

# Appendix B: Provincial Case Definitions for Reportable Diseases

Disease: Adverse Events Following Immunization (AEFIs)

Revised April 2015

# Adverse Events Following Immunization (AEFIs)

## 1.0 Provincial Reporting

Confirmed cases of AEFIs

## 2.0 Type of Surveillance

Case-by-case

Provincial reporting of AEFIs is an important component of the overall safety assessment of any vaccine. This type of surveillance, commonly called post-marketing or post-licensure surveillance, allows for monitoring of the vaccines throughout implementation in the context of “scaled up” vaccine production and expansion of the population receiving the vaccine.

Individual case reports of AEFIs represent an important source of data as they have the potential to generate signals of adverse reactions not previously recognized in clinical studies which can be further evaluated.<sup>1</sup> This is particularly important for rare adverse events which may not have been evident in clinical trials due to limited sample size.

In Ontario, reporting of AEFIs by specific health professionals is mandated under Section 38 of the *Health Protection and Promotion Act* (HPPA). AEFI reports from health professionals should be reported to the local public health unit using the “Report of Adverse Event Following Immunization (AEFI)” form available from:

<http://www.publichealthontario.ca/en/BrowseByTopic/InfectiousDiseases/Pages/Immunization-Resources.aspx#.Uqhun9JDUPZ>.

All provincially reported AEFIs that meet the confirmed case definition are reported to the Canadian Adverse Events Following Immunization Surveillance System (CAEFISS) at the Public Health Agency of Canada (PHAC).<sup>2</sup>

### 2.1 Scope

Provincial AEFIs surveillance includes adverse events occurring following administration of an **active immunizing agent**.

The following are not within the scope of provincial AEFIs surveillance:

- Adverse events following the administration of a passive immunizing agent, diagnostic agent (e.g., tuberculin skin test) or any other drug product (only if active immunizing agent administered concomitantly, then report); and
- Immunization program errors not temporally associated with an adverse event.

For adverse reactions following the administration of a passive immunizing agent, diagnostic agent (e.g., tuberculin skin test) or any other drug product only, please follow the established procedure for reporting adverse drug reactions via Health Canada using the “Canada Vigilance Adverse Reaction Reporting Form” available from:

[http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/ar-ei\\_form-eng.php](http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/ar-ei_form-eng.php).

For immunization program errors not temporally associated with an adverse event, please report the event to the Canadian Medication Incident Reporting and Prevention

System (CMIRPS). Information on how to report a medication incident is available at the following link: <http://www.hc-sc.gc.ca/dhp-mps/medeff/cmiprs-scdpim-eng.php>.

## 3.0 Case Classification

### 3.1 Confirmed Case

Any reported event listed in Section 5.0 (Clinical Evidence) in a vaccine recipient which follows immunization that cannot be clearly attributed to other causes. A causal relationship with the administration of the vaccine does not need to be proven.<sup>1,3</sup>

### 3.2 Does Not Meet

Any reported event in a vaccine recipient which follows immunization that has been clearly attributed to other causes.

## 4.0 Laboratory Evidence

Please see Section 5.0 (Clinical Evidence) for laboratory evidence related to specific AEFIs, where applicable.

## 5.0 Clinical Evidence

Report events which have a temporal association with a vaccine and which cannot be clearly attributed to other causes (see Section 3.0 (Case Classification)). A causal relationship does not need to be proven. Of particular interest are those AEFIs which are of a serious nature, require urgent medical attention, or are unusual or unexpected events.<sup>3,4</sup> Additional guidance with respect to specific AEFIs is outlined below.

The temporal criteria for specific AEFIs are generally agreed upon approximate timelines. AEFIs which occur outside of these timelines may still be reported if the AEFI is assessed as clinically significant.

### **A. LOCAL REACTIONS AT THE INJECTION SITE**

#### **A.1 Pain, redness or swelling at the injection site**

Pain, redness or swelling\* at the injection site that:

- Extends past the nearest joint; or
- Persists for 4 days or more.\*\*

\* Visible enlargement of a limb at the site of injection.<sup>5</sup>

\*\* Reporting of pain, redness or swelling at the injection site, lasting less than 4 days is not required for the purposes of provincial surveillance.

#### ***Temporal criteria:***

Pain, redness or swelling at the injection site occurring within 48 hours of vaccination.<sup>6</sup>

***Discussion:***

Pain, redness and swelling at the injection site are common reactions to vaccine. The injection of foreign material into the tissues and irritation of the tissues by the process of injection can produce an inflammatory response. These local reactions are well-reported in clinical trials.<sup>6</sup>

Local reactions are not a contraindication to further doses of vaccine.

**A.2 Abscess at the injection site**

An abscess is a confirmed localized collection of material in the soft tissue occurring at the site of immunization.<sup>7</sup> The abscess is confirmed by:

- Spontaneous/surgical drainage of material from the mass;  
**OR**
- Demonstration of material by an imaging technique (such as ultrasound, CT or MRI);  
**OR**
- Fluctuance (wave-like motion on palpation due to liquid content);  
**AND**
- Physician-diagnosis.<sup>4, 7</sup>

Further characterization of the abscess as infectious or sterile requires:

**Infectious abscess**

- Laboratory confirmation (positive Gram stain or culture);  
**OR**  
One or more signs of localized inflammation (erythema, pain to light touch, warmth to touch at the injection site);  
**AND**
- Evidence of improvement related to antimicrobial therapy.<sup>4, 6</sup>

**Sterile abscess**

- Material from abscess known to be non-purulent;  
**OR**
- Absence of localized signs of inflammation;  
**OR**
- Failure to improve on antimicrobial therapy.

***Temporal criteria:***

An abscess occurring within 7 days of vaccine receipt.<sup>6</sup>

***Discussion:***

An infectious abscess may be accompanied by fever/regional lymphadenopathy and can be the result of contamination of multi-dose vials (re-entering vial with a used needle, improper

cleaning or improper storage). Sterile abscesses are typically not accompanied by fever and are primarily associated with aluminum-adsorbed vaccines and may occur when these vaccines are injected into subcutaneous tissue instead of muscle. They are believed to be the result of irritation from components of the vaccine, especially the adjuvant.<sup>6</sup>

Abscesses are not a contraindication to further doses of vaccine.

### **A.3 Nodule**

The presence of a discrete or well demarcated soft tissue mass or lump that is:

- Firm, in the absence of abscess formation, erythema, or warmth;
- Is  $\geq 2.5$  cm in diameter; and
- Persists for more than one month.<sup>8, 6</sup>

#### ***Temporal criteria:***

A nodule is generally seen within 7 days of vaccine receipt.<sup>6</sup>

#### ***Discussion:***

Nodules are mainly associated with aluminum-adsorbed vaccines, particularly if the dose is deposited subcutaneously rather than intramuscularly. Sterile nodules can take up to 1 year or more to resolve, but most commonly resolve within 2 to 3 months.<sup>6</sup>

Nodules are not a contraindication to further doses of vaccine.

### **A.4 Cellulitis**

An acute, infectious, expanding inflammatory condition of the skin, located in subcutaneous tissue, fat, fascia or muscle at the vaccine injection site. Cellulitis must be characterized by at least 3 of the 4 following local signs or symptoms:

- Pain or tenderness to touch;
- Erythema;
- Induration or swelling; or
- Warmth to touch.<sup>4, 9</sup>

#### ***Temporal criteria:***

Cellulitis at the injection site occurring within 7 days of vaccine receipt.<sup>6</sup>

#### ***Discussion:***

Cellulitis may be accompanied by fever and/or regional lymphadenopathy; however, its presence or absence should not influence reporting.<sup>1</sup> Laboratory-confirmation by culture would confirm the diagnosis; however, these results are seldom available.

Cellulitis should be distinguished from expected local reactions by the presence of intense erythema, tenderness to light touch, induration and substantial local warmth. It can result from bacterial contamination of the vaccine during the manufacturing process, contamination of a vaccine vial or injection equipment, or can be due to introduction of surface bacteria into the deeper layers of the skin.<sup>6</sup>

Cellulitis is not a contraindication to further doses of vaccine.

## **B. SYSTEMIC REACTIONS**

### **B.1 Fever in conjunction with another reportable event**

Elevation in temperature of 38°C or higher that occurs **in conjunction with** another reportable adverse event.

#### ***Discussion:***

A value of  $\geq 38^\circ\text{C}$  should be accepted as reflecting an abnormal elevation of temperature, irrespective of device, anatomic site or age.<sup>10</sup>

Fever is a common expected systemic reaction that generally occurs within 72 hours of immunization with inactivated vaccines and often at a later time following live vaccines (e.g., 5 to 14 days after MMR or varicella vaccines).<sup>6</sup>

A fever that occurs following immunization may not be due to the vaccine. Viral and bacterial illnesses are very common in children and can result in signs and symptoms similar to those which may occur following immunization. Consider intercurrent illness and other potential causes when interpreting an adverse event following immunization.<sup>6</sup>

### **B.2 Rash**

A skin or mucosal change (either new or an exacerbation of a previous condition) other than urticaria (hives) following immunization\* for which no alternative cause has been identified with or without a morphologic description of the rash using standard terms (see morphologic descriptions of mucocutaneous lesions below).<sup>11</sup>

\*An urticarial rash (hives) should be reported as “Allergic reaction – skin” (see Section C.3 (Allergic Reaction – Skin)).

#### ***Temporal criteria:***

Rash occurring within 7 days of immunization with an inactivated vaccine, or 5 to 42 days following immunization with a live vaccine with the exception of vaccine-associated zoster which may occur months or years after receipt of varicella vaccine.<sup>6</sup>

#### ***Discussion:***

MMR vaccine may produce a mild, measles-like illness which can be manifested by a generalized rash and fever lasting up to 3 days.<sup>12</sup> It occurs in 5 to 10% of persons following the first dose of MMR, usually 6 to 23 days after vaccination.<sup>12</sup> It is much less common following the second dose of MMR.<sup>6</sup> Measles-like rash is rarely transmissible.

An erythematous, maculopapular, measles-like rash should be distinguished from a petechial rash. Petechiae are small, purplish, hemorrhagic spots on the skin that do not blanch with pressure. Petechial rashes should be referred for consultation to determine if further doses of the vaccine should be administered (see Section E.1 (Thrombocytopenia)).

A localized varicella-like rash occurs at the injection site in 3 to 5% of individuals after a first dose of varicella vaccine, and in 1% of individuals after a second dose.<sup>12</sup> A similar proportion of individuals will develop a small number of generalized varicella-like papules or vesicles. Lesions usually appear within 5 to 26 days of immunization.<sup>12</sup> A varicella-like rash is rarely transmissible. For specific guidance on the management of post-varicella vaccine rash in healthcare workers, please refer to the Canadian Immunization Guide,

Evergreen Edition (or as current).<sup>12</sup> Post-varicella vaccine zoster with laboratory confirmation of vaccine-strain virus may also be reported as “rash” with supporting documentation noting the exception above under temporal criteria with respect to delayed time to onset.

Most rashes occurring in children, even those temporally-related to immunization, are caused by intercurrent viral illness. Rashes other than petechial rashes are not a contraindication to further doses of a vaccine.<sup>6</sup>

### ***Morphologic descriptions of mucocutaneous lesions***

#### *Primary mucocutaneous lesions (morphology):*

1. Bulla: A fluid-filled cavity or elevation  $\geq 1$  cm in diameter. Fluid can be clear, serous, hemorrhagic, or pus-filled.
2. Cyst: A closed cavity or sac containing fluid or semisolid material. A cyst may have an epithelial, endothelial, or membranous lining.
3. Macule: A flat, generally  $< 0.5$  cm area of skin or mucous membranes with different colour or texture from surrounding tissue.
4. Nodule\*: A dermal or subcutaneous, firm, well-defined lesion.
5. Papule: A discrete, solid, elevated body usually  $< 0.5$  cm in diameter. Papules are further classified by shape, size, colour, and surface change.
6. Plaque: A discrete, solid, elevated body usually broader than it is thick measuring  $> 0.5$  cm in diameter. Plaques may be further classified by shape, size, colour, and surface change.
7. Pustule: A superficial vesicle containing a cloudy or purulent fluid. Pustules are usually  $< 0.5$  cm in diameter.
8. Vesicle: Fluid filled cavity or elevation  $< 1$  cm in diameter. Fluid may be clear, serous, or hemorrhagic.
9. Wheal (hive)\*: An edematous, transitory papule or plaque.<sup>11</sup>

#### *Secondary mucocutaneous changes:*

1. Erosion: A localized loss of the epidermal or mucosal epithelium.
2. Crusting: Dried exudates of plasma.
3. Scaling: Whitish scales or flakes are present on the skin.
4. Atrophy: Thinning or absence of the dermis or subcutaneous fat.
5. Excoriations: Oval or linear depressions in the skin with complete removal of the epidermis, exposing a broad section of red dermis.
6. Fissures: Linear, wedge-shaped cracks in the epidermis which may extend down to the dermis.
7. Ulcer: A circumscribed loss of the epidermis or mucosa extending to dermis.

\*Nodule and wheal (hive) if observed should be reported under Sections A.3 (Nodule) and C.3 (Allergic Reaction – Skin), respectively.

### **B.3 Adenopathy/lymphadenopathy**

Enlargement of one or more lymph nodes that are:

- $\geq 1.5$  cm in diameter; and/or
- Draining sinus over a lymph node; and
- Physician-diagnosed.<sup>6</sup>

***Temporal criteria:***

Adenopathy/lymphadenopathy occurring within 7 days following immunization with an inactivated vaccine, or 5 to 42 days following immunization with a live vaccine.<sup>6</sup>

***Discussion:***

Live vaccines produce a low-grade infection which can include adenopathy. With any vaccine injection, if bacteria contaminate the injection site, adenitis may occur as part of the resulting infection. Adenitis in injection site-associated infections would usually occur first in the lymph nodes draining the injection site.<sup>6</sup>

Adenopathy/lymphadenopathy are not contraindications to further doses of vaccine.

**B.4 Hypotonic-Hyporesponsive Episode (HHE)**

The sudden onset, in a child aged **less than 2 years**, of:

- Hypotonia (muscle limpness);
- Hyporesponsiveness or unresponsiveness;
- Pallor or cyanosis; and is
- Physician-diagnosed.<sup>13, 6</sup>

***Temporal criteria:***

HHE within 48 hours following immunization.<sup>6</sup>

***Discussion:***

With a HHE, there is an acute decrease in sensory awareness or loss of consciousness, accompanied by pallor and muscle hypotonicity. Children are initially irritable and may be febrile. They then become pale, limp, and unresponsive or hyporesponsive. Respirations are shallow and cyanosis is frequently noted. As a result, parents may report that the child was not breathing. These episodes are usually transient (lasting a few minutes) and self-limiting.

HHE has been documented to occur after immunization with diphtheria, tetanus, Haemophilus influenzae type b, and hepatitis B vaccines. Most reported episodes have followed administration of pertussis-containing vaccines; there has been a decline in these reports with the use of acellular pertussis vaccines. HHE has also been observed most frequently during the primary immunization series, mainly after the first dose. The cause of these episodes is unknown but they are most consistent with fainting spells.

Follow-up of children who have had HHEs has demonstrated complete recovery without persistent neurologic or developmental defects. No treatment is necessary. If the HHE does not resolve spontaneously, other underlying problems should be sought and ruled out or treated.<sup>6</sup>

HHE is not a contraindication to further doses of the same vaccine.

**B.5 Persistent Crying/Screaming**

The presence of crying in infants and young children following immunization that is continuous, unaltered (i.e., the quality of crying does not change throughout the episode) and lasts for three or more hours.<sup>14</sup>

***Temporal criteria:***

Screaming/persistent crying occurring within 72 hours following immunization.<sup>6</sup>



***Discussion:***

Crying in children is a common reaction to painful stimuli. Most often, the crying immediately following immunization is short-lived, has a familiar sound, and is viewed as normal by parents. However, parents are concerned when crying is prolonged, persistent, and high-pitched, and the infant is inconsolable.<sup>6</sup> Persistent crying is not a contraindication to further doses of vaccine.

**B.6 Severe Vomiting/Diarrhea**

Three or more episodes of vomiting and/or diarrhea (increase above normal baseline) in a 24 hour period where vomiting and/or diarrhea is severe (i.e., projectile vomiting or explosive, watery diarrhea).<sup>15, 6</sup>

***Temporal criteria:***

Vomiting and/or diarrhea occurring within 72 hours following immunization with an inactivated vaccine, or 42 days following immunization with a live vaccine.<sup>6</sup>

***Discussion:***

Nausea and diarrhea have been particularly associated with oral typhoid vaccine, human diploid cell rabies vaccine (HDCV), and Japanese B encephalitis vaccine. In clinical trials there has been a small but statistically significant increased rate of vomiting and diarrhea following receipt of pentavalent rotavirus vaccine (Rot-5) but not Rot-1.<sup>12</sup> Treat severe vomiting/diarrhea symptomatically to prevent dehydration and electrolyte imbalance.<sup>6</sup>

Severe vomiting or diarrhea is not a contraindication to further doses of a vaccine.

**B.7 Parotitis**

Inflammation of one or both parotid salivary glands that is:

- Following receipt of a mumps-containing vaccine; and
- Physician-diagnosed.<sup>6</sup>

***Temporal criteria:***

Parotitis occurring 5 to 30 days following immunization.<sup>6</sup>

***Discussion:***

Parotitis is a common manifestation of mumps infection. Since the mumps vaccine is a live virus vaccine, low-grade infection following immunization can occasionally produce the same manifestation. It is transient and self-limiting, and can be managed with analgesics as required and adequate fluid intake.<sup>6</sup>

Parotitis is not a contraindication to a future dose of a mumps-containing vaccine.

**C. ALLERGIC REACTIONS**

**C.1 Event Managed as Anaphylaxis**

Anaphylaxis should be reported if it is managed as anaphylaxis (e.g., epinephrine administered) at the time of occurrence.

***Temporal criteria:***

Anaphylaxis occurring within 24 hours of immunization.<sup>6, 12</sup>

### ***Discussion:***

Anaphylaxis is set apart from simple allergic reactions by the simultaneous involvement of several organ systems. The Brighton Collaboration case definition for anaphylaxis is divided into levels of diagnostic certainty with level one being the highest. For all levels of diagnostic certainty anaphylaxis is a clinical syndrome characterized by sudden onset, rapid progression of signs and symptoms and involving multiple ( $\geq 2$ ) organ systems, as follows:<sup>16</sup>

#### *Level 1 of diagnostic certainty*

- ( $\geq 1$  major dermatological<sup>i</sup>) AND ( $\geq 1$  major cardiovascular<sup>ii</sup> AND/OR  $\geq 1$  major respiratory<sup>iii</sup> criterion);

#### *Level 2 of diagnostic certainty*

- $\geq 1$  major cardiovascular<sup>ii</sup> AND  $\geq 1$  major respiratory<sup>iii</sup> criterion;

**OR**

- ( $\geq 1$  major cardiovascular<sup>ii</sup> OR respiratory criterion<sup>iii</sup>) AND ( $\geq 1$  minor criterion involving  $\geq 1$  different system (other than cardiovascular or respiratory systems));

**OR**

- ( $\geq 1$  major dermatologic<sup>i</sup>) AND ( $\geq 1$  minor<sup>iv</sup> cardiovascular AND/OR minor respiratory criterion);

#### *Level 3 of diagnostic certainty*

- ( $\geq 1$  minor<sup>iv</sup> cardiovascular OR respiratory criterion) AND ( $\geq 1$  minor<sup>iv</sup> criterion from each of  $\geq 2$  different systems/categories).

Not all cases reported as anaphylaxis will meet the diagnostic levels as outlined by the Brighton Collaboration case definitions. Suspected anaphylaxis managed appropriately and promptly avoids escalation of symptoms and progression to a severe outcome. *Any event managed as anaphylaxis (e.g., where epinephrine was administered) should be reported as such.*

Anaphylaxis must be distinguished from fainting (vasovagal syncope), breath-holding spells and anxiety, which are not reportable. Symptoms that are progressive or increasing in severity are more likely to represent anaphylaxis.

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<sup>i</sup> Generalized urticarial (hives) or generalized erythema; or angioedema (localized or generalized); or generalized pruritus with skin rash.

<sup>ii</sup> Measured hypotension; or clinical diagnosis of uncompensated shock, indicated by a combination of at least 3 of the following: tachycardia, capillary refill time  $>3$  sec., reduced central pulse volume, decreased level of consciousness or loss of consciousness.

<sup>iii</sup> Bilateral wheeze; or stridor; or upper airway swelling (lip tongue, throat, uvula, larynx); or respiratory distress indicated by 2 or more of the following: tachycardia, increased use of accessory respiratory muscles, recession, cyanosis, grunting.<sup>16</sup>

<sup>iv</sup> Minor criterion include: dermatologic/mucosal – generalized pruritus without skin rash, generalized prickle sensation, localized injection site urticarial or red, itchy eyes; cardiovascular – reduced peripheral circulation as indicated by the combination of at least 2 of tachycardia, capillary refill time of  $>3$  seconds without hypotension or decreased level of consciousness; respiratory – persistent dry cough, hoarse voice, difficulty breathing without wheeze or stridor, sensation of throat closure, sneezing or rhinorrhea; gastrointestinal – diarrhea, abdominal pain, nausea, vomiting; laboratory – mast cell tryptase elevation greater than upper normal limit.

For guidance on the initial management of anaphylaxis in non-hospital settings please refer to Part 2 of the Canadian Immunization Guide, Evergreen Edition (or as current).<sup>12</sup>

A true anaphylactic reaction to a vaccine is a contraindication to receipt of further doses of the same vaccine or to a component of a vaccine. Referral to the primary care physician for consultation with an allergist may be sought to identify the component to which the client has hypersensitivity. It is important to avoid leaving clients inadequately immunized if they unnecessarily avoid vaccines to which they are not, in fact, allergic. In addition, not knowing the particular component of a vaccine to which the client is allergic may pose a risk from future vaccines containing the same component.<sup>6</sup>

## **C.2 Oculorespiratory Syndrome (ORS)**

The onset of bilateral red eyes and one or more of the following respiratory symptoms: cough, wheeze, chest tightness, difficulty breathing, difficulty swallowing, hoarseness or sore throat, with or without facial swelling.<sup>4,12</sup> As of 2012, this syndrome has only been associated with receipt of influenza vaccine.

### ***Temporal criteria:***

ORS occurring within 24 hours of immunization.<sup>6</sup>

### ***Discussion:***

Most people who have experienced ORS can be safely revaccinated. Among those who have had ORS after a previous dose of influenza vaccine, most do not experience it again and about 5 to 34% experience another episode but it is usually milder.

When an individual has had severe ORS symptoms such as wheeze, chest tightness/discomfort, difficulty breathing or severe throat constriction/difficulty swallowing following influenza vaccine and has not received influenza vaccine since, this is considered to be a precaution to future receipt of influenza vaccine. Such individuals who wish to receive influenza vaccine should consult with their primary care provider. The medical officer of health should provide expert review to distinguish between severe ORS and any anaphylaxis risk.<sup>6</sup>

## **C.3 Allergic Reaction – Skin**

An allergic reaction of the skin\* including urticaria (hives), erythema, pruritus, prickle sensation, and localized or generalized edema (in the deeper layers of the skin, subcutaneous tissues or mucosa lining the throat, airways and gut).<sup>6</sup>

\*An allergic reaction of the skin occurring in the context of a suspected anaphylactic reaction should be reported as “Event managed as anaphylaxis” (see Section C.1 (Event Managed as Anaphylaxis)) with the appropriate documentation of the observed clinical symptoms.

### ***Temporal criteria:***

Allergic reactions of the skin occurring within 48 hours of immunization.<sup>6</sup>

### ***Discussion:***

An allergic reaction is an acquired hypersensitivity to an antigen that does not normally produce such a reaction. Antigen-antibody complexes stimulate the release of chemicals, such as histamine, that produce overt signs and symptoms of hypersensitivity. An allergic reaction can occur in response to a component of a vaccine in a person previously sensitized (i.e.,

antibodies must be present from a previous exposure to the antigen). When reported as an adverse event, enquire about a history of allergies and possible exposure to other allergens during the same time period.

For guidance on the management of hives and swelling at the injection site refer to Part 2 (Early vaccine reactions including anaphylaxis) in the Canadian Immunization Guide, Evergreen Edition (or as current).<sup>12</sup>

Recommendations following the occurrence of urticaria (hives) depend on the time from receipt of vaccine to onset. Individuals with generalized hives occurring between 0 to 2 hours after immunization should be referred to their primary care provider, with a recommendation for further assessment by an allergist prior to receiving further doses of the same vaccine or its components.

If hives occurred between 2 and 48 hours following immunization, consider providing the next dose of the vaccine in a physician's office or an emergency setting and observe the patient for one to two hours following immunization. If there is no reaction following this dose, further immunization can be given in the routine setting. If a hive-like rash reappears with this dose, particularly a generalized rash appearing within 48 hours of vaccination then the individual should be referred to a primary care provider with a recommendation for further assessment by an allergist prior to further doses of the same vaccine or its components.

For those that experience hives more than 48 hours after immunization, consider giving the next vaccine dose under routine conditions. As well, consider other potential causes of the hives, particularly if there was no reaction at the injection site.<sup>6</sup>

## **D. NEUROLOGIC EVENTS**

### **D.1 Convulsions/Seizure**

An episode of unconsciousness accompanied by generalized motor manifestations that may be tonic, clonic, tonic-clonic or atonic.<sup>4, 17</sup>

#### ***Temporal criteria:***

Seizure occurring within 72 hours following immunization with an inactivated vaccine, or 5 to 42 days following immunization with a live vaccine.<sup>6</sup>

#### ***Discussion:***

Seizures include paroxysms of generalized tonic skeletal muscle contractions and generalized clonic jerking, usually associated with decreased level of consciousness. Seizures may last for several minutes or more. A seizure may be febrile or afebrile. A febrile seizure should always be specified as such in the AEFI report by indicating if a fever of  $\geq 38^{\circ}\text{C}$  was present at the time of the seizure.

An abrupt rise in temperature is a risk factor for febrile seizures in susceptible children. Febrile seizures are the most common seizure disorder of childhood, and are age-dependent. They are rare prior to 6 months of age and after 5 years of age, with peak onset at 14 to 18 months of age. Incidence in this age group approaches 2 to 5%, with greater risk in those with a family history. While simple febrile seizures are disturbing for the child and parents, they have a uniformly excellent prognosis without residual sequelae and resolve on their own as

the child ages. There are no long-term sequelae, such as permanent brain damage, associated with simple febrile seizures.<sup>6</sup>

Uncomplicated febrile seizures are not a contraindication to further doses of a vaccine. When febrile seizures are multiple or prolonged (complex seizures, status epilepticus), or when the seizures are afebrile, referral should be made to the primary care provider with a recommendation for a consultation with a paediatrician or paediatric neurologist, to rule out an underlying disorder.<sup>6</sup>

## **D.2 Encephalopathy/Encephalitis**

An illness diagnosed by a physician as encephalitis or encephalopathy with no other cause identified.

### ***Temporal criteria:***

Encephalitis/encephalopathy occurring within 15 days of receipt of an inactivated vaccine, or 5 to 42 days following immunization with a live vaccine.<sup>6</sup>

### ***Discussion:***

Encephalopathy is a term used to describe a constellation of signs and symptoms reflecting a generalized disturbance in brain function. Encephalitis refers to inflammation of the brain.

Encephalopathy and encephalitis are severe but rare adverse events that must be diagnosed by a physician in order to be included. An AEFI report of encephalopathy or encephalitis should include appropriate medical documentation, physicians' assessments and test results.

The national case definition of encephalopathy, based on Brighton criteria, includes:

- At least one listed indicator of central nervous system inflammation<sup>v</sup>; and
- Either >24 hours depressed or altered consciousness with one or more signs of reduced responsiveness<sup>vi</sup> or one or more signs of focal or multi-focal central nervous system abnormality<sup>vii</sup>.<sup>4, 18</sup>

Immunizations may very rarely lead to acute encephalitis, particularly with live-attenuated viral vaccines. The risk of encephalitic complications from viral infections (1/1000 cases of measles; 1/6000 cases of rubella) is greater than the risk following vaccination (1/1,000,000 following MMR).

Encephalopathy itself is not a contraindication to further vaccination. Deferral of immunization may be considered until the neurologic condition has been diagnosed or is stable. If no other cause is found and the encephalopathy is temporally-related to a combination vaccine, referral to a paediatric neurologist may be made to determine which components of the vaccine may be continued.<sup>6</sup>

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<sup>v</sup> Indicators of central nervous system inflammation: fever  $\geq 38.0^{\circ}\text{C}$ , CSF pleocytosis ( $>15$  WBC/mm<sup>3</sup> if  $< 2$  months old;  $>5$  WBC/mm<sup>3</sup> if  $\geq 2$  months), EEG findings consistent with encephalitis, Neuroimaging consistent with encephalitis.

<sup>vi</sup> Signs of reduced responsiveness (global cerebral dysfunction): decreased or absent response to environment as defined by response to loud noise or painful stimuli, decreased or absent eye contact, inconsistent or absent response to external stimuli, decreased arousability, seizure associated with loss of consciousness.

<sup>vii</sup> Signs of focal or multifocal central nervous system abnormality: focal cortical signs (e.g., aphasia, alexia, agraphia, cortical blindness), cranial nerve abnormality/abnormalities, visual field defect(s), presence of primitive reflexes (e.g., Babinski's sign, sucking reflex), motor weakness (diffuse or focal), sensory abnormalities (positive or negative), altered deep tendon reflexes (asymmetry, hypo/hyperreflexia), cerebellar dysfunction (e.g., ataxia, dysmetria, cerebellar nystagmus)

### **D.3 Meningitis**

An acute illness, diagnosed by a physician as meningitis with no other cause identified.

#### ***Temporal criteria:***

Meningitis occurring within 15 days following immunization with an inactivated vaccine, or 5 to 42 days following immunization with a live vaccine.<sup>6</sup>

#### ***Discussion:***

Meningitis is an infection or inflammation of the membranes covering the brain and spinal cord. It is characterized by sudden onset of fever, intense headache, nausea and vomiting, and pain and stiffness in the neck. Aseptic meningitis is a syndrome characterized by acute onset of signs and symptoms of meningeal inflammation, pleocytosis in the cerebrospinal fluid and the absence of microorganisms on Gram stain and/or on routine culture.<sup>19</sup>

An AEFI report of meningitis should include appropriate medical documentation, physicians' assessments and test results.

Measles and mumps viruses were important causative agents of aseptic meningitis before introduction of measles and mumps vaccines. Cases of aseptic meningitis have been reported after immunization with several live attenuated vaccines, including oral polio, MMR vaccine, varicella, yellow fever and smallpox. The postulated mechanism for aseptic meningitis following attenuated live virus vaccines is infection of the meninges with the vaccine virus. Such a causal relationship was established with the Urabe strain of mumps virus (1 case reported per 62,000 vaccinations), which is no longer used in vaccines in Canada.<sup>20</sup> There is no evidence of a causal association with the Jeryl-Lynn strain of mumps used in MMR, or with any of the other routinely used live virus vaccines. Aseptic meningitis following immunization typically resolves without sequelae.<sup>6</sup>

Further vaccines should be deferred until a determination is made as to the cause of the meningitis.

### **D.4 Anaesthesia/Paraesthesia**

Anaesthesia (the loss of normal feeling or sensation; numbness) or paraesthesia (abnormal physical sensation such as tingling, burning or prickling) that lasts 24 hours or more and is physician-diagnosed.<sup>6</sup>

#### ***Temporal criteria:***

Anaesthesia/paraesthesia occurring within 15 days following immunization with an inactivated vaccine, or within 42 days following immunization with a live vaccine.<sup>6</sup>

#### ***Discussion:***

The cause of anaesthesia or paraesthesia following vaccination is often not determined. It may be related to deposition of the vaccine close to a nerve, with subsequent pressure causing symptoms. There is no specific treatment. Investigation by a neurologist should be done to rule out permanent nerve damage.

If the cause is related to injection technique, avoid the site for future injections. In most cases, immunizations can continue. Proper land-marking of the injection site is important.<sup>6</sup>

### **D.5 Paralysis**

Loss of muscle tone and function with or without loss of sensation that is physician-diagnosed and with no other cause identified.

***Temporal criteria:***

Paralysis occurring within 15 days following immunization with an inactivated vaccine, or 5 to 42 days following immunization with a live vaccine.<sup>6</sup>

***Discussion:***

Oral polio vaccine (OPV), which is not used in Canada but is used elsewhere in the world, can cause paralytic disease in recipients and incompletely immunized contacts at a rate of approximately 1 per 2.4 million doses distributed.<sup>12</sup> Ontario has used inactivated polio vaccine (IPV) exclusively since April 1993, and OPV has not been used since that time. However, there is a potential risk to individuals travelling or living abroad who may be exposed to OPV.

The decision to continue immunization must be made on a case-by-case basis. All cases should be evaluated by a neurologist.

**D.6 Bell's palsy**

A unilateral paralysis or weakness of facial muscles that is physician-diagnosed.

***Temporal criteria:***

Bell's palsy occurring within 3 months of immunization.<sup>6</sup>

***Discussion:***

The cause of Bell's palsy is not clear. There is a consideration that a viral infection such as viral meningitis or the herpes virus may be linked to Bell's palsy, since these infections can cause inflammation that can damage the nerve that controls muscles on one side of the face.

Although some variation in the prevalence of Bell's palsy has been reported, it does not appear to occur in a seasonal pattern. Influenza infection does not appear to be a precipitating event for Bell's palsy.<sup>21</sup>

In only a single instance was Bell's palsy known to be causally related to vaccine. An intranasal influenza vaccine used only in Switzerland was removed from the market after an increase in cases of Bell's palsy was noted.<sup>22</sup>

A temporal association between vaccine receipt and Bell's palsy onset is expected to be coincidental. Bell's palsy would not be a contraindication to further doses of vaccine.

**D.7 Guillain-Barré Syndrome (GBS)**

A physician-diagnosed illness that includes:

- Acute onset of bilateral flaccid weakness/paralysis of the limbs;
- Decreased or absent deep tendon reflexes; and
- Monophasic illness pattern and interval between onset and peak of weakness between 12 hours and 28 days and subsequent clinical plateau.<sup>4, 23</sup>

CSF test results, if available, must either be normal, or have <50 WBC/mm.

***Temporal criteria:***

GBS occurring 1 to 8 weeks following immunization.

***Discussion:***

GBS is also called acute afebrile polyneuritis or acute idiopathic polyneuritis. It is a subacute, usually symmetrical ascending paralysis, with associated sensory disturbances. It can appear as a sequelae to a variety of infections after an interval of 1 to 8 weeks; approximately two-thirds of patients with GBS report an antecedent infectious illness, most commonly a diarrheal or respiratory illness, prior to the onset of neurologic signs; *Campylobacter jejuni* is the most commonly reported pathogen in adults. A maximum degree of weakness is reached from 12 hours to 28 days after onset, followed by a clinical plateau and then either improvement or death. Overall, approximately 5 to 15% of patients die, and continued disability after one year has been estimated to be seen among 20% of patients. Studies in developed countries have suggested an incidence of 1 to 2 per 100,000 population per year.

There is limited evidence of an association between tetanus toxoid and GBS, and OPV and GBS, in addition to a swine influenza vaccine (1976) that is no longer in use. While cases of GBS have been reported temporally associated with other vaccines (e.g., Menactra®), there is no evidence of a causal relationship.

There are no contraindications to immunization in persons with a previous history of GBS unrelated to vaccination. If GBS occurs in temporal relationship to a vaccine without an alternate (e.g., infectious) cause, subsequent doses of the same vaccine should only be given if the benefits of vaccination outweigh the risk of GBS recurrence.

Although the available evidence is inadequate to accept or reject a causal relationship between GBS in adults and seasonal influenza vaccination, avoiding subsequent influenza vaccination of persons known to have had GBS within six weeks of a previous influenza vaccination appears prudent at this time. However, the potential risk of GBS recurrence associated with influenza vaccination must be balanced against the risk of GBS associated with influenza infection itself.<sup>24</sup>

**D.8 Other Neurologic Diagnosis****D.8.1 Myelitis**

An illness diagnosed by a physician as myelitis.

***Temporal criteria:***

Myelitis occurring within 15 days following immunization with an inactivated vaccine or 5 to 42 days following immunization with a live vaccine.

***Discussion:***

Myelitis is an illness in which there is clinical evidence of myelopathy accompanied by at least one indicator of spinal cord inflammation. Indicators of central nervous system inflammation include fever  $\geq 38^{\circ}\text{C}$ , CSF pleocytosis ( $>15$  WBC/mm<sup>3</sup> if  $<2$  months old;  $>5$  WBC/mm<sup>3</sup> if  $\geq 2$  months) or neuroimaging findings that demonstrate acute inflammation ( $\pm$  meninges), or spinal cord demyelination.<sup>4, 18</sup>



## **D.8.2 Acute Disseminated Encephalomyelitis (ADEM)**

An illness diagnosed by a physician as acute disseminated encephalomyelitis.

### ***Temporal criteria:***

ADEM occurring within 15 days following immunization with an inactivated vaccine or 5 and 42 days following immunization with a live vaccine.

### ***Discussion:***

ADEM is an illness in which there are one or more focal or multifocal findings referable to the central nervous system. Signs of focal or multifocal central nervous system abnormality include: Depressed or altered level of consciousness, lethargy or personality change lasting >24 hours, focal cortical signs (e.g., aphasia, alexia, agraphia, cortical blindness), cranial nerve abnormality/abnormalities, visual field defect(s), presence of primitive reflexes (e.g., Babinski's sign, sucking reflex), motor weakness (diffuse or focal), sensory abnormalities (positive or negative), altered deep tendon reflexes (asymmetry, hypo/hyperreflexia) or cerebellar dysfunction (e.g., ataxia, dysmetria, cerebellar nystagmus).<sup>4, 18</sup>

## **E. OTHER EVENTS OF INTEREST**

### **E.1 Thrombocytopenia**

A condition that is physician-diagnosed with a platelet count of less than  $150 \times 10^9/L$  and confirmed by:

- Blood smear examination; or
- Clinical signs and/or symptoms of spontaneous bleeding.<sup>viii</sup>

### ***Temporal criteria:***

Thrombocytopenia occurring within 30 days following vaccination.<sup>6</sup>

### ***Discussion:***

Thrombocytopenia is an abnormal hematological condition in which the number of platelets is reduced below normal (150-450,000/mm). Thrombocytopenia can occur in persons of all ages. Approximately 70% of cases occur following viral illnesses, often in children. It can also occur as a complication of a variety of medications. Many cases are idiopathic. Most cases in children are mild and transient, although hemorrhagic complications can occur.

The incidence rate of thrombocytopenia is estimated to be between one in 25,000 to one in 40,000 doses of MMR.<sup>25-27</sup> Most cases occur following vaccination with the first dose of measles-containing vaccine; the risk of recurrence is not known, but is thought to be low. Thrombocytopenia has also been reported following other vaccines such as diphtheria, pertussis, tetanus and varicella vaccines.<sup>27</sup>

Children with a history of thrombocytopenia may be at increased risk for developing thrombocytopenia after MMR vaccination. Such children should generally still be

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<sup>viii</sup> Presentations of spontaneous (i.e., non-traumatic) bleeding include purpura (i.e., petechiae, purpura sensu stricto, ecchymosis), hemorrhagic oozing of skin lesions including rashes, hematoma, bruising, hematemesis, hematochezia, occult bleeding per rectum, epistaxis, hemoptysis, hematuria, vaginal bleeding other than menstruation, conjunctival bleeding, intracranial bleeding.

immunized because the benefits of immunization outweigh the risks. The risk of thrombocytopenia following natural measles or rubella infection is greater than the risk following immunization.<sup>6</sup>

## **E.2 Arthritis/Arthralgia**

Joint pain (arthralgia) or joint inflammation with swelling, redness and/or warmth that:

- Is physician-diagnosed; and
- Lasts 24 hours or longer.

### ***Temporal criteria:***

Arthritis/arthralgia occurring within 15 days following immunization with an inactivated vaccine or between 1 and 3 weeks following immunization with a live vaccine.

### ***Discussion:***

Acute transient arthritis or arthralgia may occur 1 to 3 weeks after immunization with a rubella-containing vaccine, persisting for approximately 1 to 3 weeks and rarely recurring. These reactions are uncommon in children, but the frequency and severity increase with age. They are more common in post-pubertal females, among whom arthralgia develops in 25% and arthritis-like signs and symptoms in 10% after immunization with rubella vaccine.<sup>12</sup> Arthritis/arthralgia can also occur in children and adolescent and adult men, but at much lower rates. Persistence or recurrence of these symptoms is rare.<sup>28</sup> Both the frequency and severity of adverse reactions are less than those associated with natural disease, and serious adverse reactions are rare.<sup>12</sup>

Transient arthritis or arthralgia is not a contraindication to a further dose of vaccine.

## **E.3 Intussusception (IS)**

The invagination of one segment of the intestine into a segment of distal intestine which:

- Is physician-diagnosed; and
- Follows receipt of rotavirus vaccine.<sup>29</sup>

### ***Temporal criteria:***

IS occurring within 42 days following immunization.<sup>6</sup>

### ***Discussion:***

IS is the invagination or “telescoping” of one segment of intestine into a segment of the distal intestine. IS is the most common cause of acute intestinal obstruction in infants and young children.<sup>29</sup> Most cases occur in infants who are less than 12 months of age.<sup>30</sup> If untreated, intestinal infarction or perforation may occur; therefore, IS is a potentially life threatening condition and early diagnosis and treatment are essential, however death from IS in Canada is rare.

Earlier versions of the rotavirus vaccine were associated with IS. Data currently available from post-marketing studies of Rotarix™ and RotaTeq® are conflicting but signal the possibility of an increased risk of IS shortly after the first dose of rotavirus vaccine in some populations.<sup>31, 32</sup> However, considering that the benefits of rotavirus vaccination are great, the vaccine continues to be recommended to prevent severe rotavirus disease in infants.<sup>33</sup>

IS following rotavirus vaccine is a contraindication for further doses of vaccine.

#### **E.4 Syncope with injury**

Syncope (vasovagal reaction), or fainting that results in an injury\* to the vaccine recipient.

\*Syncope that does not result in injury does not need to be reported for the purposes of provincial surveillance.

##### ***Temporal criteria:***

Syncope with injury occurring within 30 minutes following immunization.<sup>6</sup>

##### ***Discussion:***

Syncope can be triggered by various stimuli, and is observed to occur before, during or after immunization, perhaps triggered by pain or emotional reaction to the immunization process itself. During fainting, the individual suddenly becomes pale, loses consciousness and collapses to the ground. Fainting is sometimes accompanied by brief clonic seizure activity (i.e., rhythmic jerking of the limbs). Recovery occurs within 1 to 2 minutes.

The risk of fainting is the more common reason to keep vaccine recipients under observation for 15 minutes post-immunization. For further information on the management of syncope refer to the chapter on “Initial Management of Anaphylaxis in Non-hospital Settings” in the Canadian Immunization Guide, Evergreen Edition (or as current).<sup>12</sup>

Syncope with injury has been reported following HPV vaccine and H1N1 vaccine receipt.<sup>34-38</sup> These reports include head injuries after syncope-related falls. These events are potentially serious: life threatening or resulting in death; requiring hospitalization; or resulting in a residual disability. They are related to the process of immunization, rather than to a specific vaccine. Immunizers should be aware of pre-syncope manifestations and take appropriate measures to prevent injuries if weakness, dizziness or loss of consciousness occurs.

Syncope is not a contraindication to further immunizations.

#### **E.5 Other severe/unusual events**

Report other severe or unusual events with a temporal association to immunization, and for which there is no other known cause, and which are not covered under the categories previously described including:

- Any death of a vaccine recipient temporally linked (within one month) to immunization, where no other clear cause of death can be established;<sup>39</sup>
- Fetal death that occurs following immunization of a pregnant woman; and
- Respiratory manifestations which are not associated with an event managed as anaphylaxis or any other event listed above.

Provide all details of the event, and include all necessary documentation (e.g., autopsy report when available) with the report.

The severity of the adverse event and the plausibility of an association with vaccination will determine whether further doses of the implicated vaccine will be continued.<sup>6</sup>

## 6.0 ICD Code(s)

### 6.1 ICD-10 Code(s)

ICD 10 Code T88.1

## 7.0 Comments

Some of the content of this Appendix is based upon the British Columbia Centre for Disease Control (BCCDC) *Communicable Disease Control Manual*, Chapter 2: Immunization Program, Section IX - Adverse Events Following Immunization (AEFI) available from: <http://www.bccdc.ca/dis-cond/comm-manual/CDManualChap2.htm>. It has been adapted with permission from BCCDC.

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## 9.0 Document History

**Table 1: History of Revisions**

Revision Date	Document Section	Description of Revisions
April 2015	General	Throughout the document, removed “between” from “inactivated vaccine or between 5 to 42 days following immunization with a live vaccine.”
April 2015	2.0 Type of Surveillance	Added: “In Ontario, reporting of AEFIs by specific health professionals is mandated under Section 38 of the <i>Health Protection and Promotion Act</i> (HPPA). AEFI reports from health professionals should be reported to the local public health unit using the “Report of Adverse Event Following Immunization (AEFI)” form available from: <a href="http://www.publichealthontario.ca/en/BrowseByTopic/InfectiousDiseases/Pages/Immunization-Resources.aspx#.Uqhun9JDUPZ">http://www.publichealthontario.ca/en/BrowseByTopic/InfectiousDiseases/Pages/Immunization-Resources.aspx#.Uqhun9JDUPZ</a> .”
April 2015	2.1 Scope	New Section added.
April 2015	5.0 Clinical Evidence	Added: “(see Section 3.0 (Case Classification))” to “Report events which have a temporal association with a vaccine and which cannot be clearly attributed to other causes (see <b>Section 3.0 (Case Classification)</b> ).”
April 2015	5.0 Clinical Evidence A.1 Pain, redness or swelling at the injection site	Revised “Pain, redness and swelling at the injection site” to “Pain, redness <b>or</b> swelling* at the injection site”. Added: “**Reporting of pain, redness or swelling at the injection site, lasting less than 4 days is not required for the purposes of provincial surveillance.”
April 2015	5.0 Clinical Evidence A.2 Abscess at the injection site	Added: “Physician-diagnosis” as bullet 4 Removed “physician-diagnosis” from: “Further characterization of the abscess as infectious or sterile requires <b>physician-diagnosis</b> ”.
April 2015	5.0 Clinical Evidence B.2 Rash	Added: “*An urticarial rash (hives) should be reported as “ <b>Allergic reaction – skin</b> ” (see Section C.3 (Allergic Reaction – Skin))”.
April 2015	5.0 Clinical Evidence B.2 Rash <i>Temporal criteria</i>	Added: “with the exception of vaccine-associated zoster which may occur months or years after receipt of varicella vaccine.”



<b>Revision Date</b>	<b>Document Section</b>	<b>Description of Revisions</b>
April 2015	5.0 Clinical Evidence B.2 Rash <i>Secondary mucocutaneous changes</i>	Added: “(hive)” to “*Nodule and wheal ( <b>hive</b> )”.
April 2015	5.0 Clinical Evidence B.6 Severe Vomiting/Diarrhea <i>Discussion</i>	Added: “In clinical trials there has been a small but statistically significant increased rate of vomiting and diarrhea following receipt of pentavalent rotavirus vaccine (Rot-5) but not Rot-1.”
April 2015	5.0 Clinical Evidence C.1 Event Managed as Anaphylaxis	Updated reference to the latest Evergreen Edition of the Canadian Immunization Guide.
April 2015	5.0 Clinical Evidence C.3 Allergic Reaction - Skin	Updated reference to the latest Evergreen Edition of the Canadian Immunization Guide.
April 2015	5.0 Clinical Evidence D.7 Guillain-Barré Syndrome (GBS) <i>Discussion</i>	Previous paragraph 3 removed and language updated in revised paragraph 3 and new paragraph 4.
April 2015	5.0 Clinical Evidence E.4 Syncope with injury	Added: “*Syncope that does not result in injury does not need to be reported for the purposes of provincial surveillance.”
April 2015	7.0 Comments	Updated link.
April 2015	8.0 References	References updated.

