Managing Adverse Events Following Immunization: Resource for Public Health

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Contents

INTRODUCTION

Purpose: The purpose of this document is to provide an overview of the Adverse Events Following Immunizations (AEFIs) seen at the Canadian Special Immunization Clinics (SICs), and to provide assistance to Medical Officers of Health (MOHs) and other public health officials who review AEFI reports and make recommendations to vaccine providers regarding continuing immunization and indications for specialist referral. We hope that this document will aid MOHs in their review and assessment of AEFIs. This document was developed by the Special Immunization Clinic (SIC) Network Investigators and has been adapted for public health use. This document is not comprehensive and may not include all specific AEFIs which are investigated or reported in your jurisdiction. It is also not intended to supersede Provincial or Territorial Guidelines or clinical judgement. For information on public health reporting requirements, refer to your provincial or territorial guidelines.

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SIC Network: The SIC network, which is part of the Canadian Immunization Research Network, aims to improve the evaluation and management of patients with medically challenging AEFIs and underlying medical conditions that may complicate immunization. The network was established across Canada in 2013 by infectious disease specialists and allergists. There are 11 special immunization clinics across six Canadian provinces: British Columbia, Saskatchewan, Nova Scotia, Alberta (two clinics), Ontario (three clinics), and Quebec (three clinics).(CIRN, 2018).

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LIST OF ABBREVIATIONS AND ACRONYMS

AEFIs	Adverse events following immunization(s)
ALE	Allergic-like events
APTI	Apnea in preterm infants
ARD	Acute respiratory disease
CI	Confidence interval
CIRN	Canadian Immunization Research Network
DTaP	Diphtheria-tetanus-acellular pertussis vaccine
DTaP-IPV-Hib	Diphtheria-tetanus-acellular pertussis-inactivated polio-*Haemophilus influenzae* type b conjugate vaccine
DTwP	Diphtheria-tetanus-whole-cell pertussis vaccine
ELS	Extensive limb swelling
ESPRI	Programme de surveillance des effets secondaires possiblement reliés à l'immunisation
GBS	Guillain-Barré syndrome
GI	Gastrointestinal
Hep B	Hepatitis B vaccine
HHE	Hypotonic-hyporesponsive episode
HPV	Human papillomavirus vaccine
HSP	Henoch-schönlein purpura
IDT	Intradermal dilutional testing
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IM	Intramuscular
LLR	Large local reaction
LR	Local reaction at the injection site
MMR	Measles, mumps-rubella vaccine
MMRV	Measles-mumps-rubella-varicella vaccine
MOH	Medical Officer of Health
ORS	Oculo-respiratory syndrome
PCV	Pneumococcal conjugate vaccine
RCT	Randomized controlled trial

SIC	Special Immunization Clinic
Tdap	Tetanus toxoid, reduced diphtheria toxoid, acellular pertussis vaccine
Tdap-IPV	Tetanus toxoid, reduced diphtheria toxoid, acellular pertussis, inactivated poliomyelitis vaccine
TIV	Trivalent inactivated influenza vaccine
TP	Thrombocytopenia
WAO	World Allergy Organization

ALLERGIC-LIKE EVENTS (INCLUDING ANAPHYLAXIS)

Definitions:

Allergic-like events (ALE)

- 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
- *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

Anaphylaxis (World Allergy Organization definition)

- 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

Management:

Specific condition	Management	Relevant Vaccines
Symptoms of anaphylaxis with onset <24 hours after immunization*	Refer for further assessment	All vaccines
	Do not give vaccines with the same components or excipients as the implicated vaccine pending evaluation	
Symptoms of non-anaphylactic immediate hypersensitivity with onset <1 hour after immunization*	Refer for further assessment	All vaccines
	Do not give vaccines with the same components or excipients as the implicated vaccine pending evaluation	
Symptoms of non-anaphylactic immediate hypersensitivity with onset 1–24 hours after immunization	Revaccinate under supervision	All vaccines
	Consider specialist referral	
Type III or IV hypersensitivity reactions or severe cutaneous reactions**	Refer for further assessment	All vaccines
	Do not give vaccines with the same components or excipients as the implicated vaccine pending evaluation	

**For patients with symptoms suggestive of type I hypersensitivity with onset within 1 hour after vaccination, it is important to distinguish such events from vasovagal reactions, panic attack and HHE.*

***Patients with type III or IV hypersensitivity reactions: Revaccination may be considered based on risk-benefit assessment after investigation for possible other triggers. For those with severe cutaneous reactions (e.g., Stevens Johnson Syndrome, toxic epidermal necrolysis) and no evidence of other triggers, revaccination is generally contraindicated.*

When to Refer:

All patients who have experienced anaphylaxis within 24 hours following immunization as well as those with symptoms of non-anaphylactic immediate hypersensitivity within 1 hour after immunization should be recommended for further assessment at a SIC or by an allergist. Further assessment may be considered for patients with symptoms suggestive of immediate hypersensitivity with onset 1–24 hours after immunization. Patients with symptom onset >24 hours suggestive of type III or type IV hypersensitivity or severe cutaneous reactions should be referred for further assessment to a SIC, allergist, or infectious disease specialist.

Supporting Literature (See Appendix for more details):

Non-anaphylactic allergic-like events

In a systematic review across 8 studies of non-anaphylactic ALEs, the pooled estimate of recurrence risk among 594 revaccinated patients was 4% (95% confidence interval (CI): 0–10%) (Zafack et al, 2017). None experienced anaphylaxis on revaccination. In a chart review in Quebec, the risk of recurrence of ALE was highest when onset of initial ALE was within 1 hour after vaccination (24%, 8/34) (Zafack et al, 2016). Recurrences occurred in 0 of 15 patients whose primary ALE had onset 1–4 hours after vaccination and 1 of 34 (3%) patients with ALE onset >4 hours after vaccination. In the Quebec ESPRI database (1998-2016), 76/659 patients (12%) with ALEs developed a recurrence of the ALE after revaccination.

Anaphylaxis

A systematic review identified two studies which reviewed the risk of recurrence of anaphylaxis after immunization among 133 patients and no recurrences (0%) were observed (Zafack et al, 2017). All but 1 patient had negative skin testing against the vaccine prior to revaccination. In Quebec, 8 patients with anaphylaxis were revaccinated after allergy evaluation and no recurrences were reported. (ESPRI 1998-2016).

APNEA IN PRETERM INFANTS (APTI)

Definition:

- Cessation of breathing for ≥20 seconds or breathing pause <20 seconds accompanied by bradycardia (<100 bpm), cyanosis or pallor
  - Usually self-limited and without long-term sequelae
  - Generally seen in preterm infants born at <37 weeks gestation who are <67 days of age at the time of vaccination
  - Differential diagnosis includes: cardiac or respiratory congenital malformation, infection

Management:

Specific condition	Management	Relevant Vaccines
APTI with any vaccine	Consider specialist referral	All vaccines
	If outpatient, consider hospital admission for cardiorespiratory monitoring for at least 24 hours after revaccination	
	Advise parents of risk of recurrence	

When to Refer:

Infants <12 months of age with a history of new onset apnea or >50% increase in frequency of apnea from baseline within 24 hours after vaccination may be referred to the SIC or assessed by a pediatrician, infectious disease specialist or neonatologist. Referral is specifically recommended for infants who are not hospitalized at the time of the first vaccination and/or those who are expected to be discharged prior to the next vaccine dose.

Supporting Literature:

Two studies assessed the risk of recurrence of apnea after immunization among preterm infants and found an overall recurrence risk of 18% (13 of 71) (95% CI: 10-28%) (Clifford et al, 2011; Flatz-Jequier et al 2008). Only one study assessed recurrence of apnea among term infants and there were 0 recurrences among 8 infants revaccinated (Clifford et al, 2011).

ARTHRALGIA/ARTHRITIS

Definition:

- Pain in one or more joints, with or without joint effusion (swelling), erythema or warmth

Arthralgia and rubella-containing vaccines: An increased risk of transient arthralgia and arthritis with onset 1-3 weeks after immunization has been associated with rubella-containing vaccines (e.g., MMR). Symptoms may last for 1-3 weeks and recurrence is rare. There is no increased risk of chronic arthropathy after MMR.

Management:

Specific condition	Management	Relevant Vaccines
Arthralgia/arthritis	Revaccinate	All vaccines

When to Refer:

Patients who experienced self-limited arthralgia/arthritis after vaccination can be safely revaccinated by Public Health or their primary care physician. Patients who develop recurrent or chronic arthritis after vaccination should be assessed by a rheumatologist. Patients who have experienced clinically significant arthralgia/arthritis occurring **within 5 to 30 days** of vaccination may be seen at a SIC or by a pediatrician or infectious disease specialist.

Supporting Literature:

There is a paucity of literature regarding revaccination after arthralgia. One study showed no recurrence (0%) for 7 patients revaccinated after a previous myalgia/arthralgia lasting longer than 3 days (McMahon et al., 1992). In Quebec, among 24 patients revaccinated, 6 (25%) had recurrences, none of which were more severe than the initial episode. Three patients with arthralgia after MMR vaccine received a second dose of MMR and none experienced a recurrence. (ESPRI, 1998-2016).

FEVER

Definition:

- Elevation of body temperature ≥38°C from any site

Management:

Specific condition	Management	Relevant Vaccines
History of any fever	Revaccinate	All vaccines
	Advise parents about risk of recurrence	
	Consider treatment with acetaminophen or ibuprofen at onset of fever. Prophylactic use of antipyretics is not recommended	

When to Refer:

Fever is one of the most common AEFIs and is generally mild and self-limited. Patients who experienced fever after vaccination can be revaccinated by their primary care physician or Public Health. Patients who have experienced recurrent fevers of ≥**40.5°C (105°F)** within **72 hours** after an inactivated vaccine or **within the appropriate interval after a live vaccine** (e.g., 5-12 days after MMR) may be referred to a SIC, pediatrician or infectious disease specialist.

Supporting Literature:

Across 5 studies of revaccination of patients with previous fever after various vaccines, the pooled estimated risk of fever recurrence was 33% (95% CI: 16-53%) (Zafack et al, 2017). In Quebec, 15% of patients with previous fever reported a recurrence. The recurrence was considered more severe in only two cases (22%) (ESPRI, 1998-2016). The risk of recurrence did not differ by the height of the recorded temperature (39°C to 40.4°C versus ≥40.5°C). There is no evidence that prophylactic use of antipyretics reduces the risk of post-immunization fever.

GUILLAIN-BARRÉ SYNDROME (GBS)

Definition:

- 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.

Management:

Specific condition	Management	Relevant Vaccines
GBS within 6 weeks of influenza vaccination	Refer for further assessment	Influenza vaccine
	Do not vaccinate unless the patient is at high risk of severe influenza complications	
	Consider antiviral chemoprophylaxis in high-risk individuals	
	If revaccinated, advise patients of possible risk of recurrence	
GBS within 6 weeks of Tetanus toxoid-containing vaccine	Refer for further assessment	Tetanus toxoid-containing vaccines
	Consider the risks and benefits of revaccination, particularly for those who have not completed the primary series	
GBS within 6 weeks of other vaccines	Consider revaccination	Non-tetanus or influenza-containing vaccines

Previous GBS outside of the 6 week interval post-vaccination	Vaccinate	All vaccines

When to Refer:

Patients with a history of GBS not associated with vaccination can be vaccinated by their primary care physician or Public Health. No GBS recurrences after revaccination were observed in one study; however, there is a theoretical risk of recurrence after influenza or tetanus-containing vaccines. Patients with GBS post-vaccination may be safely revaccinated by their primary care physician or Public Health. Patients with a history of GBS with onset within 6 weeks following a vaccine, especially an influenza and tetanus toxoid-containing vaccine, should be referred to the SIC, a neurologist and/or an infectious disease specialist.

Supporting Literature:

Only one study has assessed the risk of recurrence of GBS after revaccination (Baxter et al, 2012). Two of 18 patients with GBS occurring within 6 weeks after influenza vaccination were revaccinated and none (0%) experienced a recurrence. Among 550 GBS cases identified overall, 279 received one or more vaccines after diagnosis and none (0%) experienced a recurrence of GBS. There is one reported case of a patient with 3 episodes of GBS that each followed tetanus toxoid injection.

HENOCH-SCHÖNLEIN PURPURA (HSP)

Definition:

- Systemic small vessel vasculitis which can affect the skin, joints, bowel and kidneys
- No confirmed causal associations with vaccination

Management:

Specific condition	Management	Relevant Vaccines
HSP following any vaccine	Consider referral for further assessment	All vaccines
	In case of revaccination, monitor for 4-6 weeks post-vaccination	

When to Refer:

Patients with HSP within 6 weeks of vaccination may be referred for further assessment to a SIC, pediatrician, infectious disease specialist, or rheumatologist.

Supporting Literature:

In one study of HSP after meningococcal B vaccine, 1 of 6 patients (17%) developed a recurrence after the second dose but none occurred after the third dose (Sexton et al, 2009).

HYPOTONIC-HYPORESPONSIVE EPISODE (HHE)

Definition:

- 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

Management:

Specific condition	Management	Relevant Vaccines
HHE	Revaccinate	All vaccines

When to Refer:

Patients who have experienced HHE can be safely reimmunized by Public Health or their primary care physician. Where there is parental or health care provider concern, patients with HHE occurring within **48 hours** of vaccination could be referred to a SIC, pediatrician or infectious disease specialist.

Supporting Literature:

In a meta-analysis of studies published before 2017 presenting revaccination data on children after a previous HHE, there were only 3 cases of recurrence, giving a pooled estimated risk of recurrence of 0.8% (95% CI: 0.2-2.2%) (Zafack et al 2017). In Quebec (1998-2016), of 50 children with a previous HHE that were revaccinated, one (2%) had a recurrence that was less severe than the initial episode. A study of 235 cases of HHE identified 7 recurrences for a recurrence rate of 3% (95% CI, 1–6%) (Crawford et al, 2018).

LOCAL REACTIONS AT THE INJECTION SITE (LRs)

Types of Local Reactions:

Large local reaction (LLR)

- 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
    - When erythema/swelling crosses joint or extends joint-to-joint, it is referred to as "extensive limb swelling" (ELS)
    - This is the most frequently reported AEFI

Arthus reaction (Type III hypersensitivity)

- Reaction at the injection site characterized by inflammation and skin necrosis in severe cases
- Can be extensive and involve entire limb
- Skin biopsy typically shows evidence of local vasculitis and deposition of antigen-antibody complexes

Abscess

- 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)*
    - Sterile abscesses (e.g., *cold abscesses*) are collections of fluid in the absence of signs of infection/inflammation
- Some LRs may mimic an infectious abscess, but are due to intense inflammatory reactions, hypersensitivity or administration errors (e.g., short needle and/or subcutaneous injection instead of intramuscular)
- Differential diagnosis includes LLR, hypersensitivity reactions (Type III), nodules, and cellulitis

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
- The above symptoms may be accompanied by fever (≥38°C) and/or regional lymphadenopathy
- Distinguished from LLRs 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
- If there is evidence of abscess on clinical exam (e.g., fluctuance) or on ultrasound, manage as for abscess

Management:

Specific condition	Management	Relevant Vaccines
LLR	Revaccinate	All vaccines
	Advise of risk of recurrence	
	Symptomatic management as clinically indicated post-vaccination (e.g., analgesics, antihistamines)	
ELS after 4th dose DTaP-IPV-Hib	Consider use of reduced antigen Tdap-IPV for 5th dose (routinely used in some provinces)	DTaP-containing vaccines
Arthus reaction in children <6 months of age	Refer for further assessment	All vaccines
	Defer subsequent doses until assessed and/or ≥6 months of age	
Arthus reaction after tetanus/diphtheria-containing vaccines	Monitor anti-toxin levels and expand interval between doses to ≥10 years	Tetanus/diphtheria-containing vaccines
Sterile abscess	Revaccinate*	All vaccines
	Use alternate site for next dose	
Infectious abscess	Revaccinate	All vaccines
	Consider alternate site for next dose	
Infectious or non-infectious cellulitis	Revaccinate	All vaccines

**If revaccinating a patient with scarring from a previous abscess, evaluate the risk-benefit of revaccination and/or delaying next dose.*

When to Refer:

Patients who experienced LLRs can be safely revaccinated by Public Health or their primary care physician. Patients with LLRs and sterile abscess should be advised that they may experience a recurrent reaction following revaccination (approximately 20-50% risk based on data available); however, such events are only rarely more severe than the first event. Consider referral to a SIC, allergist or infectious disease specialist for patients who have experienced Arthus reactions, especially children <6 months of age, recurrent LLRs ≥10cm, recurrent abscess (sterile or pyogenic), or recurrent cellulitis following vaccination.

Supporting Literature:

Large local reactions: Most studies included patients with LRs of small size (2.5 to <10cm) and none reported the risk of recurrence restricted to LLRs (≥10 cm). In the SIC network from 2013 to 2015, 6 of 14 patients (43%) who were revaccinated developed a recurrent LLR (Top et al, 2016). In the Quebec ESPRI database (1998-2016), recurrence after a LLR occurred in 22% (44/203) revaccinated patients and was considered more severe than the first event in 9% of these cases. A systematic review found that in 3 studies the risk of recurrence of ELS after DTaP or Tdap was 56% among children with a LLR after DTaP dose 4 (Zafack et al, 2017).

Abscesses: No study of abscess recurrence was found in the medical literature. Data from the Quebec ESPRI database suggests that there may be a high rate of recurrence of sterile abscesses or nodules (10/21, 48%); recurrence was considered more severe in 2 of 9 cases (22%). For infectious abscesses, recurrence occurred in 1 of 4 cases and none of the recurrences was considered more severe than the first event.

Cellulitis: In Quebec (1998-2016), of the 12 patients with cellulitis who were revaccinated, one had a recurrence that was not more severe than the initial cellulitis.

OCULO-RESPIRATORY SYNDROME (ORS)

Definition:

- 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

**If there is a cutaneous rash, manage as an allergic-like event*

Management:

Specific condition	Management	Relevant Vaccines
ORS without severe respiratory symptoms	Revaccinate	Influenza vaccine
ORS with severe respiratory symptoms*	Refer for further assessment	Influenza vaccine

**Severe respiratory symptoms are defined as those associated with respiratory compromise as per the World Allergy Organization definition of anaphylaxis: dyspnea, wheeze/bronchospasm, stridor, cyanosis/hypoxemia*

When to Refer:

Patients with mild to moderate symptoms of ORS can be revaccinated by their primary care physician or Public Health. Patients who have experienced ORS with severe respiratory symptoms within 24 hours following immunization should be referred for further assessment such as a SIC, allergist, or infectious disease specialist. The clinical presentation of ORS with severe respiratory symptoms can overlap with the presentation of anaphylaxis. If anaphylaxis is a concern, please refer to the section on allergic-like reactions for further information.

Supporting Literature:

Studies presenting data on the revaccination of cases with previous ORS symptoms show recurrence in 5-44%. In a systematic review, recurrence of ORS was assessed in 4 studies and the pooled estimated recurrence risk was 21% (95% CI: 7-39%). Most recurrences were considered mild.

PERSISTENT CRYING

Definition:

- 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

Management:

Specific condition	Management	Relevant Vaccines
Persistent crying ≥3 hours	Revaccinate	All vaccines
	Advise parents about possibility of recurrence	
	Consider pain management with acetaminophen or ibuprofen	

When to Refer:

Patients who have experienced persistent crying lasting ≥3 hours can be safely reimmunized by Public Health or their primary care physician. Where there is parental or health care provider concern, patients with persistent crying at least 3 hours with onset within 48 hours after vaccination may be seen at a SIC, by a pediatrician, or infectious disease specialist.

Supporting Literature:

A systematic review found two studies of revaccination of children with previous persistent/prolonged crying and showed an overall recurrence risk of 24% (95% CI: 20-29%) (Zafack et al, 2016). In Quebec, recurrence occurred in 8 of 49 cases (16%) with persistent crying and was considered more severe in one case (13%) (ESPRI, 1998-2016).

SEIZURES

Definition:

- Episode(s) of hyperactivity in the brain most commonly resulting in sudden, involuntary muscle contractions and abnormal behaviour, with or without loss or impairment of consciousness
    - Generalized seizure is defined as sudden loss of consciousness with generalized, tonic, clonic, tonic-clonic, or atonic motor manifestations
    - Febrile seizures are brief, generalized or focal (partial) seizures occurring in association with fever in children 6 months to 6 years of age

Febrile seizure after MMR and MMRV: MMRV (measles-mumps-rubella-varicella) administered as the first dose of measles-containing vaccine has been associated with a 2-fold increased risk of febrile seizure 7-10 days after immunization when compared with MMR and varicella given as separate vaccines on the same day.(Klein et al, 2010; MacDonald et al, 2014). When MMRV is given as the second dose of measles-containing vaccine, the risk of febrile seizure is not increased (Macartney et al, 2017). Febrile seizure after MMR or MMRV is associated with development of a protective immune response to measles and patients can be reassured that febrile seizures are not expected to recur following the second dose. Previous history of seizure is not a contraindication to receiving vaccines.

Management:

Specific condition	Management	Relevant Vaccines
Seizure after immunization	Revaccinate. Use of antipyretics does not prevent febrile seizure	All vaccines
Status epilepticus after immunization	Consider neurology referral prior to revaccination	All vaccines

When to Refer:

Most patients with febrile and afebrile seizures after immunization can be safely revaccinated by a primary care physician or Public Health. Patients with seizures occurring **within 72 hours** of an **inactivated vaccine** or **within 5 to 14 days of a live vaccine** can be seen at a SIC, or by a pediatrician or infectious disease specialist. Patients with status epilepticus or afebrile seizures after immunization should be referred to a neurologist.

Supporting Literature:

In a systematic review, three studies assessed the risk of recurrence of seizure in which 0 of 60 patients developed a recurrence (0% recurrence, 95% CI: 0-3%) (Zafack et al, 2017).

In the SIC network, 2 of 8 patients (25%) developed recurrence of seizure after revaccination (Top et al, 2016). In Quebec, 3 of 49 patients (6%) with seizure had a recurrence upon revaccination. None of the recurrences were considered more severe than the initial event. Of 33 patients with febrile seizures following MMR±V, none had a recurrence following revaccination. (ESPRI, 1998-2016).

THROMBOCYTOPENIA (TP)

Definition:

- Platelet count of less than 150 x 10^9/L
- When platelet counts drop well below 50 x 10^9/L, patients may present with petechiae, purpura, ecchymosis, epistaxis, or gingival, gastrointestinal, pulmonary, or intracranial bleeding

Management:

Specific condition	Management	Relevant Vaccines
TP within 6 weeks of MMR or MMRV vaccination	Refer for further assessment	MMR/MMRV vaccine
	Test for measles, mumps, rubella IgG in serum. A positive test result is an acceptable alternative to revaccination	
	If patient is revaccinated, monitor for 4-6 weeks post-vaccination	
TP within 6 weeks of administration of non-MMR-containing vaccine	Consider risks and benefits of revaccination. If revaccinated, monitor for 4-6 weeks post-vaccination	Vaccines other than MMR/MMRV
TP outside of the 6-week interval post-vaccination	Revaccinate	All vaccines

When to Refer:

Patients with idiopathic thrombocytopenia purpura within 6 weeks of vaccination may be referred to the SIC, a pediatrician, infectious disease specialist, or hematologist. Patients with thrombocytopenia within 6 weeks of MMR vaccine should be referred for further assessment including serologic testing.

Supporting Literature:

Three studies assessed the risk of recurrence of TP after MMR and other vaccines; no recurrences were observed among 65 patients (Zafack, 2017). In Quebec, 2 of 7 patients (29%) with TP after vaccination had a recurrence upon revaccination. (ESPRI, 1998-2016).

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GLOSSARY OF TERMS

Abscess

Collection of fluid located in the soft tissues at the injection site

Allergic-like events (ALE)

The presence of signs and symptoms suggestive of a hypersensitivity reaction, and include: mucocutaneous symptoms, cardiovascular symptoms, respiratory symptoms, and gastrointestinal (GI) symptoms

Anaphylaxis

Acute onset of illness within minutes to hours with involvement of: skin and/or mucosa **and** respiratory compromise **or** decreased blood pressure/end organ dysfunction; 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

The following occurring within minutes or hours after exposure to known allergen for that patient: decreased blood pressure (World Allergy Organization)

Apnea in preterm infants (APTI)

Cessation of breathing for ≥20 seconds or breathing pause <20 seconds accompanied by bradycardia (<100 bpm), cyanosis or pallor in an infant born at <37 weeks gestational age

Arthralgia

Pain in one or more joints, with or without joint effusion (swelling), erythema or warmth

Arthritis

Pain in one or more joints, with joint effusion (swelling), erythema or warmth

Arthus reaction (Type III hypersensitivity)

Injection-site reaction characterized by inflammation with skin necrosis

Cellulitis

Acute, expanding inflammatory condition of the skin at the vaccine injection site that is characterized by at least 3 of 4 symptoms/signs: localized pain or tenderness; erythema; induration or swelling; and/or warmth

Extensive limb swelling (ELS)

When erythema/swelling at the injection site crosses joint or extends joint-to-joint

Fever

Elevation of body temperature ≥ 38° C measured at any site

Fisher (or Miller-Fisher) syndrome:

Variant of Guillain-Barré syndrome characterized by paralysis of ocular movements with bilateral reduced reflexes and ataxia without limb weakness

Guillain-Barré syndrome (GBS)

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

Henoch-Schönlein purpura (HSP)

Systemic small vessel vasculitis which can affect the skin, joints, bowel and kidneys

Hypotonic-hyporesponsive episode (HHE)

Sudden onset in a child <2 years of age of hypotonia (reduced muscle tone) hyporesponsiveness, pallor or cyanosis

Large local reaction (LLR)

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 ≥10 cm in diameter

Oculo-respiratory syndrome (ORS)

Bilateral red eyes and/or facial swelling and/or respiratory symptoms occurring within 24 hours of influenza immunization

Persistent crying

Continuous and unaltered crying/screaming of infants and children, which is not interrupted by activities such as feeding or naps and persists ≥ 3 hours uninterrupted

Seizure

Episode of hyperactivity in the brain most commonly resulting in sudden, involuntary muscle contractions and abnormal behaviour, with or without loss or impairment of consciousness

Generalized seizure: Sudden loss of consciousness with generalized, tonic, clonic, tonic-clonic, or atonic motor manifestations

Febrile seizures: Brief, generalized or focal (partial) seizures occurring in association with fever in children 6 months to 6 years of age

Type III hypersensitivity reaction

Occurs when antigen-antibody immune complexes develop and fix complement leading to systemic symptoms such as high fever, rash, and arthritis. Onset is generally days to weeks after immunization

Type IV hypersentivity reaction

Delayed onset cell-mediated immune response that leads to development of cutaneous and systemic symptoms with onset generally >48 hours after immunization

Thrombocytopenia (TP)

Platelet count of less than 150 x 109/L

APPENDIX 1: SUPPORTING LITERATURE

ALLERGIC-LIKE EVENTS (ALEs)

Non-anaphylactic allergic-like events

Study	Vaccine	N	AEFI	Skin testing	Recurrences	Severity/ Comments
Micheletti, 2012	Various	352	ALE & Anaphylaxis (n ≤5)	As per clinician	19 (5%)	Only 1 ALE required treatment
Rouleau, 2012	Influenza (pandemic)	25	ALE	Yes	0 (0%) Anaphylaxis 5 ALE (20%)	Delayed self-limiting allergic-like symptoms, none of which were likely due to an IgE-mediated allergy ALE reported included 2 oculo-respiratory syndrome (ORS)-like reactions, delayed urticaria (1), anxiety reaction (1)
Cronin, 2012	Various	63	ALE or Reaction to previous dose	No	0 (0%)	Patients had history of ALEs, but most were not consistent with hypersensitivity reaction, per study authors
Gold, 2000	Various	33	ALE (Skin rash)	No	0 (0%)	
Jacobs, 1982	Td	38	ALE (Generalized non-specific rash)	Yes	0 (0%)	38 cases of generalized non-specific rash were skin tested and challenged. No recurrence was observed after revaccination
Top et al., 2016	Various	21	ALE	As per clinician	2 (10%)	1 mild recurrence in patient with neg skin testing 1 mild-mod recurrence in patient without skin testing
Zafack et al., 2017	Various	34 15 34	ALE onset ≤1h ALE onset 1-4h ALE onset >4h	-	8 (24%) 0 (0%) 1 (3%)	
TOTAL		**615**				

Anaphylaxis

Study	Vaccine	N	Skin testing	Recurrences	Severity/ Comments
Rouleau, 2012	Influenza (pandemic)	3	Yes	0 (0%) Anaphylaxis	No case of anaphylaxis was observed among 3 revaccinated cases of anaphylaxis; all had negative skin test results
Seitz, 2009	Various	38	Yes	0 (0%)	All patients tested had negative skin tests to the vaccine, but patients were only prick tested with undiluted vaccine (no IDT performed). All were challenged, none had cutaneous or systemic symptoms. Ten were also rechallenged with additional doses without AEFIs
Kang, 2008	HPV (Gardasil)	18	Yes	1 (6%)	Fractioned administration was done in 18 cases with negative skin tests. One patient reported limited urticaria over limbs and trunk 4 hours after 2nd dose
Jacobs, 1982	Td	95	Yes	0 (0%)	95 cases of anaphylaxis to Td were skin tested and revaccinated. Skin tests were negative in 94. No recurrences.
TOTAL		**154**			

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Cronin J, Scorr A, Russell S, McCoy S, Walsh S, O'Sullivan R. A review of a paediatric emergency department vaccination programme for patients at risk of allergy/anaphylaxis. *Acta Paediatr*. 2012 Sep;101(9):941-945.

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 Aug;83(2):128-131.

Jacobs RL, Lowe RS, Lanier BQ. Adverse reactions to tetanus toxoid. *JAMA*. 1982 Jan 1;247(1):40-42.

Kang LW, Crawford N, Tang ML, Buttery J, Royle J, Gold M, Ziegler C, Quinn P, Elia S, Choo S. Hypersensitivity reactions to human papillomavirus vaccine in Australian schoolgirls: retrospective cohort study. *BMJ*. 2008 Dec 2;337:a2642.

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Zafack JG, De Serres G, Rouleau I, Gariépy M-C, Gagnon R, Drolet J-P, et al. Clinical approach used in medical consultations for allergic-like events following immunization: Case series report in relation to practice guidelines. *J Allergy Clin Immunol Pract*. 2017 Jun;5(3):718–727.e1.

APNEA IN PRETERM INFANTS (APTI)

Study	Vaccine	Number of revaccinated patients with previous APTI	Number with recurrence	Severity/ Comments
Clifford et al., 2011	Various	38	7 (18%)	5/7 infants with recurrent APTI received their 3rd dose of vaccine without further events Predictors of recurrent apnea: -Lower birth weight: a 10 g increase in birth weight was associated with a 6% reduction in recurrent apnea (odds ratio 0.94 [95% CI 0.89-1.00]) -Hospitalization: Infants who were hospitalized were more likely to have a recurrence than those who were not. (OR 23 [95% CI 2–272])
Flatz-Jequier et al., 2008	DTaP	33	6 (18%)	
TOTAL		**71**		

References:

Clifford V, Crawford NW, Royle J, et al. Recurrent apnoea post immunisation: Informing re-immunisation policy. *Vaccine*. 2011 Aug 5;29(34):5681-5687.

Flatz-Jequier A, Posfay-Barbe KM, Pfister RE, et al. Recurrence of cardiorespiratory events following repeat DTaP-based combined immunization in very low birth weight premature infants. *The Journal of Pediatrics*. 2008 Sep;153(3):429-431.

ARTHRALGIA

Study	Vaccine	Number of revaccinated patients with previous Arthralgia	Number with recurrence	Severity/ Comments
McMahon et al., 1992	Hep B	7	0 (0%)	Previous myalgia/arthralgia lasting longer than 3 days
TOTAL		**7**	**0 (0%)**	

References:

McMahon BJ, Helminiak C, Wainwright RB et al. Frequency of adverse reactions to Hepatitis B vaccine in 43 618 persons. *The American Journal of Medicine*. 1992;92:254-256.

FEVER

Study	Vaccines	Number of revaccinated patients with previous fever	Number with recurrence	Severity/ Comments
Baraff et al., 1984	DTP	193	113 (59%)	Fever ≥38°C
		9	2 (22%)	Fever ≥39°C
Broos et al., 2010	Influenza A H1N1 (Pandemrix)	349	184 (53%)	Fever ≥38°C *After 1st dose*
Deloria et al., 1995	DTwP	58	19 (33%)	Fever >38°C *After 2nd dose*
		77	30 (39%)	Fever >38°C *After 3rd dose*
	DTaP	28	6 (31%)	Fever >38°C *After 2nd dose*
		76	14 (18%)	Fever >38°C *After 3rd dose*
Long et al., 1990	DTP	131	84 (64%)	Fever ≥38.3°C *After 1st dose*
		244	152 (62%)	Fever ≥38.3°C *After 2nd dose*
Nicolosi et al., 2014	Various	24	0 (0%)	
Top et al., 2016	Various	4	3 (75%)	2 less/equal severity to first event 1 more severe than first event
TOTAL		**1193**		

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Baraff LJ, Cherry JD, Cody CL, Marcy SM and Manclark CR. DTP Vaccine reactions: effect of prior reactions on rate of subsequent reactions. *Dev Biol Stand*. 1985;61:423-428.

Broos N, Van Puijenboaek EP and Van Grootheest K. Fever following immunization with Influenza A (H1N1) vaccine in children. *Drug Saf*. 2010:33(12):1109-1115.

Deloria MA, Blackwelder WC, Decker MD et al. Association of reactions after consecutive acellular or whole-cell Pertussis vaccine immunizations. *Pediatrics*. 1995;96:592-594.

Long SS, Deforest A, Smith DG, Lazaro C and Wassilak SG. Longitudinal study of adverse reactions following diphtheria-tetanus-pertussis vaccine in infancy. *Pediatrics*. 1990;85:294-302.

Nicolosi L, Vittucci A, Mancini R, et al. Vaccine risk assessment in children with a referred reaction to a previous vaccine dose: 2009-2011 retrospective report at the Bambino Gesu' children hospital, Rome, Italy. *Italian journal of pediatrics*. 2014 Mar;40:31.

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GUILLAIN-BARRÉ SYNDROME (GBS)

Study	Vaccine	Number of revaccinated patients with previous GBS	Number with recurrence	Severity/ Comments
Baxter et al., 2012	Various	2/18 patients with GBS within 6 weeks of influenza vaccine	0 (0%)	25 patients received a vaccine (any type) within 6 weeks of onset of 1st episode of GBS, not known how many of those were revaccinated
		279/550 patients with GBS received a vaccine after diagnosis	0 (0%)	6 confirmed recurrences, none occurred after immunization
TOTAL		**18**		

References:

Baxter R, Lewis N, Bakshi N, Vellozzi C, Klein NP, CISA Network. Recurrent Guillain-Barre syndrome following vaccination. *Clin Infect Dis*. 2012 Mar;54(6):800–804.

Pollard JD, Selby B. Relapsing neuropathy due to tetanus toxoid: Report of a case. *J Neurol Sci.* 1978 Jun;37(1-2):113-125.

HENOCH-SCHONLEIN PURPURA (HSP)

Study	Vaccine	Number of revaccinated patients with previous HSP	Number with recurrence	Severity/ Comments
Sexton et al., 2009	New Zealand Meningococcal B vaccine	6	1 (17%)	-Child with a recurrence received the third vaccine dose without further events -HSP occurring within 30 days following vaccination considered to be possibly associated with the vaccine
TOTAL		**6**		

References:

Sexton K, McNicholas A, Galloway Y, et al. Henoch-Schonlein purpura and meningococcal B vaccination. *Archives of Disease in Childhood*. 2009 Mar;94(3):224-226.

HYPOTONIC-HYPORESPONSIVE EPISODE (HHE)

Study	Vaccine	Number of revaccinated patients with previous HHE	Number with recurrence	Severity/ Comments
DuVernoy et al., 2000	Pertussis containing vaccine	12	0 (0%)	
Andrews et al., 1998	DTPw	5	1 (20%)	Recurrence occurred in a 6-month-old child who had HHE after 2 previous doses of DTwP. Child recovered spontaneously; physician was not consulted
Vermeer-de-Bondt et al., 1998	DTP-IPV + Hib	84	0 (0%)	
Goodwin et al., 1999	59 DTP containing vaccines	64	0 (0%)	
Gold et al., 2000	Pertussis containing vaccine	68	0 (0%)	
Nicolosi et al., 2014	Various	7	0 (0%)	
Top et al., 2016	DTaP + PCV + various	10	0 (0%)	
Crawford et al, 2018	DTaP-IPV-Hib-HepB + PCV + various	235	7 (3%)	
TOTAL		**485**		

References:

Andrews RM, Kempe AE, Sinn KK, Herceg A. Vaccinating children with a history of serious reactions after vaccination or of egg allergy. *MJA*. 1998;168:491-494.

Crawford NW, McMinn A, Royle J, Lazzaro T, Danchin M, Perrett KP, Buttery J, Elia S, Orr K, Wood N. Recurrence risk of a hypotonic hyporesponsive episode in two Australian specialist immunisation clinics. *Vaccine*. 2018; 36:6152-6157.

DuVernoy TS, Braun MM and the VAERS Working Group. Hypotonic-hyporesponsive episodes reported to the Vaccine Adverse Event Reporting System (VAERS), 1996-1998. *Pediatrics*. 2000;106;e52.

Gold M, Goodwin H, Botham S et al. Revaccination of 421 children with a past history of an adverse vaccine reaction in a special immunisation service. *Arch Dis Child*. 2000;83:128-131.

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Nicolosi L, Vittucci A, Mancini R, et al. Vaccine risk assessment in children with a referred reaction to a previous vaccine dose: 2009-2011 retrospective report at the Bambino Gesu' children hospital, Rome, Italy. *Italian journal of pediatrics*. 2014 Mar;40:31.

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Vermeer-de Bondt P, Labadie J, Rumke HC. Rate of recurrent collapse after vaccination with whole cell pertussis vaccine: follow-up study. *BMJ*. 1998;316:902-903.

LOCAL REACTIONS AT THE INJECTION SITE (LRs)

Study	Vaccine	Number of revaccinated patients with previous LR	Number with recurrence	Severity/ Comments
Quinn et al., 2011	DTaP	53 27 DTaP 26 Tdap	39 (74%)	-18/39 (46%) swelling injection site to an adjacent joint -19/39 (49%) redness >10 cm -14/39 (36%) symptom lasting more than 4 days -Half reported no pain associated with the LLR
Rennels et al., 2008	DTaP	20	4 (20%) 7 (35%) 8 (40%)	-Entire upper arm swollen -Swelling >5 cm -Redness >5 cm
Marshall et al., 2006	DTaP	13 DTaP 12 Tdap	12 (48%)	Swelling and redness >5 cm considered ELS
Baraff, 1984	DTwP	196 ≥2.5 cm 66 ≥5.0 cm 241 ≥2.5 cm 86 ≥5.0 cm	50 (26%) 6 (9%) 70 (29%) 10 (12%)	Redness Swelling
Deloria et al., 1995	DTwP dose 2	58 ≥2.0 cm 30 ≥2.0 cm	19 (33%) 1 (3%)	Swelling Redness
	DTwP dose 3	30 ≥2.0 cm 19 ≥2.0 cm	4 (13%) 3 (16%)	Swelling Redness
	DTaP dose 2	29 ≥2.0 cm 22 ≥2.0 cm	6 (21%) 2 (9%)	Swelling Redness
	DTaP dose 3	23 ≥2.0 cm 5 ≥2.0 cm	5 (22%) 15 (33%)	Swelling Redness
Top et al., 2016	Various	14	6 (43%)	Redness and swelling ≥10cm
TOTAL		**840**		

References:

Baraff LJ, Cherry JD, Cody CL, Marcy SM, Manclark CR. DTP vaccine reactions: effect of prior reactions on rate of subsequent reactions. *Dev Biol Stand*. 1985;61:423-428.

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OCULO-RESPIRATORY SYNDROME (ORS)

Study	Vaccine	N	Recurrences	Severity/ Comments
De Serres, 2004	Influenza TIV 2002-2003	146	52 (36%) vaccine 16 (11%) placebo	RCT of patients with previous ORS
	Fluviral	73	31 (42%) vaccine 6 (8%) placebo	Risk difference: 34% (95% CI 21-47)
	Vaxigrip	73	21 (29%) vaccine 10 (14%) placebo	Risk difference: 15% (95% CI 2-28)
Grenier, 2004	Influenza TIV	366	42 (11%)	In 2001 and 2002, 10% considered the recurrence to be more severe than the initial episode
	2001-2002	*178*	*14 (8%)*	
	2002-2003	*188*	*28 (15%)*	
Skowronski, 2003 (RCT)	Influenza TIV 2001-2002	34	15 (44%) vaccine 3 (11%) placebo ARD: 33%	88% of recurrent cases resolved spontaneously within 48h, and were considered mild
Skowronski, 2002 (CMAJ)	Influenza TIV 2001-2002	122	6 (5%)	Most of the patients enrolled had mild ORS with their first episode, which might underestimate recurrences
TOTAL		**595**		

References:

De Serres G, Skowronski DM, Guay M, Rochette L, Jacobsen K, Fuller T, Duval B. Recurrence risk of oculorespiratory syndrome after influenza vaccination: randomized controlled trial of previously affected persons. Arch Intern Med. 2004 Nov 8;164(20):2266-72. Erratum in: *Arch Intern Med*. 2005 Jan 24;165(2):145. PubMed PMID: 15534165.

Grenier JL, Toth E, De Serres G, Ménard S, Roussel R, Tremblay M, Landry M, Robert Y, Skowronski DM. Safety of revaccination of patients affected by the oculo-respiratory syndrome (ORS) following influenza vaccination. *Can Commun Dis Rep*. 2004 Jan 15;30(2):9-16. English, French. PubMed PMID: 14964915.

Skowronski DM, De Serres G, Scheifele D, Russell ML, Warrington R, Davies HD, Dionne M, Duval B, Kellner J, MacDonald J. Randomized, double-blind, placebo-controlled trial to assess the rate of recurrence of oculorespiratory syndrome following influenza vaccination among persons previously affected. *Clin Infect Dis*. 2003 Oct 15;37(8):1059-1066. Epub 2003 Sep 26. PubMed PMID: 14523770.

Skowronski DM, Strauss B, Kendall P, Duval B, De Serres G. Low risk of recurrence of oculorespiratory syndrome following influenza revaccination. *CMAJ*. 2002 Oct 15;167(8):853-858. PubMed PMID: 12406942; PubMed Central PMCID: PMC128396.

PERSISTENT CRYING

Study	Vaccines	Number of revaccinated patients with previous persistent crying / screaming	Number with recurrence	Severity/ Comments
Andrews et al., 1998	Pertussis containing vaccine and Td	20	0 (0%)	Previous persistent crying/screaming >3 hours
Baraff et al., 1984	DTP	66	3 (5%)	Previous persistent crying >1 hour
Long et al., 1990	DTwP	35	6 (17%)	History of prolonged crying *After 1st dose*
		28	2 (7%)	History of prolonged crying *After 2nd dose*
Top et al., 2016	DTaP + PCV + various	2	0 (0%)	
TOTAL		**151**		

References:

Andrews RM, Kempe AE, Sinn KK, Herceg A. Vaccinating children with a history of serious reactions after vaccination or of egg allergy. *MJA*. 1998;168:491-494.

Baraff LJ, Cherry JD, Cody CL, Marcy SM and Manclark CR. DTP Vaccine reactions: effect of prior reactions on rate of subsequent reactions. *Dev Biol Stand*. 1985;61:423-428.

Long SS, Deforest A, Smith DG, Lazaro C and Wassilak SG. Longitudinal study of adverse reactions following diphtheria-tetanus-pertussis vaccine in infancy. *Pediatrics*. 1990;85:294-302.

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SEIZURES

Study	Vaccine	Number of revaccinated patients with previous seizures	Number with recurrence	Severity/ Comments
Crawford et al., 2011	HPV-4	8	0	
Gold et al., 2000	Various	35	0	
Nicolosi et al., 2014	Various	17	0	
Top et al., 2016	Various	5 Febrile seizures 3 afebrile seizures	1 febrile 1 afebrile	Recurrence after DTaP Recurrence after PCV
TOTAL		**68**		

References:

Crawford, Clothier H, Elia S, Lazzaro T, Royle J and Jim P Buttery. Syncope and seizures following human papillomavirus vaccination: a retrospective case series. *MJA.* 2011;194:16–18.

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THROMBOCYTOPENIA (TP)

Study	Vaccine	Number of revaccinated patients with previous TP	Number with recurrence	Severity/ Comments
Black et al., 2003	MMR	-2 patients with TP within 6 weeks of MMR vaccination	0 (0%)	
		-11 patients with non-MMR associated TP	0 (0%)	- Of 11 children with history TP prior to receiving MMR vaccination, none developed a recurrence after subsequent vaccination (including 7 vaccinated with MMR)
France et al., 2008	MMR	31 patients with TP (associated or not with MMR vaccination)	0 (0%)	-Platelet count ≤50 000/μL -Two children received MMR vaccination within 8 weeks of their immune TP resolution date without AEFI
Miller et al., 2001	MMR	-14 children aged 12-23 months with non-MMR associated TP	0 (0%)	-No recurrences within six weeks of immunization (the number who receive MMR was not specified)
		-7 children aged 1 to 12 months with non-MMR associated TP	0 (0%)	-All 7 children received MMR vaccine and none had a vaccine associated recurrence
Top et al., 2016	MMR	2	0 (0%)	
TOTAL		**67**		

References:

Black C, Kaye JA, Jick H. MMR vaccine and idiopathic thrombocytopaenic purpura. *Br J Clin Pharmacol*. 2003 Jan;55(1):107‑111.

France EK, Glanz J, Xu S, Hambidge S, Yamasaki K, Black SB, et al. Risk of immune thrombocytopenic purpura after measles-mumps-rubella immunization in children. *Pediatrics*. 2008 Mar;121(3):e687-692.

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