

Ontario Public Health Standards:
Requirements for Programs, Services and Accountability

Infectious Disease Protocol

Appendix 1: Provincial Case Definitions for Diseases of Public Health Significance

Adverse Events Following Immunization (AEFIs)

Effective: May 2022

Adverse Events Following Immunization (AEFIs)

- Communicable
- Virulent

[Health Protection and Promotion Act \(HPPA\)](#)

[Ontario Regulation \(O. Reg.\) 135/18 \(Designation of Diseases\)](#)

Provincial Reporting Requirements

- Confirmed case
- Probable case
- Does not meet

As per Requirement #3 of the "Reporting of Infectious Diseases" section of the *Infectious Diseases Protocol, 2018* (or as current), the minimum data elements to be reported for each case are specified in the following:

- [O. Reg. 569](#) (Reports) under the HPPA;
- The Case and Contact Management (CCM) software guides;
- For certain vaccines, information to be entered into the applicable provincial inventory system (i.e., Panorama or COVaxON); and
- Bulletins and directives issued by Public Health Ontario (PHO).

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 events not previously recognized in clinical studies which can be further evaluated.¹ This is particularly important for rare adverse events which may not have been evident in clinical trials due to limited sample size.²

In Ontario, passive vaccine safety surveillance relies on reporting of AEFIs by health care providers, vaccine recipients or their caregivers to their local public health unit (PHU).³ AEFI reports received by PHUs are investigated, assessed, and documented according to provincial surveillance guidelines, as required by the Ontario Public Health Standards (OPHS). PHO conducts provincial surveillance of AEFIs and provides advice and support for local PHUs in the investigation and management of AEFI reports. All provincially reported AEFIs that meet the confirmed case definition are reported by PHO to the [Canadian Adverse Events Following Immunization Surveillance System \(CAEFISS\) at the Public Health Agency of Canada](#) (PHAC).⁴

In Ontario, a physician, nurse practitioner or pharmacist who administer immunizations for specified diseases are mandated under Section 38 of the HPPA and its Regulations to report all reportable events, as that term is defined in s. 38 of the HPPA, that may be related to such immunizing agents as defined in the Act. AEFI reports from those health care providers should be reported to the local PHU using the "[Report of Adverse Event Following Immunization \(AEFI\) form](#)", available from PHO.

Provincial AEFI surveillance includes adverse events occurring following the administration of an immunizing agent.

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

- Adverse events following the administration of a passive immunizing agent (e.g., immune globulin), diagnostic agent (e.g., tuberculin skin test) or any other drug product or any immunizing agent administered for a disease not specified under the HPPA; and
- Immunization program errors (e.g., incorrect site or dose) not temporally

associated with an adverse event.

For adverse events following only the administration of a passive immunizing agent, diagnostic agent (e.g., tuberculin skin test) or any other drug product listed above, please follow the established procedure for reporting adverse drug reactions to Health Canada using the "[Canada Vigilance Adverse Reaction Reporting Form](#)". These events can be reported to Health Canada by either the PHU or health care provider.

Note: If an adverse event follows an active immunizing agent administered at the same time as a passive immunizing agent, diagnostic agent or drug, then it can be reported as an AEFI subject to Section 3.0 (Case Classification), below.

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).

Historical AEFIs (i.e., a newly reported adverse events associated with vaccine administration occurring in the past) may be reported if there is enough information available to determine if the adverse event(s) meets the confirmed case definition (see Section 3.1 (Confirmed Case)).

Case Definition

Confirmed Case

Any untoward medical occurrence in a vaccine recipient which follows immunization that cannot be clearly attributed to other causes. The adverse event may be any unfavourable or unintended sign, abnormal laboratory finding, symptom or disease.⁶

A causal relationship with the administration of the vaccine does not need to be established in order to be reported as a confirmed case.^{1,7}

See Section 5.0 (Types of Adverse Events) for criteria used to further classify specific types of adverse events.

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Does Not Meet

Any reported event in a vaccine recipient which:

- Does not have a temporal relationship with vaccine administration (i.e., does not follow immunization);
- Has been clearly attributed to other causes;
- Is not within the scope of provincial AEFI surveillance (refer to section 2.1 Scope).

Types of Adverse Events

The following section outlines criteria used to further classify specific types of AEFIs. This is required for all AEFIs classified as a “Confirmed Case” for provincial surveillance and reporting purposes.

For adverse events that include physician-diagnosis as part of the reporting criteria, where appropriate and based on current scope of practice, the diagnosis may also be made by a Nurse Practitioner.

The temporal criteria for specific types of AEFIs are provided as generally agreed upon approximate timelines based on expert scientific consensus/opinion.⁶ AEFIs which occur outside of these timelines may still be reported if the event is assessed as clinically significant.

Within the discussion section of each case definition, information on contraindications/precautions are provided and may be used to inform recommendations for future immunization as determined by the Medical Officer of Health (MOH) or designate. Further information regarding public health management of AEFIs can be found in the [“Managing Adverse Events Following Immunization: Resource for Public Health”](#).

A. LOCAL REACTIONS AT THE INJECTION SITE

A.1 Pain or redness or swelling

Pain or redness or swelling⁷ at the injection site that:⁸

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

Temporal Criteria

Pain or redness or swelling at the injection site occurring 0-2 days following immunization with an inactivated vaccine or 0-7 days following immunization with a live vaccine.⁶

Discussion

Pain, or redness or swelling at the injection site are common and expected reactions to vaccine administration. The injection of foreign material into the tissues and irritation of the tissues by the process of injection can produce a localized inflammatory response. These local reactions are well-reported in clinical trials.²

Shoulder injury related to vaccine administration (SIRVA) is a preventable event resulting from improper vaccine administration technique (e.g., incorrect technique or land marking). The proposed mechanism of injury is the unintentional injection of antigenic material into the synovial tissue resulting in an immune-mediated inflammatory reaction.⁹ The main symptoms of SIRVA include persistent shoulder pain and a limited range of motion.¹⁰ In most cases pain and reduced range of motion develop within a few hours of vaccination, although delayed onset of up to four days has been observed.⁹ These reports can be included within this category, specifying "pain/redness/swelling lasting greater than 10 days", where appropriate.

Reports of systemic reactions which include the injection site (e.g., generalized

⁷ Visible enlargement of a limb at the site of injection

urticarial [C.3- Allergic reaction – Skin] or other distinct entities or conditions like lymphadenopathy [B.3 Adenopathy/Lymphadenopathy]) that may be near the injection site should be reported under the appropriate systemic reaction(s) listed in the sections below.

Pain, or redness, or swelling at the injection site is not a contraindication to further doses of vaccine.

A.2 Abscess

An abscess at the injection site is a confirmed localized collection of material in the soft tissue occurring at the site of immunization.¹¹ The abscess is confirmed by physician- diagnosis and:^{2,6,11}

- 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).

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.^{2,6}

Sterile abscess

- Material from abscess known to be non-purulent;

OR

- Absence of localized signs of inflammation;

OR

- Failure to improve on antimicrobial therapy.^{2,6}

Temporal Criteria

An abscess occurring 0-7 days following immunization.⁶

Discussion

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.¹² An infectious abscess may be accompanied by fever and/or regional lymphadenopathy and can be the result of contamination of multi-dose vials (e.g., re- entering vial with a used needle, improper cleaning or storage).

Sterile abscesses are collections of fluid in the absence of signs of infection/inflammation.¹² They are primarily associated with aluminum-absorbed vaccines and may occur when these vaccines are injected into subcutaneous tissue instead of muscle.²

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 at the injection site that is:^{2,13}

- Firm, in the absence of abscess formation, erythema, and warmth;
- Is ≥ 2.5 cm in diameter; and
- Persists for more than one month.

Temporal Criteria

A nodule is generally seen 0-7 days following immunization.⁶

Discussion

The discrete (i.e., well-demarcated) clinical feature of a nodule at injection site sufficiently differentiates it from the more common clinical picture of acute induration or swelling at the injection site, which are more diffuse and shorter in duration.¹³ Nodules are mainly associated with aluminum-adsorbed vaccines, particularly if the dose is deposited subcutaneously rather than intramuscularly (IM). Sterile nodules can take up to 1 year or more to resolve, but most commonly resolve within 2 to 3 months.²

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 physician-diagnosed and characterized by at least 3 of the 4 following local signs or symptoms:^{2,6,14}

- Localized pain or tenderness to touch;
- Erythema;
- Induration or swelling; or
- Warm to touch.

Temporal Criteria

Cellulitis occurring 0-7 days following immunization.⁶

Discussion

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

seldom available.²

Cellulitis should be distinguished from local reactions described above, and only one reported, by the presence of intense erythema, tenderness to light touch, induration and substantial local warmth. Cellulitis is excluded if resolution is rapid and spontaneous.¹² It can result from contamination of a vaccine vial or injection equipment, or can be due to introduction of surface bacteria into the deeper layers of the skin.² Because cellulitis is usually caused by a bacterial infection, it is commonly treated with antimicrobial agents.

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.

Reporting of fever that is not accompanied by any other reportable event is not required for provincial AEFI surveillance.

Temporal Criteria

Fever occurring 0-3 days following immunization with an inactivated vaccine, or 0-42 days following immunization with a live vaccine.⁶

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.¹⁵

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 Measles, Mumps, and Rubella [MMR] or varicella vaccines).²

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 as an adverse event following immunization.²

B.2 Rash

A skin or mucosal change (either new or an exacerbation of a previous condition) for which no alternative cause has been identified.¹⁶

NOTE: An urticarial rash (hives) should be reported under section C.3 Allergic reaction – skin. If skin changes occur only at (or near) the injection site and the adverse event meets criteria for a local reaction (A. Local reactions at the injection site) it should be reported as such.

Temporal Criteria

Rash occurring 0-7 days following immunization with an inactivated vaccine, or 0-42 days following immunization with a live vaccine with the exception of vaccine-associated zoster (shingles) which may occur months or years after receipt of varicella vaccine.⁶

Discussion

A report of rash following immunization may include a description of changes in the appearance of the skin or mucosa consistent with morphologic description of mucocutaneous lesions described in the Brighton Collaboration case definition.¹⁶ While it is an expected reaction, particularly following receipt of a live vaccine, and may not always be reported by individuals or providers for this reason, reports of rash that meet criteria should be included in provincial AEFI surveillance.

MMR vaccine may produce a mild, measles-like illness which can be manifested by a generalized rash and fever lasting up to 3 days.² It occurs in 5 to 10% of persons following the first dose of MMR, usually 6 to 23 days after vaccination.² It is much less common following the second dose of MMR.² Measles-like rash following MMR

vaccine is not transmissible.¹⁷

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. Expert referral should be considered for individuals who develop thrombocytopenia (a cause of petechial rash) within six weeks of immunization, to assist with future immunization advice (see Section E.1 (Thrombocytopenia)).²

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.^{2,18} 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.^{2,18} Transmission of varicella following a varicella vaccine related rash is rare but can occur.¹⁹

For specific guidance on the management of post-varicella vaccine rash in healthcare workers, please refer to the [Canadian Immunization Guide](#).¹⁸ Post-varicella or post- MMR vaccine -rashes with laboratory (genotype) confirmation of vaccine-strain virus, including vaccine-strain zoster (shingles) which may occur months or years after receipt of varicella vaccine, may be reported as “rash”.

Most rashes occurring in children, even those temporally-related to immunization, are caused by intercurrent viral illness. Rashes other than petechial rashes associated with significant thrombocytopenia, are not a contraindication to further doses of a vaccine.²

B.3 Adenopathy/Lymphadenopathy

Enlargement of one or more lymph nodes that is physician-diagnosed.²

Temporal Criteria

Adenopathy/lymphadenopathy occurring 0-7 days following immunization with an inactivated vaccine, or 0-42 days following immunization with a live vaccine.⁶

Discussion

Adenopathy or lymphadenopathy can include:

- Regional adenopathy: abnormal enlargement of the lymph nodes closest to the injection site (e.g., inguinal adenopathy when associated with an IM injection in the thigh, axillary adenopathy associated with an IM injection in the deltoid).
- Lymphadenitis: inflammation of one or more lymph nodes, usually caused by a primary focus of infection elsewhere in the body.
- Lymphangitic streaking: painful and inflamed red streaks below the skin's surface, following the path of lymph draining from the site of infection via lymphatic vessels to regional lymph nodes.

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.²

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

B.4. Hypotonic-Hyporesponsive Episode (HHE)

HHE is physician-diagnosed and involves the sudden onset, in a child aged **less than 2 years**, of:^{2,6,20}

- Hypotonia (muscle limpness); and/or
- Hyporesponsiveness or unresponsiveness; and/or
- Pallor or cyanosis.

Temporal Criteria

HHE occurring 0-2 days following immunization. ⁶

Discussion

With an HHE, there is an acute decrease in sensory awareness or loss of consciousness, accompanied by pallor and/or 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.²

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.²

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.²

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.²¹

Temporal Criteria

Screaming/persistent crying occurring 0-3 days following immunization.⁶

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.²

Persistent crying is not a contraindication to further doses of vaccine.

B.6 Severe Vomiting/Diarrhea

Vomiting and/or diarrhea that is:

- Increased above normal baseline (i.e., three or more episodes in a 24-hour period); and
- Severe enough to interfere with daily routine (e.g., projectile vomiting or explosive diarrhea).^{2,22}

Temporal Criteria

Vomiting and/or diarrhea occurring 0-3 days following immunization with an inactivated vaccine, or 0-42 days following immunization with a live vaccine.²

Discussion

Nausea and diarrhea have been particularly associated with oral typhoid vaccine, human diploid cell rabies vaccine (HDCV), and Japanese B encephalitis vaccine.² 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-1.²³ Treat severe vomiting/diarrhea symptomatically to prevent dehydration and electrolyte imbalance.²

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 physician-diagnosed and follows receipt of a mumps-containing vaccine.²

Temporal Criteria

Parotitis occurring 0-30 days following immunization.⁶

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.²

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

C. ALLERGIC REACTIONS

C.1 Event Managed as Anaphylaxis

All events managed as anaphylaxis (e.g., epinephrine administered) at the time of occurrence should be reported.

Anaphylaxis is a rare but potentially life-threatening allergic reaction. It is a clinical syndrome characterized by sudden onset, rapid progression of signs and symptoms and multiple (≥ 2) organ systems.

Temporal Criteria

Anaphylaxis occurring 0-24 hours following immunization.⁶

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

most specific for the condition. Brighton Level 1 is defined as ≥ 1 major dermatological criterion **AND** (≥ 1 major cardiovascular **AND/OR** ≥ 1 major respiratory criterion).²⁴

Suspected anaphylaxis that is managed appropriately and promptly, avoids escalation of symptoms and progression to a severe outcome.² Brighton Collaboration Levels 2 and 3 of diagnostic certainty were designed to be broad enough to include such cases presenting differently due to appropriate and early treatment initiation.

In most cases symptoms begin within one hour of exposure, but in a minority of cases symptoms may present up to 12 hours following immunization and biphasic presentation has been noted up to 72 hours following immunization.²⁴

Anaphylaxis must be distinguished from fainting (vasovagal syncope), breath-holding spells and anxiety, which are not reportable adverse events. Symptoms that are progressive or increasing in severity are more likely to represent anaphylaxis.² For guidance on the initial management of anaphylaxis in non-hospital settings please refer to Part 2 of the [Canadian Immunization Guide](#).²⁵

A true anaphylactic reaction to a vaccine is a contraindication to receipt of further doses of the same vaccine or to a component of the vaccine. Referral to the primary care provider for consultation with an allergist may be sought to identify the component to which the client has hypersensitivity. It is important not to leave clients underimmunized 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.²

A report of an event managed as anaphylaxis should be accompanied by a completed "[Enhanced Reporting Form for Events Managed as Anaphylaxis Following Immunization](#)" available from PHO.

C.2 Oculo-Respiratory Syndrome (ORS)

The onset of bilateral red eyes plus 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.^{2,6,25} This syndrome has only been described after immunization with influenza vaccine.

Temporal Criteria

ORS occurring 0-24 hours following immunization.⁶

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.²

Individuals who have experienced ORS without lower respiratory tract symptoms may be safely revaccinated with influenza vaccine. Expert referral (i.e., allergist or infectious diseases specialist) should be considered for individuals who experienced ORS with lower respiratory tract symptoms to assist in future immunization advice.¹²

C.3 Allergic Reaction – Skin

An allergic reaction of the skin[†] including any one of the following: urticaria (hives), erythema, pruritus, prickle (or tingling) sensation, localized or generalized edema (in the deeper layers of the skin, subcutaneous tissues or mucosa lining the throat, airways and gut).²

[†] 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 0-2 days following immunization.⁶

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, inquire about a history of allergies and possible exposure to other allergens during the same time period.²

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](#).²⁵

Recommendations for future vaccine doses following the occurrence of urticaria (hives) depend on the time from receipt of the vaccine to urticaria (hives) onset. Individuals with generalized hives occurring between 0 to 2 hours after immunization may 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.²

For further recommendations on the management of allergic reactions refer to "[Managing Adverse Events Following Immunization: Resource for Public Health](#)".¹²

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.^{6,26}

Temporal Criteria

Seizure (febrile or afebrile) occurring 0-3 days following immunization with an inactivated vaccine, or 0-42 days following immunization with a live vaccine. ⁶

Discussion

Seizures include paroxysms of generalized tonic skeletal muscle contractions and generalized clonic jerking, usually associated with decreased level of consciousness. Atonic seizures are associated with a sudden loss of muscle strength or tone. Seizures may last for several minutes or more and 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.²

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 (i.e., single generalized tonic-clonic seizures of up to 15 min duration²⁶) 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.²

When the first dose of measles-containing vaccine is administered to children 12 to 23 months of age as MMRV vaccine, there is an increased risk of fever and febrile seizures in the 7 to 10 days after immunization, when compared to the separate administration of MMR vaccine and univalent varicella vaccine at the same visit. This risk is estimated at approximately 1 additional febrile seizure for every 2,300 to 2,800 doses of MMRV vaccine.²⁷

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, a referral may be made to the primary care provider with a recommendation for a consultation with a paediatrician or

paediatric neurologist, to rule out an underlying seizure disorder.²

D.2 Encephalopathy/Encephalitis

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

Temporal Criteria

Encephalitis/encephalopathy occurring 0-42 days following immunization.⁶

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.²

Encephalopathy and encephalitis are severe but rare adverse events that require physician-diagnosis. An AEFI report of encephalopathy or encephalitis should include appropriate medical documentation, physicians' assessments, and test results.²

The case definition of encephalopathy, based on Brighton Collaboration criteria, includes:²⁸

- At least one listed indicator of central nervous system inflammation[‡]; and
- Either >24 hours depressed or altered consciousness with one or more signs of reduced responsiveness[§] or one or more signs of focal or multi-focal

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

[§] 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.

central nervous system abnormality.”

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 much greater than the risk following vaccination (1/1,000,000 following MMR).²

Expert referral should be considered for individuals with encephalitis/encephalopathy following immunization to assist in future immunization advice.

D.3 Meningitis

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

Temporal Criteria

Meningitis occurring 0-15 days following immunization with an inactivated vaccine, or 0- 42 days following immunization with a live vaccine. ⁶

Discussion

Meningitis is an infection or inflammation of the membranes covering the brain and spinal cord. It is characterized by a 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

“ 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).

stain and/or on routine culture.^{2,29}

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.² 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.^{2,30} There is no evidence of a causal association with the Jeryl-Lynn strain of mumps used in MMR vaccine, or with any of the other routinely used live virus vaccines. Aseptic meningitis following immunization typically resolves without sequelae.²

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.²

Temporal Criteria

Anaesthesia/paraesthesia occurring 0-42 days following immunization. ⁶

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 or other specialist may be considered to assess nerve functioning.²

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.²

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 0-42 days following immunization. ⁶

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.³¹ 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.²

D.6 Bell's Palsy

A unilateral or bilateral paralysis or weakness of facial muscles innervated by cranial nerve seven that is physician-diagnosed.³²

Temporal Criteria

Bell's palsy occurring 0-3 months following immunization. ⁶

Discussion

The cause of Bell's palsy is not clear. 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 nerves that control muscles on one side of the face.² Influenza infection does not appear to be a precipitating event for Bell's palsy.²

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

D.7 Guillain-Barré Syndrome (GBS)

A physician-diagnosed illness that includes:^{2,33}

- 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. CSF test results, if available, must either be normal, or have <50 WBC/mm.³

Temporal Criteria

GBS occurring 1 to 8 weeks following immunization.²

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, in the days or weeks prior to the onset of neurologic signs. Infection with *Campylobacter jejuni* is one of the most risk factors for GBS, although it has also been associated with other infections including influenza. A maximum degree of weakness is reached within 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 occur in 20% of patients. Studies in developed countries have suggested an incidence of 1 to 2 per 100,000 population per year.²

There is limited evidence of an association between GBS and tetanus toxoid, OPV and the 1976 swine influenza vaccine, (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.²

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.²

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.³⁴

D.8 Myelitis/Transverse Myelitis

An illness diagnosed by a physician as myelitis or transverse myelitis.

Temporal Criteria

Myelitis occurring 0-42 days following immunization.²

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 (CNS) inflammation include fever $\geq 38^{\circ}\text{C}$, Cerebral Spinal Fluid (CSF) pleocytosis (>15 WBC/ mm^3 if <2 months old; >5 WBC/ mm^3 if ≥ 2 months) or neuroimaging findings that demonstrate acute inflammation (\pm meninges), or spinal

cord demyelination.²⁸

Transverse myelitis is an abrupt onset, inflammatory demyelinating condition of the spinal cord that affects almost the entire thickness of the spinal cord but spans only one or a few vertebral segments.²

In its recently published safety review of a number of vaccines, the Institute of Medicine (IOM) concluded that the evidence is inadequate to accept or reject a causal relationship between MMR, varicella, influenza, hepatitis A and B, HPV, DPT and meningococcal vaccines and transverse myelitis.³⁵

The decision to continue immunization must be made on a case-by-case basis. All cases should be evaluated by a neurologist.²

D.9 Acute Disseminated Encephalomyelitis (ADEM)

An illness diagnosed by a physician as acute disseminated encephalomyelitis.

Temporal Criteria

ADEM occurring 0-42 days following immunization.⁶

Discussion

ADEM is an illness in which there are one or more focal or multifocal central nervous system findings. 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).²⁸

Individuals diagnosed with ADEM following immunization should be referred for expert clinical assessment to inform advice on future immunizations.

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:²

- Blood smear examination; or
- Clinical signs and/or symptoms of spontaneous bleeding.^{††}

Temporal Criteria

Thrombocytopenia occurring 0-42 days following immunization. ⁶

Discussion

Thrombocytopenia is an abnormal hematological condition in which the number of platelets is reduced below normal ($150-450,000/mm^3$). 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.²

Rarely, thrombocytopenia occurs within 6 weeks following immunization with measles- containing vaccine (MMR or MMRV).²⁷ The incidence of thrombocytopenia after MMR vaccine is estimated to be between one in 25,000 to one in 40,000 doses of MMR.³⁶⁻³⁸

Most cases occur following vaccination with the first dose of measles-containing

^{††} 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.

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.³⁸ The risk of thrombocytopenia following natural measles or rubella infection is greater than the risk following immunization.²

Children with a history of thrombocytopenia may be at increased risk for developing thrombocytopenia after MMR vaccination. Such children should generally still be immunized because the benefits of immunization outweigh the risks. Expert referral should be considered for individuals who develop thrombocytopenia within six weeks of immunization to assist in future immunization advice.¹²

E.2 Arthritis/Arthralgia

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

- Is associated with limitation of regular activities; and
- Lasts 24 hours or longer.

Temporal Criteria

Arthritis/arthralgia occurring 0-30 days following immunization with an inactivated vaccine or 0-42 days following immunization with a live vaccine.⁶

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.³⁹ Arthritis/arthralgia can also occur in children and adolescent and adult men, but at much lower rates.² Persistence or recurrence of these symptoms is rare.^{2,40} Both the frequency and severity of adverse reactions are less than those associated with natural disease, and serious adverse

reactions are rare.³⁹

Acute aseptic arthritis is one presentation of arthritis commonly defined by acute onset of joint inflammation, increased white blood cell count in the synovial fluid and the absence of an identifiable causative organism.⁴¹ Reports of physician-diagnosed acute aseptic arthritis should be included in provincial AEFI surveillance (refer to the Brighton Collaboration case definition for further information⁴¹).

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

E.3 Intussusception

The invagination (or “telescoping”) of one segment of the intestine into a segment of the distal intestine which is physician-diagnosed and occurring following receipt of rotavirus vaccine.⁴²

Temporal Criteria

Intussusception occurring 0-42 days following immunization.⁶

Discussion

Intussusception is the most common cause of acute intestinal obstruction in infants and young children.⁴² Most cases occur in infants who are less than 12 months of age.⁴³ If untreated, intestinal infarction or perforation may occur; therefore, intussusception is a potentially life-threatening condition and early diagnosis and treatment are essential, however death from intussusception in Canada is rare.

Data currently available from post-marketing studies of Rotarix™ and RotaTeq® show a small increased risk of intussusception, particularly during the 7 days following the first dose.⁴⁴ However, considering that the benefits of rotavirus vaccination are great, the vaccine continues to be recommended to prevent severe rotavirus disease in infants.⁴⁵

Intussusception following rotavirus vaccine is a contraindication for further doses of the vaccine.^{2,45}

A report of intussusception should be accompanied by a completed

["Intussusception Investigation Form"](#) available from PHO.

E.4 Syncope with injury

Reporting of vasovagal syncope without injury is not required for provincial AEFI surveillance.

Temporal Criteria

Syncope with injury occurring 0-30 minutes following immunization.²

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.² 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): this is not reportable unless it results in injury.²⁵ Recovery occurs within 1 to 2 minutes.²

The risk of fainting is the more common reason to keep vaccine recipients under observation for 15 minutes post-immunization.² For further information on the management of syncope refer to the chapter on "Early vaccine reactions including anaphylaxis" in the [Canadian Immunization Guide](#)²⁵ and the World Health Organization (WHO) resource: "[Immunization stress-related response: a manual for program managers and health professionals to prevent, identify and respond to stress-related responses following immunization](#)".⁴⁶

Syncope with injury has been reported following immunization with HPV vaccine and H1N1 vaccine.⁴⁷⁻⁵¹ 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.²

Syncope is not a contraindication to further immunizations.

E.5 Kawasaki Disease

An illness that is diagnosed by a physician as Kawasaki disease (KD).

Temporal Criteria

KD occurring 0-42 days following immunization.⁶

Discussion

KD is a systemic vasculitis affecting medium-sized muscular arteries⁵², characterized by systemic inflammation (manifested by fever) and mucocutaneous involvement.⁵³ It occurs mainly in children under the age of 6 years⁵² and rarely in adults. KD is typically a self-limited condition, however potentially life-threatening changes in the coronary arteries of some children may develop.⁵²

The cause of KD is unknown however it has been linked with a variety of etiologic agents from bacteria such as *Staphylococcus*, *Streptococcus*, *Propionibacterium* and *Chlamydia* to viruses including Epstein–Barr virus, parvovirus, coronavirus, and retroviruses.⁵⁴ Although a temporal relationship with immunization has been observed, evidence for an increased risk or a causal association is lacking.⁵⁵

There is no single diagnostic test or unique clinical distinguishing KD from other acute febrile exanthems of childhood⁵⁶, therefore the diagnosis relies on identification of principal clinical findings and exclusion of similar clinical entities with known causes.⁵⁶ KD can be stratified as complete (also referred to as classic or typical) or incomplete (atypical) depending on the number of clinical findings characteristic to the disease. The Brighton Collaboration case definition for KD includes three levels of diagnostic certainty based on the presence of principal clinical features which include fever (persisting for 4 days or more), bilateral bulbar conjunctival injection without exudate, changes in extremities, polymorphous exanthema, changes in the lips and/or oral cavity, and cervical lymphadenopathy.⁵²

E.6 Other Severe OR Unusual Events

This category is reserved for reports of other severe or unusual events with a temporal association to immunization, for which there is no other known cause, and which are not covered under the categories previously described. The event must be clinically important or epidemiologically interesting, usually requiring medical attention.² This category also includes:

- Any death of a vaccine recipient temporally linked (within one month) to immunization, where no other clear cause of death can be established; or⁵⁷
- Pregnancy-related events (e.g., maternal death, miscarriage/stillbirth).

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.²

E.7 Other Adverse Events of Special Interest (AESI) for COVID-19 vaccine(s)

Information regarding additional AESI following administration of COVID-19 vaccine(s) not covered under the categories above can be found in supplementary guidance.

For further information about human diagnostic testing, contact the [Public Health Ontario Laboratories](#).

Please refer to [PHO's Reportable Disease Trends in Ontario reporting tool](#) for the most up-to-date information on infectious disease trends in Ontario.

For additional national and international epidemiological information, please refer to the Public Health Agency of Canada and the World Health Organization

ICD-10 Code(s)

T88.1 Other complications following immunization, not elsewhere classified

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). It has been adapted with permission from BCCDC.

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Document History

Revision Date	Document Section	Description of Revisions
April 2022	Entire Document	New template. Appendix A and B merged. No material content changes.
April 2022	Epidemiology: Occurrence section	Removed.
April 2022	ICD Codes	Removed.