B. Immunogenomics and systems biology of vaccines. Immunol Rev. 2011;

2. Government of Canada. Page 3: Canadian Immunization Guide: Part 1-Key Immunization [Internet]. Canadian Immunization Guide. 2016 [cited 2019 Jan 26]. Available from: https://www.canada.ca/en/public-health/services/publications/healthy-living/canadian-immunization-guide-part-1-key-immunization-information/page-3-benefits-immunization.html#p1c2a1

3. Centers for Disease Control and Prevention. Ten Great Public Health Achievements 2001-2010 US. MMWR Morb Mortal Wkly Rep. 2011;60(19):605–9.

4. Zafack JG, De Serres G, Kiely M, Gariépy M-C, Rouleau I, Top KA-M. Risk of Recurrence of Adverse Events Following Immunization: A Systematic Review. Pediatrics [Internet]. 2017 Sep 1;140(3). Available from: http://pediatrics.aappublications.org/content/140/3/e20163707.abstract

5. National Advisory Committee on Immunization [Internet]. Canadian Immunization Guide, Part 2. Vaccine Safety. Evergreen Edition. Ottawa (Ontario), Canada: Public Health Agency of Canada. 2017 [cited 2018 Oct 12]. Available from: https://www.canada.ca/en/public-health/services/publications/healthy-living/canadian-immunization-guide-part-2-vaccine-safety.html

6. Molly M, Adele B, Frank D, Jane G. N, Claudia V, Ushma M. Vaccine Safety Basics - Learning Manual. 2013;207. Available from: http://www.who.int/vaccine_safety/initiative/tech_support/Vaccine-safety-E-course-manual.pdf?ua=1

7. Global Manual on Surveliance of Adverse Events Following Immunization [Internet]. 2014. Available from: https://www.who.int/vaccine_safety/publications/Global_Manual_revised_12102015.pdf?ua=1

8. CIOMS/WHO Working Group on Vaccine Pharmacovigilance. Definition and Application of Terms for Vaccine Pharmacovigilance [Internet]. Council for International Organizations of Medical Sciences. 2012. p. 39. Available from: http://www.who.int/vaccine_safety/initiative/tools/CIOMS_report_WG_vaccine.pdf

9. Top KA, Zafack J, De Serres G, Halperin SA. Canadian paediatricians' approaches to managing patients with adverse events following immunization: The role of the Special Immunization Clinic network. Paediatr Child Heal. 2014;

10. Singh AK, Wagner AL, Joshi J, Carlson BF, Aneja S, Boulton ML. Application of the revised WHO causality assessment protocol for adverse events following immunization in India. Vaccine. 2017;

11. Eldred BE, Dean AJ, McGuire TM, Nash AL. Vaccine components and constituents: Responding to consumer concerns. Med J Aust. 2006;

12. Halsey NA. The science of evaluation of adverse events associated with vaccination. Semin Pediatr Infect Dis. 2002;

13. National Advisory Committee on Immunization. Canadian Immunization Guide, Part 2. Vaccine Safety [Internet]. Evergreen edition. Ottawa(Ontario), Canada: Public Health Agency of Canada. 2017. Available from: https://www.canada.ca/en/public-health/services/publications/healthy-living/canadian-immunization-guide-part-2-vaccine-safety/page-2-vaccine-safety.html

14. Miller E, Waight P, Farrington P. Safety assessment post-licensure. DevBiolStand. 1998;

15. Causality Assessment of an Adverse Event Following Immunization (AEFI): 2018 User Manual [Internet]. World Health Organization. 2018 [cited 2018 Nov 1]. Available from: http://apps.who.int/iris/bitstream/handle/10665/259959/9789241513654-eng.pdf?sequence=1

16. Varricchio F, Iskander J, Destefano F, Ball R, Pless R, Braun MM, et al. Understanding vaccine safety information from the Vaccine Adverse Event Reporting System. Pediatric Infectious Disease Journal. 2004.

17. Crawford NW, Clothier H, Hodgson K, Selvaraj G, Easton ML, Buttery JP. Active surveillance for adverse events following immunization. Expert Review of Vaccines. 2014.

18. Davis RL, Kolczak M, Lewis E, Nordin J, Goodman M, Shay DK, et al. Active surveillance of vaccine safety: A system to detect early signs of adverse events. Epidemiology. 2005;

19. Aichinger G, Ehrlich HJ, Aaskov JG, Fritsch S, Thomasser C, Draxler W, et al. Safety and immunogenicity of an inactivated whole virus Vero cell-derived Ross River virus vaccine: A randomized trial. Vaccine [Internet]. 2011;29(50):9376–84. Available from: http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L51686400

20. World Health Organization. Sentinel Surveillance. Immunization, Vaccines and

Biologicals. 2020.
21. Redlberger-Fritz M, Kundi M, Popow-Kraupp T. Detailed report on 2014/15 influenza virus characteristics, and estimates on influenza virus vaccine effectiveness from Austria's sentinel physician surveillance network. PLoS One. 2016;

22. Murray J, Cohen AL. Infectious Disease Surveillance. In: International Encyclopedia of Public Health. 2016.

23. Scheifele DW, Halperin SA, Morris R, Déry P, Lebel M, Moore D, et al. Immunization Monitoring Program, Active: A model of active surveillance of vaccine safety. Semin Pediatr Infect Dis. 2003;

24. Top KA, Macartney K, Bettinger JA, Tan B, Blyth CC, Marshall HS, et al. Active surveillance of acute paediatric hospitalisations demonstrates the impact of vaccination programmes and informs vaccine policy in Canada and Australia. Euro Surveill. 2020;

25. Parascandola M, Weed DL. Causation in epidemiology. J Epidemiol Community Health. 2001;

26. Koch R. The etiology of tuberculosis. germ theory Dis. 1882;221–30.

27. Inglis TJJ. Principia ætiologica: Taking causality beyond Koch's postulates. Journal of Medical Microbiology. 2007.

28. World Health Organization. Causality Assessment of an Adverse Event Following Immunization (AEFI) [Internet]. World Health Organization. 2013 [cited 2018 Oct 29]. p. 8. Available from: http://www.who.int/vaccine_safety/publications/aevi_manual.pdf

29. Tozzi AE, Asturias EJ, Balakrishnan MR, Halsey NA, Law B, Zuber PLF. Assessment of causality of individual adverse events following immunization (AEFI): A WHO tool for global use. Vaccine. 2013;

30. Collet JP, MacDonald N, Cashman N, Pless R, Collet JP, MacDonald N, et al. Monitoring signals for vaccine safety: The assessment of individual adverse event reports by an expert advisory committee. Bull World Health Organ. 2000;

31. Deloria MA, Blackwelder WC, Decker MD, Englund JA, Steinhoff MC, Pichichero ME, et al. Association of reactions after consecutive acellular or whole-cell pertussis vaccine immunizations. Pediatrics. 1995;

32. Halperin SA, Scheifele D, Mills E, Guasparini R, Humphreys G, Barréto L, et al. Nature, evolution, and appraisal of adverse events and antibody response associated with the fifth consecutive dose of a five-component acellular pertussis-

based combination vaccine. Vaccine. 2003;

33. Edwards, K., Decker M. Acellular pertussis vaccines for infants. N Engl J Med. 1996;332(6):391–2.

34. Tseng HF, Sy LS, Liu ILA, Qian L, Marcy SM, Weintraub E, et al. Postlicensure safety surveillance for 13-valent pneumococcal conjugate vaccine. Am J Epidemiol [Internet]. 2013;177:S130. Available from: http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L71079639

35. Nuorti JP, Whitney CG, Centers for Disease Control and Prevention (CDC). Prevention of pneumococcal disease among infants and children - use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine - recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm reports Morb Mortal Wkly report Recomm reports [Internet]. 2010;59(RR-11):1–18. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21150868

36. Falsey AR, Treanor JJ, Tornieporth N, Capellan J, Gorse GJ. Randomized, Double-Blind Controlled Phase 3 Trial Comparing the Immunogenicity of High-Dose and Standard-Dose Influenza Vaccine in Adults 65 Years of Age and Older. J Infect Dis. 2009;

37. Govaert TM, Dinant GJ, Aretz K, Masurel N, Sprenger MJ, Knottnerus JA. Adverse reactions to influenza vaccine in elderly people: randomised double blind placebo controlled trial. BMJ. 2009;

38. Gonzalez M, Pirez MC, Ward E, Dibarboure H, Garcia A, Picolet H. Safety and immunogenicity of a paediatric presentation of an influenza vaccine. Arch Dis Child. 2000;

39. Neuzil KM, Dupont WD, Wright PF, Edwards KM. Efficacy of inactivated and cold-adapted vaccines against influenza A infection, 1985 to 1990: The pediatric experience. Pediatr Infect Dis J. 2001;

40. Piedra PA, Yan L, Kotloff K, Zangwill K, Bernstein DI, King J, et al. Safety of the Trivalent, Cold-Adapted Influenza Vaccine in Preschool-Aged Children. Pediatrics. 2004;

41. Tam JS, Capeding MRZ, Lum LCS, Chotpitayasunondh T, Jiang Z, Huang LM, et al. Efficacy and safety of a live attenuated, cold-adapted influenza vaccine, trivalent against culture-confirmed influenza in young children in Asia. Pediatr Infect Dis J. 2007;

42. Vesikari T, Karvonen A, Korhonen T, Edelman K, Vainionpää R, Salmi A, et al. A randomized, double-blind study of the safety, transmissibility and phenotypic and genotypic stability of cold-adapted influenza virus vaccine. Pediatr Infect Dis J. 2006;

43. Shinefield H, Black S, Digilio L, Reisinger K, Blatter M, Gress JO, et al. Evaluation of a quadrivalent measles, mumps, rubella and varicella vaccine in healthy children. Pediatr Infect Dis J. 2005;

44. Goh P, Lim FS, Han HH, Willems P. Safety and immunogenicity of early vaccination with two doses of tetravalent Measles-Mumps-Rubella-Varicella (MMRV) vaccine in healthy children from 9 months of age. Infection. 2007;

45. White CJ, Kuter BJ, Ngai A, Hildebrand CS, Isganitis KL, Patterson CM, et al. Modified cases of chickenpox after varicella vaccination: Correlation of protection with antibody response. Pediatr Infect Dis J. 1992;

46. Nicoll A, Ramsay M. Adverse Events Associated with Childhood Vaccines: Evidence Bearing on Causality. BMJ. 1995;

47. Black C, Kaye JA, Jick H. MMR vaccine and idiopathic thrombocytopaenic purpura. 2003;107–11.

48. Children MI, France EK, Glanz J, Xu S, Hambidge S, Yamasaki K, et al. Risk of Immune Thrombocytopenic Purpura After. 2008;121(3).

49. O'Leary ST, Glanz JM, McClure DL, Akhtar A, Daley MF, Nakasato C, et al. The Risk of Immune Thrombocytopenic Purpura After Vaccination in Children and Adolescents. Pediatrics. 2012;

50. Autret E, Jonville Bera AP, Galy Eyraud C, Hessel L. [Thrombocytopenic purpura after isolated or combined vaccination against measles, mumps and rubella]. Therapie. 1996;

51. Miller E, Waight P, Farrington P, Andrews N, Stowe J, Taylor B, et al. Idiopathic thrombocytopenic purpura and MMR vaccine. 2001;227–9.

52. Nieminen U, Peltola H, Syrjälä M, Mäkipernaa A, Kekomäki R. Acute thrombocytopenic purpura following measles, mumps and rubella vaccination. A report on 23 patients. Acta Pædiatrica. 1993;

53. S.C. D, N.A. H, J.M. K, R.A. W, D.S. H, K.M. E, et al. International Consensus (ICON): Allergic reactions to vaccines. World Allergy Organ J [Internet]. 2016;9(1). Available from: http://www.embase.com/search/results?subaction=viewrecord&from=export&id=

L612177351
54. Immunology AA of AA and. Allergic Reactions Definition. A - Z conditions dictionary: common allergy, asthma and immunology terms. 2020.

55. Rajakulendran M, Tham EH, Soh JY, Bever HP van. Novel strategies in immunotherapy for allergic diseases. Asia Pac Allergy [Internet]. 2018;8(2). Available from: http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L622003657

56. Chung EH. Vaccine allergies. Clin Exp Vaccine Res. 2014;

57. Special Immunization Clinic Network [Internet]. 2018 [cited 2018 Oct 15]. Available from: http://cirnetwork.ca/network/special-immunization/

58. Press W. 05 Global Manual on surveillance of Adverse Events Following Immunization. 2016;(WA 115):13,15,38,43.

59. Moore DL, Le Saux N, Scheifele D, Halperin SA. Lack of evidence of encephalopathy related to pertussis vaccine: Active surveillance by IMPACT, Canada, 1993-2002. Pediatr Infect Dis J. 2004;

60. Tam J, Tran D, Bettinger JA, Moore D, Sauvé L, Jadavji T, et al. Review of pediatric encephalitis and encephalopathy cases following immunization reported to the Canadian Immunization Monitoring Program Active (IMPACT) from 1992 to 2012. Vaccine. 2020;

61. M. Š, V. U, A. K, I. K. Adverse events following school-based vaccination of girls with quadrivalent human papillomavirus vaccine in Slovenia, 2009 to 2013. Eurosurveillance [Internet]. 2016;21(14). Available from: http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L609918749

62. Zafack, JG., Toth, E., Landry, M., Drolet, JP., Top, KA., De Serres G. Rate of Recurrence of Adverse Events Following Immunization: Results of 19 Years of Surveillance Ii Quebec, Canada. Pediatr Infect Dis J [Epub ahead print] [Internet]. 2019; Available from: https://www.ncbi.nlm.nih.gov/pubmed/30204662

63. Crawford NW, Mcminn A, Royle J, Lazzaro T, Danchin M, Perrett KP, et al. Recurrence risk of a hypotonic hyporesponsive episode in two Australian specialist immunisation clinics. Vaccine [Internet]. 2019;36(41):6152–7. Available from: https://doi.org/10.1016/j.vaccine.2018.08.062

64. Zafack, Joseline., De Serres, Gaston., Kiely, Marilou., Gariépy, Marie-Claude., Rouleau, Isabelle., Top KA-M. Risk of Recurrence of Adverse Events Following Immunization: A systematic review. Pediatrics. 2017;140(3).

65. Silcock R, Crawford NW, Selvaraj G, McMinn A, Danchin M, Lazzaro T, et al. Subcutaneous nodules following immunization in children; in Victoria, Australia from 2007 to 2016. Vaccine. 2020;

66. Kelso JM, Greenhawt MJ, Li JT, Nicklas RA, Bernstein DI, Blessing-Moore J, et al. Adverse reactions to vaccines practice parameter 2012 update. J Allergy Clin Immunol. 2012;

67. Gold M, Goodwin H, Botham S, Burgess M, Nash M, Kempe A. Re-vaccination of 421 children with a past history of an adverse vaccine reaction in a special immunisation service. Arch Dis Child. 2000;

68. Andrews RM, Kempe AE, Sinn KK, Herceg A. Vaccinating children with a history of serious reactions after vaccination or of egg allergy. 1998;168(May):491–4.

69. Top KA, Billard MN, Gariepy MC, Rouleau I, Pernica JM, Pham-Huy A, et al. Immunizing patients with adverse events after immunization and potential contraindications to immunization: A report from the special immunization clinics network. Pediatr Infect Dis J. 2016;

70. Micheletti F, Peroni D, Piacentini G, Schweiger V, Mirandola R, Chiesa E, et al. Vaccine allergy evaluation and management at the specialized Green Channel Consultation Clinic. Clin Exp Allergy. 2012;

71. Donà D, Masiero S, Brisotto S, Gottardello L, Lundin R, Borgia E, et al. Special immunization service: A 14-year experience in Italy. PLoS One. 2018;

72. Armstrong PK, Dowse GK, Effler P V., Carcione D, Blyth CC, Richmond PC, et al. Epidemiological study of severe febrile reactions in young children in Western Australia caused by a 2010 trivalent inactivated influenza vaccine. BMJ Open. 2011;

73. Therapeutic Goods Administration. Investigation Into Febrile Reactions in Young Children Following 2010 Seasonal Trivalent Influenza Vaccination. 2010;(September):7. Available from: https://www.tga.gov.au/sites/default/files/alerts-medicine-seasonal-flu-100702.pdf

74. Di Pasquale A, Bonanni P, Garçon N, Stanberry LR, El-Hodhod M, Tavares Da Silva F. Vaccine safety evaluation: Practical aspects in assessing benefits and risks. Vaccine. 2016;

75. Gust DA, Campbell S, Kennedy A, Shui I, Barker L, Schwartz B. Parental Concerns and Medical-Seeking Behavior After Immunization. Am J Prev Med. 2006;

76. Parrella A, Gold M, Marshall H, Braunack-Mayer A, Baghurst P. Parental perspectives of vaccine safety and experience of adverse events following immunisation. Vaccine [Internet]. 2013;31(16):2067–74. Available from: http://dx.doi.org/10.1016/j.vaccine.2013.02.011

77. Parrella A, Gold M, Marshall H, Braunack-mayer A, Watson M, Baghurst P. Parental views on vaccine safety and future vaccinations of children who experienced an adverse event following routine or seasonal influenza vaccination in 2010. Hum Vaccin Immunother. 2012;8(5):662–7.

78. Woo EJ, Ball R, Bostrom A, Shadomy S V., Ball LK, Evans G, et al. Vaccine risk perception among reporters of autism after vaccination: Vaccine adverse event reporting system 1990-2001. Am J Public Health. 2004;

79. Kimmel SR, Burns IT, Wolfe RM, Zimmerman RK. Addressing immunization barriers, benefits, and risks. Journal of Family Practice. 2007.

80. Kempe A, Daley MF, McCauley MM, Crane LA, Suh CA, Kennedy AM, et al. Prevalence of parental concerns about childhood vaccines: The experience of primary care physicians. Am J Prev Med. 2011;

81. Barański K, Gajda M, Braczkowska B, Kowalska M. Parental declaration of adverse event following immunization in a cross-sectional study in Poland. Int J Environ Res Public Health. 2019;

82. Smith LE, Amlôt R, Weinman J, Yiend J, Rubin GJ. Why do parents not re-vaccinate their child for influenza? A prospective cohort study. Vaccine. 2020;

83. Smith LE, Weinman J, Amlôt R, Yiend J, Rubin GJ. Parental Expectation of Side Effects Following Vaccination Is Self-fulfilling: A Prospective Cohort Study. Ann Behav Med. 2019;

84. BC Centre for Disease Control . Communicable Disease Control Manual, Chapter 2 Immunization, Part 5- Adverse Events Following Immunization [Internet]. 2019. Available from: http://www.bccdc.ca/resource-gallery/Documents/Guidelines and Forms/Guidelines and Manuals/Epid/CD Manual/Chapter 2 - Imms/Part_5_AEFI.pdf

85. Alberta Health . Adverse Events Following Immunization (AEFI) Policy for Alberta Immunization Providers. 2019.

86. Government of Saskatchewan . Saskatchewan Immunization Manual, Chapter 11- Adverse Events Following Immunization. 2017.

87. Ministry of Health and Long-Term Care . Infectious Disease Protocols, Appendix

B: Provincial Case Definitions for Diseases of Public Health Significance. 2019.

88. Sante et Services sociaux Quebec . Vaccinologie pratique, Contre-indications [Internet]. 2019. Available from: https://www.msss.gouv.qc.ca/professionnels/vaccination/piq-vaccinologie-pratique/contre-indications/

89. Nova Scotia Department of Health and Wellness . Nova Scotia Immunization Manual. 2019.

90. Public Health Agency of Canada. Reporting Adverse Events Following Immunization (AEFI) in Canada: User Guide to Completion and Submission of the AEFI Reports. 2011; Available from: www.phac-aspc.gc.ca/im/pdf/AEFI-ug-gu-eng.pdf

91. Wood RA, Berger M, Dreskin SC, Setse R, Engler RJM, Dekker CL, et al. An algorithm for treatment of patients with hypersensitivity reactions after vaccines. Pediatrics [Internet]. 2008;122(3):e771–7. Available from: http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L354417544

92. Ansotegui IJ, Melioli G, Canonica GW, Caraballo L, Villa E, Ebisawa M, et al. IgE allergy diagnostics and other relevant tests in allergy, a World Allergy Organization position paper. World Allergy Organ J. 2020;

93. P. Vatcheva K, Lee M. Multicollinearity in Regression Analyses Conducted in Epidemiologic Studies. Epidemiol Open Access. 2016;

94. © SAS Institute Inc. Usage Note 60240: Regularization, regression penalties, LASSO, ridging, and elastic net [Internet]. [cited 2019 Jul 5]. Available from: http://support.sas.com/kb/60/240.html

95. Hajian-Tilaki K. Receiver Operating Characteristic (ROC) Curve Analysis for Medical Diagnostic Test Evaluation. Casp J Intern Med. 2013;

96. Schafer JL, Graham JW. Missing data: Our view of the state of the art. Psychol Methods. 2002;

97. Micheletti F, Peroni D, Piacentini G, Schweiger V, Mirandola R, Chiesa E, et al. Vaccine allergy evaluation and management at the specialized Green Channel Consultation Clinic. Clin Exp Allergy [Internet]. 2012;42(7):1088–96. Available from: http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L365050050

98. K.A. T, M.-N. B, M.-C. G, I. R, J.M. P, A. P-H, et al. Immunizing patients with adverse events after immunization and potential contraindications to immunization: A report from the special immunization clinics network. Pediatr Infect Dis J [Internet]. 2016;35(12):e384–91. Available from: http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L612180024

99. J.G. Z, E. T, M. L, J.-P. D, K.A. T, G. DS. Rate of Recurrence of Adverse Events Following Immunization: Results of 19 Years of Surveillance In Quebec, Canada. Pediatr Infect Dis J [Internet]. 2019;38(4):377–83. Available from: http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L626857227

100. Baxter D, Ghebrehewet S, Falconer M. Referrals to a pediatric immunization service: Findings from a practice-based audit of a UK specialist immunization clinic. Hum Vaccin. 2010;

101. Council for International Organizations of Medical Sciences (CIOMS). Definition and Application Pharmacovigilance. Defin Appl Terms Vaccine Pharmacovigil. 2009;41.

102. Rothstein E, Kohl KS, Ball L, Halperin SA, Halsey N, Hammer SJ, et al. Nodule at injection site as an adverse event following immunization: Case definition and guidelines for data collection, analysis, and presentation. Vaccine. 2004;

103. Bonhoeffer J, Menkes J, Gold MS, De Souza-Brito G, Fisher MC, Halsey N, et al. Generalized convulsive seizure as an adverse event following immunization: Case definition and guidelines for data collection, analysis, and presentation. Vaccine. 2004;

104. J.J. S, K.S. K, R. B, D. B, T. C, J. G, et al. Encephalitis, myelitis, and acute disseminated encephalomyelitis (ADEM): Case definitions and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine [Internet]. 2007;25(31):5771–92. Available from: http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L47049772

Appendix 1

SIC risk-benefit assessment tool

Risk of vaccination	
High	Patient at risk of high impact or serious AEFI (e.g., anaphylaxis, severe neurologic complications, Stevens Johnson Syndrome)
Moderate	Patient at moderate to high risk of recurrent moderate impact AEFI (e.g., febrile seizure, persistent crying)
Low	Patient at low risk of recurrent moderate risk AEFI or at risk of only low impact AEFI (e.g., extensive limb swelling, non-urticarial rash)
Estimated risk of vaccination Low Moderate High	
Benefit of vaccination	
High	Patient at increased risk of disease and/or complications without further vaccination (e.g., anticipated travel to measles-endemic area, immunocompromised patient)
Moderate	Patient at standard risk of disease and its complications without further vaccinations (i.e., non-immune but healthy patient, no active outbreaks or specific risk factors)
Low	Patient is adequately protected from disease or at low risk of serious disease without further vaccination (e.g., 2 doses HPV vaccine at least 3 months apart; completed primary DTP series with adequate tetanus/diphtheria titres)
None	Patient no longer requires further doses (e.g., Hib in patient >5 years of age; 1 dose of MMR with positive titres to all components)
Estimated benefit of vaccination Low Moderate High None	
Overall risk assessment	
Risk of vaccination outweighs benefit Risks and benefits are similar Benefit of vaccination outweighs risk	

Appendix 2

AEFI type definitions from the Council for International Organizations of Medical Sciences with the World Health Organization Working Group on Vaccine Pharmacovigilance.[101]

AEFI type	Definition
Injection site reaction	
Abscess (infectious)	Collection of fluid located in the soft tissues at the injection site. Infectious abscesses are most commonly due to bacterial infection following introduction of microorganisms into the skin at the injection site or contamination of multi-dose vials (e.g. *hot abscess)*.[57]
Abscess (sterile)	Collection of fluid located in the soft tissues at the injection site. Sterile abscesses (e.g., *cold abscesses*) are collections of fluid in the absence of signs of infection/inflammation.[57]
Cellulitis	Acute, expanding inflammatory condition of the skin at the vaccine injection site that is characterized by at least 3 of the following four symptoms/signs: localized pain or tenderness; erythema; induration or swelling; warmth. Symptoms may be accompanied by fever (≥38°C) and/or regional lymphadenopathy. Distinguished from large local reactions by more intense erythema, tenderness to light touch, induration and warmth. Can be infectious or simply due to severe inflammatory process without bacterial infection. Cellulitis is excluded if resolution is rapid and spontaneous.[57]
Nodule	Discrete, well demarcated soft tissue mass or lump at the vaccination site that has a firm texture and is not accompanied by erythema, warmth or abscess formation.[102]
Large local reaction	Any description of morphological or physiological change at or near the injection site, including redness and/or swelling (visible enlargement of a limb) that is ≥10cm in diameter. Extensive limb swelling is erythema/swelling crosses joint or extends joint-to-joint.[57]
Allergic-like events	
Anaphylaxis	Acute onset of illness within minutes to hours with involvement of: skin and/or mucosa (see above) AND respiratory compromise (dyspnea, wheeze/ bronchospasm, stridor, cyanosis) OR decreased blood pressure/end organ dysfunction (collapse, syncope, incontinence) OR Two or more of the following that occur rapidly after exposure to *likely allergen* for that patient: skin and/or mucosa, respiratory compromise, decreased blood pressure/end organ dysfunction, persistent GI symptoms OR Decreased blood pressure occurring within minutes or hours after exposure to *known allergen* for that patient: Differential diagnosis includes vaso-vagal syncope, breath-holding spells, anxiety, and asthma exacerbation.[57]
Non-anaphylaxis immediate hypersensitivity with onset <4 hours	Allergic-like events involve the presence of signs and symptoms suggestive of a hypersensitivity reaction, which include the following: Mucocutaneous symptoms: urticaria, angioedema, pruritus, flushing, conjunctivitis; Cardiovascular symptoms: tachycardia, hypotension, palpitations, confusion, loss of consciousness; Respiratory symptoms: dyspnea, wheeze/bronchospasm, stridor, cyanosis, cough, sensation of throat tightness/airway swelling, difficulty swallowing, chest tightness, rhinorrhea; Gastrointestinal (GI) symptoms: abdominal cramping, diarrhea, nausea, vomiting.[57]
Oculo-respiratory syndrome	Bilateral red eyes and/or facial swelling and/or respiratory symptoms (cough, wheeze, chest tightness, difficulty breathing, difficulty swallowing, hoarseness or sore throat) occurring within 24 hours of influenza immunization.[57] **If there is a cutaneous rash, manage as an allergic-like event.*
Delayed urticaria/angioedema with onset ≥4 hours	*Type III and IV hypersensitivity reactions*: Delayed onset hypersensitivity reactions such as serum-sickness-like reactions (high fever, rash, arthritis) or severe cutaneous reactions such as erythema multiforme major/Stevens Johnson syndrome have been reported rarely after immunization. Onset is generally days to weeks after immunization.[57]
Neurologic AEFI	

AEFI type	Definition
Seizure	Witnessed sudden loss of consciousness *AND* generalized, tonic, clonic, tonic–clonic, or atonic motor manifestations.[103]
Anaesthesia/paraesthesia	Based on physician diagnosis.
Peripheral neuropathy	Based on physician diagnosis.
Encephalitis	Demonstration of acute inflammation of central nervous system parenchyma (+/– meninges) by histopathology.[104]
Myelitis	Demonstration of acute spinal cord inflammation (+/– meninges) by histopathology.[104]
Acute disseminated encephalomyelitis	Demonstration of diffuse or multifocal areas of demyelination by histopathology, and focal OR Multifocal findings referable to the central nervous system, including one or more of the following: 1. Focal cortical signs (including but not limited to: aphasia, alexia, agraphia, cortical blindness), 2. Cranial nerve abnormality/abnormalities, 3. Visual field defect/defect(s), 4. Presence of primitive reflexes (Babinski's sign, glabellar reflex, snout/sucking reflex), 5. Motor weakness (either diffuse or focal; more often focal) 6. Sensory abnormalities (either positive or negative; sensory level), 7. Altered deep tendon reflexes (hypo- or hyperreflexia, reflex asymmetry), 8. Cerebellar dysfunction.[104]
Meningitis	Based on physician diagnosis.
Guillain-Barré/Fisher-Miller Syndrome	Rare but serious autoimmune disorder involving peripheral motor and sensory nerves, including cranial nerves. GBS is characterized by bilateral, flaccid weakness of the limbs and decreased or absent deep tendon reflexes that gradually progresses to reach a nadir of weakness between 12 hours and 28 days after onset, followed by a clinical plateau and gradual recovery. Cerebrospinal fluid analysis showing elevation of protein with mild or no elevation of white blood cells (suggestive of GBS) and/or electrophysiological studies can help to confirm the diagnosis. Fisher (or Miller-Fisher) variant of GBS is characterized by paralysis of ocular movements with bilateral reduced reflexes and ataxia without limb weakness.[57]
Other systemic AEFI	
Fever	Elevation of body temperature ≥38˚C from any site.[57]
Hypotonic-hyporesponsive episode	Sudden onset in a child <2 years of age of hypotonia (reduced muscle tone) hyporesponsiveness, pallor or cyanosis. Differential diagnosis includes atonic seizures, or post-ictal state, and hypotension as sole sign of anaphylaxis.[57]
Persistent crying	Continuous and unaltered crying/screaming of infants and children. Persistent: ≥3 hours of crying/screaming. Continuous: which is not interrupted by activities such as feeding or naps.[57]
Arthralgia/arthritis	Pain in one or more joints, with or without joint effusion (swelling), erythema or warmth[57].
Thrombocytopenia	Platelet count of less than 150 x 109/L. When platelet counts drop well below 50 x 109/L, patients may present with petechiae, purpura, ecchymosis, epistaxis, or gingival, gastrointestinal, pulmonary, or intracranial bleeding.[57]
Non-urticarial rash	Based on physician diagnosis.
Vasovagal/anxiety reaction	Based on physician diagnosis.

Appendix 3

GENERAL INFORMATION			
Gender ☐ Female ☐ Male	**Date of birth:** _____ / _____ MMM YYYY	**Weight:** ☐kg ☐lbs ☐Unk	**Height:** ☐cm ☐in ☐Unk

REASON FOR CONSULTATION

Indicate primary reason for consultation: * **Visit Date: ___ ___/___ ___ ___/___ ___**
YY DD MMM

☐*AEFI ☐ *Pre-transplant: Specify type of transplant below:

☐ Kidney ☐Pancreas ☐Liver ☐Heart ☐Lung ☐Intestine ☐Bone Marrow ☐ Other:_____

☐*Pre-existing condition specify: _____

☐*In utero exposure to biologics/monoclonal antibodies

☐ *Relative contraindication due to immunosuppressive therapy

☐*Post-Solid Organ Transplant assessment for live vaccines

☐* Patients on Chronic Blood Transfusion Therapy assessment for live vaccines

Medical History	☐ **Yes**	☐ **No**		
For children under 2 years of age at Visit Date:				
Prematurity (< 37 weeks)	☐ Yes	☐ No	☐ Unk	Gestational age : _____weeks___days
Low birth weight (< 2500 g)	☐ Yes	☐ No	☐ Unk	Weight in grams: _____g
Medically diagnosed conditions:				**If yes, specify condition**
Immunodeficiency	☐ Yes	☐ No	☐Unk	_____
Anatomic/Functional asplenia	☐ Yes	☐ No	☐Unk	_____
Cardiovascular disease	☐ Yes	☐ No	☐Unk	_____
Chronic respiratory disease (eg, asthma)	☐ Yes	☐ No	☐Unk	_____
Diabetes or other metabolic disorders	☐ Yes	☐ No	☐Unk	_____
Kidney disease	☐ Yes	☐ No	☐Unk	_____
Liver disease	☐ Yes	☐ No	☐Unk	_____
Skin diseases	☐ Yes	☐ No	☐Unk	_____

Personal/Family history of seizures	☐ Yes	☐ No	☐ Unk	_____
Neurological disorders	☐ Yes	☐ No	☐ Unk	_____
Gastrointestinal diseases	☐ Yes	☐ No	☐ Unk	_____
Musculoskeletal diseases	☐ Yes	☐ No	☐ Unk	_____
Recent/upcoming organ transplantation	☐ Yes	☐ No	☐ Unk	_____
Cancer / hematologic malignancy	☐ Yes	☐ No	☐ Unk	_____
Other significant condition, specify	☐ Yes			_____
Medically diagnosed allergic diseases				
Eczema or atopic dermatitis	☐ Yes	☐ No	☐ Unk	_____
Allergic rhinitis / Respiratory allergy	☐ Yes	☐ No	☐ Unk	_____
Food allergy, specify	☐ Yes	☐ No	☐ Unk	_____
Drug allergy, specify	☐ Yes	☐ No	☐ Unk	_____
Other allergy, specify	☐ Yes			_____
Treatments ***(if consulting for AEFI, take history at the time of initial reaction)***				
Immunosupressants or chemotherapy	☐ Yes	☐ No	☐ Unk	_____
Other regular prescribed medication	☐ Yes	☐ No	☐ Unk	_____
Any previous hospitalization	☐ Yes	☐ No	☐ Unk	_____

Previous AEFI (Adverse Events Following Immunization)

☐N/A

VACCINES ADMINISTERED AND INJECTION SITE INFORMATION						
Vaccine Administered (Antigen)	**Brand Name**	**Lot #**	**Dose number (1, 2, 3 …)**	**Site**	**Route:**	**Dose**

INTERVAL BETWEEN VACCINATION AND ONSET OF ADVERSE EVENT
Date/time of vaccination: _____dd /_____mmm/_____yyyy at _____:_____(24hr)
Interval between vaccination and symptom onset: _____minutes _____hours or _____days

DESCRIPTION OF THE ADVERSE EVENT

TREATMENT AND OUTCOME OF THE ADVERSE EVENT			
Called health information line / HealthLink / Info-santé / 811	☐Yes	☐No	☐Unk
Consulted a physician	☐Yes	☐No	☐Unk
Was hospitalized (Admitted > 24 hours in hospital)	☐Yes	☐No	☐Unk
↳ Admitted to an intensive care unit (NICU / PICU / ICU)	☐Yes	☐No	☐Unk
↳ Total duration of hospitalization : _____ days			
How long did the AEFI persist? _____minutes _____ hours _____days or ☐ unresolved			
Impact of the AEFI			
☐ Low Impact *Treated in vaccine clinic by staff on site with no further action>health professional phone advice>self-prescribed medication>disabled less than 24 hours, no discernible impact*			
☐ Moderate Impact *Unscheduled MD visit – ER or other clinic/ER services called to vaccine clinic but no further care needed/new drug prescription/ increased dose of existing prescription/ disabled 1-3 days*			
☐ High Impact *Unable to do daily activities, unable to go to work, unable to attend school/hospitalized for < 24hrs /medical supervision out of hospital/needed ≥3 MD assessments for AEFI/required outpatient IV therapy/disabled 4-14 days;*			
☐ Serious *Congenital abnormality/residual disability/ hospitalized ≥ 24hrs/ prolonged existing hospitalization/ life-threatening*			

PRIMARY AEFI REQUIRING CONSULTATION
☐ Systemic AEFI *(High fever, Arthralgia, Thrombocytopenia, Unusual/Persistent crying, Hypotonic-Hyporesponsive Episode)*
☐ Injection site reaction *(Large local reactions, cellulitis, abscess, nodules)*

☐ Allergic-like reaction *(Anaphylaxis, Oculo-respiratory syndrome, other allergic symptoms)*

☐ Neurological reaction *(Encephalitis, myelitis, seizures, anesthesia/paresthesia, other neurological problem)*

☐Other, specify:

_____

GENERAL SYMPTOMS	☐ **Yes** ☐ **No (Skip to Next Page: INJECTION SITE REACTION)**			
Fever, chills, or feeling feverish	☐ Yes	☐ No	☐ Unk	
↳Highest recorded temp. _____ ☐C°☐F° mode: ☐Rectal ☐Oral ☐Axillary ☐ Tympanic				
Hypotonic-hyporesponsive episode (HHE)	☐ Yes	☐ No	☐ Unk	_____ ____
Hyporesponsiveness	☐ Yes	☐ No	☐ Unk	_____ ____
Hypotonia	☐ Yes	☐ No	☐ Unk	_____ ____
Pallor	☐ Yes	☐ No	☐ Unk	_____ ____
Cyanosis	☐ Yes	☐ No	☐ Unk	_____ ____
Onset and progression of HHE symptoms				
Sudden onset	☐ Yes	☐ No	☐ Unk	_____ ____
Rapid progression	☐ Yes	☐ No	☐ Unk	_____ ____
Unusual/Persistent crying	☐ Yes	☐ No	☐ Unk	_____ ____
Lymphangitis/Lymphadenopathy	☐ Yes	☐ No	☐ Unk	_____ ____
Arthralgia or swollen joints	☐ Yes	☐ No	☐ Unk	_____ ____
Unusual/Persistent fatigue or lethargy	☐ Yes	☐ No	☐ Unk	_____ ____
Myalgia or muscular weakness	☐ Yes	☐ No	☐ Unk	_____ ____
Headaches	☐ Yes	☐ No	☐ Unk	_____ ____

Signs of concomitant infection	☐ Yes	☐ No	☐ Unk	_____ ____
Confusion, feeling faint, or lightheadedness	☐ Yes	☐ No	☐ Unk	_____ ____
Loss of consciousness, fainting	☐ Yes	☐ No	☐ Unk	_____ ____
Nausea and/or vomiting	☐ Yes	☐ No	☐ Unk	_____ ____
Abdominal pain and/or diarrhea	☐ Yes	☐ No	☐ Unk	_____ ____
Other, specify: _____	☐ Yes			_____ ____
INJECTION SITE REACTION	☐ **Yes** ☐ **No (Skip to Next Page: ALLERGIC-LIKE SYMPTOMS)**			
Type of reaction				
Large local reaction	☐ Yes	☐ No	☐ Unk	_____ ____
Abscess	☐ Yes	☐ No	☐ Unk	_____ ____
Nodule	☐ Yes	☐ No	☐ Unk	_____ ____
Cellulitis	☐ Yes	☐ No	☐ Unk	_____ ____
Other, specify: _____	☐ Yes			_____ ____
Size/Range of reaction				
At/near the injection site (between joints)	☐ Yes	☐ No	☐ Unk	_____ ____
Joint-to-joint	☐ Yes	☐ No	☐ Unk	_____ ____
Crossing joint	☐ Yes	☐ No	☐ Unk	_____ ____
Largest diameter measured				
↳ Largest diameter of the reaction: _____	☐ mm	☐ cm	☐ in	
Symptoms				
Pain during injection	☐ Yes	☐ No	☐ Unk	_____ ____
Radiating pain (if yes, specify area)?	☐ Yes	☐ No	☐ Unk	_____ ____

Erythema, any	☐ Yes	☐ No	☐ Unk	_____
Was erythema intense/bright red?	☐ Yes	☐ No	☐ Unk	_____
Warmth	☐ Yes	☐ No	☐ Unk	_____
Swelling	☐ Yes	☐ No	☐ Unk	_____
Induration	☐ Yes	☐ No	☐ Unk	_____
Fluctuation	☐ Yes	☐ No	☐ Unk	_____
Spontaneous or surgical drainage of fluid	☐ Yes	☐ No	☐ Unk	_____
↳Pus/purulent fluid?	☐ Yes	☐ No	☐ Unk	_____
↳Was it cultured (if yes, add results)?	☐ Yes	☐ No	☐ Unk	_____
Other, specify: _____	☐ Yes			_____
Treatments				
Biopsy	☐ Yes	☐ No	☐ Unk	_____
Antibiotics	☐ Yes	☐ No	☐ Unk	_____
Other, specify: _____	☐ Yes			_____
Resolution of symptoms				
Spontaneous, without antibiotics	☐ Yes	☐ No	☐ Unk	_____
With antibiotics	☐ Yes	☐ No	☐ Unk	_____
Other, specify: _____	☐ Yes			_____
ALLERGIC-LIKE SYMPTOMS	☐ **Yes** ☐ N/A ☐ **No (Skip to Neurological symptom section)**			
Onset and progression of symptoms				

Sudden onset	☐ Yes	☐ No	☐ Unk	_____
Rapid progression	☐ Yes	☐ No	☐ Unk	_____
Skin and mucosa				
Urticaria	☐ Yes	☐ No	☐ Unk	_____
Non-urticarial rash with pruritus	☐ Yes	☐ No	☐ Unk	_____
Non-urticarial rash	☐ Yes	☐ No	☐ Unk	_____
Generalized pruritus without rash	☐ Yes	☐ No	☐ Unk	_____
Angioedema, not affecting respiratory tract	☐ Yes	☐ No	☐ Unk	_____
Ocular symptoms				
Conjunctivitis	☐ Yes	☐ No	☐ Unk	bilateral ☐ unilateral ☐
Ocular pruritus	☐ Yes	☐ No	☐ Unk	_____
Ocular discharge	☐ Yes	☐ No	☐ Unk	_____
Cardiovascular symptoms				
Measured hypotension	☐ Yes	☐ No	☐ Unk	_____
Confusion / ↓ consciousness	☐ Yes	☐ No	☐ Unk	_____
Loss of consciousness	☐ Yes	☐ No	☐ Unk	_____
Palpitations or tachycardia	☐ Yes	☐ No	☐ Unk	_____
Respiratory symptoms				
Nasal congestion	☐ Yes	☐ No	☐ Unk	_____
Rhinorrhea	☐ Yes	☐ No	☐ Unk	_____
Sneezing	☐ Yes	☐ No	☐ Unk	_____
Sore throat	☐ Yes	☐ No	☐ Unk	_____
Edema of the mouth/tongue/uvula	☐ Yes	☐ No	☐ Unk	_____
Edema of the throat/larynx	☐ Yes	☐ No	☐ Unk	_____

Sensation of throat closure (w/o edema)	☐ Yes	☐ No	☐ Unk	_____
Difficulty swallowing saliva	☐ Yes	☐ No	☐ Unk	_____
Hoarse voice/dysphonia/aphonia	☐ Yes	☐ No	☐ Unk	_____
Dyspnea	☐ Yes	☐ No	☐ Unk	_____
Wheezing	☐ Yes	☐ No	☐ Unk	_____
Stridor	☐ Yes	☐ No	☐ Unk	_____
Sensation of chest tightness	☐ Yes	☐ No	☐ Unk	_____
Tachypnea	☐ Yes	☐ No	☐ Unk	_____
Recession/indrawing	☐ Yes	☐ No	☐ Unk	_____
Cough	☐ Yes	☐ No	☐ Unk	_____
Was it a dry cough?	☐ Yes	☐ No	☐ Unk	_____
Gastrointestinal symptoms				
Nausea/ Vomiting	☐ Yes	☐ No	☐ Unk	_____
Abdominal pain / Diarrhea	☐ Yes	☐ No	☐ Unk	_____
Any other symptom, specify	☐ Yes			_____
Treatments				
Epinephrine	☐ Yes	☐ No	☐ Unk	_____
Corticosteroids	☐ Yes	☐ No	☐ Unk	_____
Antihistamines	☐ Yes	☐ No	☐ Unk	_____
Other: If Yes, specify	☐ Yes	☐ No	☐ Unk	_____

SKIN TESTING WITH VACCINE	☐ **Yes** ☐ **No (Skip to Next Page: NEUROLOGICAL SYMPTOMS)**		
Positive Control (Histamine)	☐ Positive	☐ Negative	☐ Undetermined
PRICK TEST (FULL STRENGTH) ** Add suppl. pages if testing > 3 vaccines or >1 other allergen*			
Saline	☐ Positive	☐ Negative	☐ Undetermined
Vaccine 1: _____	☐ Positive	☐ Negative	☐ Undetermined
Vaccine 2: _____	☐ Positive	☐ Negative	☐ Undetermined
Vaccine 3: _____	☐ Positive	☐ Negative	☐ Undetermined
Vaccine 4: _____	☐ Positive	☐ Negative	☐ Undetermined
Vaccine 5: _____	☐ Positive	☐ Negative	☐ Undetermined
Other allergen: _____	☐ Positive	☐ Negative	☐ Undetermined
Other allergen: _____	☐ Positive	☐ Negative	☐ Undetermined
Other allergen: _____	☐ Positive	☐ Negative	☐ Undetermined
INTRADERMAL TEST (DILUTED 1:100)			
Saline	☐ Positive	☐ Negative	☐ Undetermined
Vaccine 1: _____	☐ Positive	☐ Negative	☐ Undetermined
Vaccine 2: _____	☐ Positive	☐ Negative	☐ Undetermined
Vaccine 3: _____	☐ Positive	☐ Negative	☐ Undetermined
Vaccine 4: _____	☐ Positive	☐ Negative	☐ Undetermined
Vaccine 5: _____	☐ Positive	☐ Negative	☐ Undetermined
Other allergen: _____	☐ Positive	☐ Negative	☐ Undetermined

Other allergen: _____	☐ Positive	☐ Negative	☐ Undetermined
Other allergen: _____	☐ Positive	☐ Negative	☐ Undetermined

Other allergy testing procedures	☐ **Yes** ☐ **No (Skip to Next Page: NEUROLOGICAL SYMPTOMS)**

	Yes	No	UNK			
ImmunoCap/RAST:	☐	☐	☐			
	Yes	No	Unk			
Specify: _____	☐ Yes			☐ Positive	☐ Negative	☐ Undetermined
Specify: _____	☐ Yes			☐ Positive	☐ Negative	☐ Undetermined
Other tests:	☐ Yes	☐ No	☐ Unk			
Specify: _____	☐ Yes			☐ Positive	☐ Negative	☐ Undetermined
Specify: _____	☐ Yes			☐ Positive	☐ Negative	☐ Undetermined

NEUROLOGICAL SYMPTOMS	☐ **Yes** ☐ **No (Skip to Page 9: FINAL DIAGNOSIS)**

SEIZURES	☐ **Yes** ☐ **No** **(Skip to Next section: Anaesthesia/Paresthesia /Dysesthesia)**			
Location				
Focal/Localized	☐ Yes	☐ No	☐ Unk	_____
Generalized	☐ Yes	☐ No	☐ Unk	_____
Type of movements				
Tonic	☐ Yes	☐ No	☐ Unk	_____
Clonic	☐ Yes	☐ No	☐ Unk	_____
Tonic-clonic	☐ Yes	☐ No	☐ Unk	_____
Myoclonic	☐ Yes	☐ No	☐ Unk	_____

Atonic	☐ Yes	☐ No	☐ Unk	_____
Absence seizures	☐ Yes	☐ No	☐ Unk	_____
Other, specify: _____	☐ Yes	☐ No	☐ Unk	_____
Other				
Sudden onset was witnessed	☐ Yes	☐ No	☐ Unk	_____
Loss of consciousness	☐ Yes	☐ No	☐ Unk	_____
Post-ictal drowsiness	☐ Yes	☐ No	☐ Unk	_____
Other, specify: _____	☐ Yes			_____
Number of episodes and duration				
Number of episodes :_____ Duration of episodes:_____ minutes				
Status epilepticus	☐ Yes	☐ No	☐ Unk	_____

Anaesthesia/Paresthesia /Dysesthesia	☐ **Yes** ☐ **No (Skip to Next section: Encephalitis/Myelitis)**

Anaesthesia/Paresthesia/Dysesthesia				
Numbness, tingling, prickling	☐ Yes	☐ No	☐ Unk	_____
Hypoesthesia/Anesthesia	☐ Yes	☐ No	☐ Unk	_____
Pain	☐ Yes	☐ No	☐ Unk	_____
Burning sensation	☐ Yes	☐ No	☐ Unk	_____
Electrical shocks	☐ Yes	☐ No	☐ Unk	_____

Hyperesthesia/Allodynia	☐ Yes	☐ No	☐ Unk	_____
Area affected				
Upper limb – Vaccinated side	☐ Yes	☐ No	☐ Unk	_____
Upper limb – Unvaccinated side	☐ Yes	☐ No	☐ Unk	_____
Head/neck/ Face	☐ Yes	☐ No	☐ Unk	_____
Trunk/Back	☐ Yes	☐ No	☐ Unk	_____
Lower limb – Vaccinated side	☐ Yes	☐ No	☐ Unk	_____
Lower limb – Unvaccinated side	☐ Yes	☐ No	☐ Unk	_____
Other, specify:_____	☐ Yes			_____

Encephalitis/Myelitis	☐ **Yes** ☐ **No (Skip to Next section: Other neurological symptoms)**			
Focal cortical signs	☐ Yes	☐ No	☐ Unk	_____
Cerebellar dysfunction	☐ Yes	☐ No	☐ Unk	_____
Cranial nerve abnormality	☐ Yes	☐ No	☐ Unk	_____
Presence of primitive reflexes	☐ Yes	☐ No	☐ Unk	_____
Myelopathy	☐ Yes	☐ No	☐ Unk	_____
Personality changes lasting > 24 hours	☐ Yes	☐ No	☐ Unk	_____
Hypotonia (w/o seizures)	☐ Yes	☐ No	☐ Unk	_____
Abnormal deep tendon reflexes	☐ Yes	☐ No	☐ Unk	_____
Depressed/altered Level of consciousness >24h (w/o seizures)	☐ Yes	☐ No	☐ Unk	_____
Decreased/Absent response to noise/pain	☐ Yes	☐ No	☐ Unk	_____
Decreased/Absent eye contact	☐ Yes	☐ No	☐ Unk	_____
Decreased arousability	☐ Yes	☐ No	☐ Unk	_____

Other neurological symptoms	☐ **Yes** ☐ **No (Skip to Next section: Laboratory / Imaging Results)**			
Sensory disturbances				
Visual problems, specify	☐ Yes	☐ No	☐ Unk	_____
Speech problems, specify	☐ Yes	☐ No	☐ Unk	_____
Other, specify:_____	☐ Yes			_____
Motor disturbances				

Difficulty catching or handing objects	☐ Yes	☐ No	☐ Unk	_____
Difficulty lifting arms over head	☐ Yes	☐ No	☐ Unk	_____
Difficulty standing up from seating	☐ Yes	☐ No	☐ Unk	_____
Difficulty climbing stairs	☐ Yes	☐ No	☐ Unk	_____
Difficulty walking	☐ Yes	☐ No	☐ Unk	_____
Difficulty keeping balance	☐ Yes	☐ No	☐ Unk	_____
Other, specify:_____	☐ Yes			_____
Other				
Bowel or bladder dysfunction	☐ Yes	☐ No	☐ Unk	_____
Erectile dysfunction	☐ Yes	☐ No	☐ Unk	_____
Other, specify:_____	☐ Yes			_____

Laboratory / Imaging Results	☐ **Yes** ☐ **No (Skip to Next Page: FINAL DIAGNOSIS)**			
	Done	**Not done**	**UNK**	
Neuroimaging (CT scan, MRI, etc)	☐ Yes	☐ No	☐ Unk	Results:_____
Lumbar puncture	☐ Yes	☐ No	☐ Unk	Results:_____
Electromyography	☐ Yes	☐ No	☐ Unk	Results:_____
Other: _____	☐ Yes → Results: _____			

Other:

_____ ☐Yes → Results:

__ _____

FINAL DIAGNOSIS OF THE MAIN AEFI

Injection Site reaction	**Allergic-like reaction**
☐ Large local reaction *(≥10 cm diameter)*	☐ Anaphylaxis
☐ Cellulitis, infectious	☐ Non anaphylactic immediate hypersensitivity (onset <4 hours)
☐ Abscess, infectious	☐ Oculo-respiratory syndrome
☐ Abscess, sterile	☐ Delayed urticaria/angioedema (onset≥4 hours)
☐ Nodule	☐ Other (specify): _____
☐ Other (specify): _____	
Neurological AEFIs	**Other Systemic AEFIs**
☐ Seizures, febrile	☐ Fever
☐ Seizures, other	☐ Hypotonic-hyporesponsive episode (HHE)
☐ Anaesthesia/paresthesia	☐ Persistent crying
☐ Peripheral neuropathy	☐ Arthralgia/Arthritis
☐ Encephalitis, myelitis, or ADEM	☐ Thrombocytopenia (platelet count:_____)
☐ Meningitis (aseptic/viral/bacterial)	☐ Non-urticarial rash
☐ Guillain-Barré/Fisher-Miller Syndrome	☐ Vasovagal/Anxiety reaction
☐ Other (specify): _____	☐ Other (specify): _____

CAUSALITY ASSESSMENT

☐ **Consistent with causal association to immunization**

- ☐ Vaccine product-related reaction
- ☐ Immunization error reaction
- ☐ Immunization anxiety related reaction

☐ **Inconsistent with causal association to immunization**

- ☐ Underlying or emerging condition
- ☐ Caused by exposure other than vaccine

☐ **Indeterminate**

- ☐ Temporal association consistent but insufficient evidence
- ☐ Factors result in conflicting trends consistent and inconsistent with causal association

☐ **Unclassifiable because information is missing**

For All Patients ☐N/A

EVALUATION OF RISKS AND BENEFITS		
Physical examination		
↳Recorded temp. _____ ☐C° ☐F° mode: ☐Rectal ☐Oral ☐Axillary ☐Tympanic ☐ Temp unknown		
☐**Feeling well and examination normal** ☐**Examination was abnormal, please specify: _____** _____		
	Yes **No** **N/A**	
Serology(s) requested? (if Yes, specify) 1. _____ _____ 2. _____ _____	☐ ☐ ☐	Results: _____ Results: _____
Vaccine Name (Antigen)	**Vaccine 1:_____**	**Vaccine 2:_____**
Additional doses of the vaccine required?	**Yes** ☐ **No** ☐ **N/A** ☐	**Yes** ☐ **No** ☐ **N/A** ☐
Physician Risk/Benefit Assessment ☐Not Done		
Est. Risk of Immunization	☐ Low ☐Moderate ☐High	☐ Low ☐Moderate ☐High
Est. Benefit of Immunization	☐Low ☐Moderate ☐High ☐None	☐Low ☐Moderate ☐High ☐ None
Overall Risk Assessment	☐ Risk of immunization outweighs benefit ☐ Risks and Benefits are similar ☐ Benefit of immunization outweighs risk	☐ Risk of immunization outweighs benefit ☐ Risks and Benefits are similar ☐ Benefit of immunization outweighs risk
Recommendation for vaccination / revaccination		
Vaccination not recommended	☐ Risk considered too high for the benefit ☐ Not indicated, specify: _____	☐ Risk considered too high for the benefit ☐ Not indicated, specify: _____
Vaccination recommended	☐ Patient was revaccinated at SIC ☐ Patient will be revaccinated by GP/PH ☐ Patient will return to SIC in:_____ months :_____years ☐ Patient opted to defer immunization ☐ Patient refused immunization ☐ Dose not yet due	☐ Patient was revaccinated at SIC ☐ Patient will be revaccinated by GP/PH ☐ Patient will return to SIC in:_____ months :_____years ☐ Patient opted to defer immunization ☐ Patient refused immunization ☐ Dose not yet due

Recommendation deferred	☐ Re-assessment needed ☐ Sent to a specialist	☐ Re-assessment needed ☐ Sent to a specialist
Other, specify:	_____ _____ _____	_____ _____ _____

Notes and comments on Risks, benefits, and recommendations

EVALUATION FORMS COMPLETED BY			
Name: _____	**Signature:** _____	☐ Nurse ☐ MD ☐ Other:_____	**Date of evaluation:** _____ dd / mmm / yyyy

VACCINE(S) ADMINISTERED						
Date Administered	☐☐/☐☐☐/☐☐☐☐(dd/mmm/yyyy)					
Vaccine Name	**Brand Name**	**Lot #**	**Dose #**	**Site/Route**	**Dose (mL)**	**# of doses**
1.						☐ Single full dose ☐ Graded doses ☐ UNK
2.						☐ Single full dose ☐ Graded doses ☐ UNK
3.						☐ Single full dose ☐ Graded doses ☐ UNK
4.						☐ Single full dose ☐ Graded doses ☐ UNK
5.						☐ Single full dose ☐ Graded doses ☐ UNK
6.						☐ Single full dose ☐ Graded doses ☐ UNK

IMMEDIATE OUTCOME (<30 min post vaccine)	
AEFI occurrence ☐No AEFI ☐ AEFI reported ☐ UNK	
Nature of AEFI *(only for patients who consulted for past AEFI)*	☐ Different AEFI ☐Same AEFI ☐UNK

Relative severity of recurrent AEFI *(only for patients who consulted for past AEFI)*	☐ Milder ☐Same severity ☐More severe ☐UNK
7 DAYS POST VACCINE OUTCOME	
Follow-up Date	☐☐/☐☐☐/☐☐☐☐(dd/mmm/yyyy)
Follow-up type	☐ Phone call ☐ Email ☐ Other, specify: _____
AEFI Occurrence	☐ No AEFI ☐ AEFI reported ☐ UNK
Interval between vaccination and onset of symptom	_____hours _____days
Nature of AEFI *(only for patients who consulted for past AEFI)*	☐ Different AEFI ☐ Same AEFI ☐ UNK
Level of Medical Care Needed	☐ Called Health Info Line ☐ Consulted a physician ☐Was hospitalized ☐ None
Effect of AEFI on daily activities (DA)	☐ Unaffected DA ☐ Limited DA ☐ Prevented DA ☐ UNK
Relative severity of recurrent AEFI *(only for patients who consulted for past AEFI)*	☐ Milder ☐Same severity ☐More severe ☐UNK
Impact of AEFI *(defined on page 2)*	☐ Low ☐ Moderate ☐ High ☐ Serious
How long did AEFI persist?	Hours :_____ Days :_____
Final Diagnosis of AEFI *(defined on page 9)*	☐ Injection Site ☐ Allergic-like ☐ Neurologic ☐ Other Systemic
Causality Assessment of AEFI *(defined on page 9)*	☐ Consistent ☐ Inconsistent ☐ Indeterminate ☐ Unclassifiable

Description of the AEFI

FORM COMPLETED BY			
Name: _____	**Signature: _____**	☐ Nurse ☐ MD ☐ Other:_____	**Date of evaluation:** _____ dd / mmm / yyyy

Only for patients requiring a follow-up longer than 7 days

☐N/A