Adverse Events Following Immunization (AEFI) Policy for Alberta Immunization Providers

Alberta Health
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Adverse Events Following Immunization (AEFI) Policy for Alberta Immunization Providers
https://open.alberta.ca/publications/aefi-policy-for-alberta-immunization-providers

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I. Introduction

The monitoring of adverse events following immunization (AEFI) involving vaccines and biologicals administered in Alberta is an important evaluation component of the provincial immunization program. AEFI reporting and monitoring is also a key contributor to public confidence in vaccine programs; is critical to vaccine safety surveillance; is used to confirm results of pre-licensure clinical trials; and provides a process to identify previously unknown concerns for each product. The Public Health Agency of Canada (PHAC) and the vaccine manufacturers depend on accurate, timely and ongoing reporting of AEFI from those who administer the vaccines in order to provide the best analysis of reactogenicity of each new vaccine.

This document contains information on:

- the importance of AEFI reporting and surveillance for vaccine safety;
- how and when to report an adverse event following immunization to Alberta Health Services (AHS) Province-wide Immunization Program; and
- definitions of reportable AEFIs in Alberta.

An AEFI is defined as:

> "any untoward medical occurrence in a vaccinee which follows immunization and which does not necessarily have a causal relationship with the administration of the vaccine. The adverse event may be any unfavourable and/or unintended sign, abnormal laboratory finding, symptom or disease".[1] (National Advisory Committee on Immunization. Canadian Immunization Guide (Evergreen ed.). Ottawa, ON: Public Health Agency of Canada www.phac-aspc.gc.ca/publicat/cig-gci/p02-01-eng.php)

Details on AEFI reporting are provided in this document, including case definitions and reporting requirements. Common or expected side effects of a vaccine are usually mild, predictable and self-limited. These events do not need to be reported. It is often difficult to confirm whether or not the health concern is in any way related to either the vaccine or the immunization process, therefore immunization providers should encourage parents and clients to report any symptoms that are not expected following an immunization.

Reporting an adverse event with a temporal association to a vaccine does not imply causality. Causality assessment involves the consideration of vaccine attributable risk (whether there is a causal association between a vaccine and an adverse event) and determining whether the vaccine(s) caused the adverse event or whether the event would have occurred anyway.

The Canadian Immunization Guide provides the following guidelines in forming Alberta's policy on the reporting of AEFI as part of comprehensive vaccine safety surveillance:

- Vaccine pharmacovigilance has been defined as the science and activities related to the detection, assessment, understanding and communication of adverse events following immunization and other vaccine-related or immunization-related issues, and to the prevention of untoward effects of the vaccine or immunization. [1]
- Health care providers have essential and pivotal roles to play in gaining and maintaining public confidence in the safety of vaccines. These include providing evidence-based information on the

benefits and risks of vaccines; helping clients and patients to interpret media and Internet vaccine safety messages; and identifying and reporting adverse events following immunization.[1]

- Any single occurrence of an unusual event following immunization may be coincidental or caused by the vaccine. An accumulation of reports, sometimes as few as four or five, may signal a risk due to the vaccine. Thus, each and every report submitted by vaccine providers is important.[1]

The criteria for AEFI reporting in Alberta is based on national guidelines, and has been developed and updated using current literature and research, product monographs, experts in the field and applying lessons learned from past AEFI reporting.

Health practitioners are encouraged to consult the following as companion references to this document:

- Alberta Immunization Policy www.health.alberta.ca/professionals/immunization-policy.html
- Canadian Immunization Guide www.phac-aspc.gc.ca/publicat/cig-gci/index-eng.php
- Canadian Communicable Disease Report www.phac-aspc.gc.ca/naci-ccni/index-eng.php
- Public Health Agency of Canada User Guide to Completion and Submission of the AEFI Reports www.phac-aspc.gc.ca/im/aefi-essi_guide/index-eng.php.

II. Legislative Authority

The Adverse Events Following Immunization Policy for Alberta Immunization Providers is provided under the authority of the Public Health Act (Act) and Part 2 of the ***Immunization Regulation*** which outlines the requirements for the reporting of adverse events following immunization.

III. Purpose

The purpose of this document is to provide AEFI reporting guidance for Alberta immunization providers.

In Alberta, the management of AEFIs includes analysis of the event and interpretation for subsequent immunization. Individuals who have experienced an AEFI may unnecessarily be advised to avoid subsequent immunization, which may have important adverse personal and population health consequences.

Data from AEFI reports contribute to provincial immunization program evaluation as well as to the national AEFI surveillance. Alberta Health submits monthly electronic non-identifiable AEFI data to PHAC, which is compiled nationally to assist in monitoring emerging safety signals that may not be detected at a provincial or local level.

IV. Reporting Adverse Events Following Immunization

The reporting of AEFIs consists of two levels:

1. The first level of reporting is by any health practitioner to Alberta Health Services (AHS) Province-wide Immunization Program. This facilitates adverse event reporting using a centralized intake system and supports the monitoring of vaccine safety signals. AHS will provide and/or recommend appropriate client follow-up.
2. The second level of reporting is from AHS where adverse events that meet the case definitions for reporting (outlined in Section V) are reported to Alberta Health.

Reporting to Alberta Health Services (AHS)

1. When to report to Alberta Health Services

   Health practitioners are to report an adverse event following immunization to AHS within 3 days of determining or being informed that a patient has experienced an adverse event following immunization unless it has already been reported.

2. What to report to Alberta Health Services

   Any "adverse event following immunization" defined as an unfavourable health occurrence experienced by a patient that:
   (a) follows immunization,
   (b) cannot be attributed to a pre existing condition, and
   (c) meets one or more of the following criteria, as determined by a health practitioner:
   - (i) the health occurrence is life threatening, could result in permanent disability, requires hospitalization or urgent medical attention, or for any other reason is considered to be of a serious nature;
   - (ii) the health occurrence is unusual or unexpected, including, without limitation, an occurrence that
     - (A) has not previously been identified, or
     - (B) has previously been identified but is being reported at increased frequency;
   - (iii) the health occurrence cannot be explained by anything in the patient's medical history, including, without limitation, a recent disease or illness, or consumption of medication.

If unsure or if there are questions contact AHS.

Data elements The following data elements must be reported in respect of the adverse event following immunization:

a) patient first name and last name;
b) patient personal health number or unique lifetime identifier;
c) patient date of birth;
d) patient sex at birth;
e) description of the adverse event, including, without limitation, any applicable symptom or diagnosis listed in the *Immunization Regulation* Schedule as reported by the patient or observed

or diagnosed by the health practitioner, as the case may be, and the onset and duration of the adverse event;

f) vaccine code of the vaccine used in the immunization preceding the adverse event following immunization, if available;
g) lot number of the vaccine used in the immunization preceding the adverse event following immunization, if available;
h) manufacturer of the vaccine used in the immunization preceding the adverse event following immunization, if available;
i) date of the immunization preceding the adverse event following immunization;
j) delivery management site code for the immunization preceding the adverse event following immunization, if available;
k) first name, last name and telephone number of the person reporting.

3. How to report an Adverse event following immunization

The health practitioner shall ensure that the adverse event following immunization is reported to the AHS Central AEFI Reporting Line at 1-855-444-2324 (1-855-444-CDCI) or online at https://www.albertahealthservices.ca/info/Page16187.aspx.

Reporting to Alberta Health (Chief Medical Officer)

What is reported by AHS to Alberta Health

- All AEFIs that meet the criteria for the reportable categories outlined in this manual temporally related (i.e., related in time) to an immunization, with or without clear evidence of causality within 4 days of making that determination
- Data elements that must be included: patient first and last name identifiers, patient PHN or ULI, DOB, sex at birth, vaccine code lot number, vaccine manufacturer, immunization date, the adverse event, the recommendation provided, if any, and the delivery management site.
- Additional data elements to be included if available; dosage, route, site, number of previous doses of antigen.
- All antigens given on the same immunization date regardless if the AEFI appears to be related to one antigen in particular.
- Multiple AEFIs associated with one or more vaccines given on the same immunization date using one AEFI report. For example, if a client reports a severe local reaction and a convulsion following the administration of vaccine(s) given on the same immunization date, use the same AEFI report.
- Events that do not meet specific case definitions but are felt to be significant (i.e., serious or unusual) under Other Severe or Unusual Events.

Note: For a listing of reportable AEFI, including case definitions, see Section V**. Reportable AEFI in Alberta.**

The two exceptions to this:

- **Anaphylaxis** (including allergic reactions where epinephrine is administered) following a provincially funded vaccine; and

- Death temporally linked to a provincially funded vaccine

are to be reported to Alberta Health within 24 hours via fax (780-422-6663) or e-mail.

Supporting Documentation

In cases where an anaphylaxis or suspect anaphylaxis is reported and the client receives additional medical care, supporting documentation must be sent to Alberta Health. Supporting documentation includes, but is not limited to; Pharmacists record of care, EMS record of care if the client was transported, and Emergency Department record of care, including Nursing and Physician and other medical professional notes.

Additional documentation may be requested in other circumstances and should be provided by the individual and/or organization that provided the immunization.

In the event of a death the Medical Examiner/Pathologist documentation of assessment is also required.

V. Reportable Adverse Events Following Immunization

Summary of Reporting Criteria

AEFI	Reporting Criteria	Vaccines (Temporal criteria**)	
		Inactivated	Live
ADEM (acute disseminated encephalomyelitis)	• Physician-diagnosed encephalomyelitis AND • One or more focal or multifocal findings referable to the central nervous system	0 – 42 days	MMR 5 – 30 days Varicella 5 – 42 days
Adenopathy	• Enlargement of one or more lymph nodes, > 1.5 cm in diameter AND/OR • Draining sinus over a lymph node.	0 – 7 days **mRNA COVID-19** 0 – 30 days	5 – 30 days
Allergic Reaction	• One or more of the following signs/symptoms: hives, itching, edema, stridor, wheezing	0 – 48 hours	0 – 48 hours
Anaesthesia/ Paraesthesia	• Physician-diagnosed anaesthesia or paraesthesia lasting 24 hours or more	0 to 15 days	MMR: 0 – 30 days Varicella: 0 – 42 days
Anaphylaxis	• See anaphylaxis definition.	0 – 24 hours Typically, within seconds to minutes, usually within 1 hour.	0 – 24 hours
Arthralgia/Arthritis	• Arthralgia or arthritis lasting ≥ 24 hours	n/a	5 – 30 days
Bell's Palsy	• Physician-diagnosed Bell's palsy	0 – 3 months	0 – 3 months
Cellulitis	• Physician-diagnosed cellulitis AND • Characterized by at least three of the following local signs or symptoms: pain or	0 - 7 days	0 - 7 days

AEFI	Reporting Criteria	Vaccines (Temporal criteria**)	
		Inactivated	Live
	tenderness to touch, erythema, induration or swelling, warm to touch AND • Reaction is at the injection site		
Convulsions (febrile and afebrile)	• Seizures (febrile or afebrile) with generalized, tonic, clonic, tonic-clonic, or atonic motor manifestations, occurring within AND • History or report of loss of consciousness.	0 – 72 hours	5 – 14 days
Encephalitis	• Physician diagnosed encephalitis AND • At least one listed indicator of central nervous system inflammation AND • > 24 hours of depressed or altered consciousness with one or more signs of reduced responsiveness OR • One or more signs of focal or multi-focal central nervous system abnormality	0 – 42 days	MMR 5 – 30 days Varicella 5 – 42 days
Erythema Multiforme	• Rash specific to Erythema Multiforme • Must be diagnosed by a physician.	5 days or more	5 days or more
GBS (Guillain-Barre syndrome)	• Physician-diagnosed GBS	0 to 6 weeks	0 to 6 weeks
HHE (hypotonic-hyporesponsive episode)	• Hypotonia (muscle limpness) AND • Either hyporesponsiveness or unresponsiveness AND • Either pallor or cyanosis	0 – 72 hours	0 – 72 hours
Infected Abscess	• Spontaneous or surgical drainage of purulent material from the mass OR • Demonstration of material by an imaging technique AND • Localized sign(s) of inflammation, which would include one of the following: erythema, pain to light touch, swelling, and warmth to touch AND • Evidence of resolution/improvement temporally related to antimicrobial therapy	0 - 7 days	0 - 7 days

AEFI	Reporting Criteria	Vaccines (Temporal criteria**)	
		Inactivated	Live
Intussusception	• Physician-diagnosed intussusception following rotavirus vaccine receipt AND • Evidence of intestinal obstruction and/or invagination and/or vascular compromise	n/a	Rotavirus vaccine: 0 – 42 days
Meningitis	• Physician-diagnosed aseptic meningitis for which no other cause has been identified.	0 – 15 days	MMR: 5 – 30 days Varicella: 0 – 42 days
Myelitis	• Physician-diagnosed myelitis AND • Two or more indicators suggestive of spinal cord inflammation.	0 – 42 days	5 – 42 days
Nodule	• Firm nodule is at the injection site AND • Persists for > 1 month	0 - 7 days	0 - 7 days
ORS	• Onset of bilateral red eyes AND • One or more of the following respiratory symptoms: Cough, wheeze, chest tightness, difficulty breathing, difficulty swallowing, hoarseness, sore throat WITH or WITHOUT facial edema.	Influenza: 0 – 24 hours	n/a
Orchitis	• Physician-diagnosed orchitis	n/a	Mumps: 5 – 30 days
Paralysis	• Physician-diagnosed paralysis with no other cause identified AND • Lasting more than 24 hours	0 - 15 days	MMR or OPV: 0 – 30 days Varicella: 0 – 42 days
Parotitis	• Physician-diagnosed parotitis	n/a	Mumps: 5 – 30 days

AEFI	Reporting Criteria	Vaccines (Temporal criteria**)	
		Inactivated	Live
Rash	• Varicella-like rash with ≥ 50 lesions OR • Requiring hospitalization OR • Rashes or eruptions on the skin that are not expected, with an onset within 7 days of immunization and lasts ≥ 4 days AND either • Generalized rash: systemic eruption in two or more parts of the body OR • Localized at non-injection site; eruption localized at another part of the body, away from the injection site OR • Requires hospitalization.	0 – 7 days	Varicella: 0 – 42 days
Screaming Episode/Persistent Crying	• Presence of screaming or crying > 3 hours	0 – 72 hours	0 – 72 hours
Severe Diarrhea and/or Vomiting	• Three or more episodes of vomiting or diarrhea within a 24-hour period AND • Vomiting and/or diarrhea is severe	0 – 72 hours	0 – 72 hours
SIRVA	• Includes both pain and reduced range of motion AND these are limited to the shoulder in which the intramuscular vaccine was administered; and • No history of pain, inflammation or dysfunction of the affected shoulder prior to intramuscular vaccine administration that would explain the alleged signs, symptoms, examination findings, and/or diagnostic studies occurring after vaccine injection; including no other condition or abnormality is present that would explain the patient's symptoms. • Lasting longer than 4 days (Reported under “Other Severe or Unusual Events”)	0 – 7 days	0 – 7 days

AEFI	Reporting Criteria	Vaccines (Temporal criteria**)	
		Inactivated	Live
Sterile Abscess	• Spontaneous or surgical drainage of non-purulent material from the mass OR • Demonstration of material by an imaging technique AND • Absence of localized signs of inflammation such as erythema, pain to light touch, and warm to touch at the injection site OR • Failure to resolve or improve on antimicrobial therapy	0 - 7 days	0 - 7 days
SSPE (subacute sclerosing panencephalitis)	• Physician-diagnosed SSPE	n/a	Measles: 0 – 10 years
Swelling and/or Pain	• Swelling extends past the nearest joint OR • Severe pain that interferes with the normal use of the limb lasts > 4 days OR Reaction requires hospitalization	0 - 48 hours	0 - 48 hours
Thrombocytopenia	• Physician-diagnosed platelet count of less than 150 X 109/L	0 – 6 weeks	0 – 6 weeks
Other Severe or Unusual Events	• Not clearly covered by other reporting categories and fits description above or requires emergency room visit within 72 hours of immunization OR • Any death of a vaccine recipient temporally linked to immunization where no other clear cause of death can be established.	0 – 4 weeks	0 – 4 weeks

**Temporal criteria guidelines in this table are generally agreed upon approximate timelines. The timeframe between immunization and event onset is an important consideration in assessment of causality.

The format of the following pages include the definition of the event and conditions which make the event reportable.

Acute Disseminated Encephalomyelitis (ADEM)

Definition:

Encephalomyelitis is an inflammatory process involving both the brain and the spinal cord.[1] Acute disseminated encephalomyelitis (ADEM) is an illness, diagnosed by a physician, in which there are one or more focal or multifocal findings referable to the central nervous system.[1]

Reportable if:

Onset within 42 days following inactivated vaccines, 5 to 30 days following MMR vaccine, and 5 to 42 days following Varicella vaccine:

1. Physician-diagnosed encephalomyelitis;

   AND

2. One or more focal or multifocal findings referable to the central nervous system, including one or more of the following:[1]
   - 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 of focal).
   - Sensory abnormalities (positive or negative).
   - Altered deep tendon reflexes (asymmetry, hypo/hyperreflexia).
   - Cerebellar dysfunction (e.g. ataxia, dysmetria, cerebellar nystagmus).

Discussion:

Immunizations may very rarely lead to acute encephalitis, particularly when using live-attenuated viral vaccines. However, the introduction of immunizations has served to reduce the incidence of encephalitic complications in several viral and bacterial infections.[2] In more than 70% of cases of acute encephalitis, the etiologic agent cannot be identified.[1]

Encephalitis/encephalopathy have been reported approximately once for every three million doses of MMR vaccine distributed. It has not been shown that reactions were actually caused by this vaccine. The risk of such serious neurological disorders following live measles virus vaccine administration remains far less than that for encephalitis and encephalopathy with wild-type measles (one per two thousand reported cases).[3]

Adenopathy

Definition:

Adenopathy or lymphadenopathy is enlargement of one of more lymph nodes.[4]

Regional lymphadenopathy: 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, etc.).[4] Lymphadenitis is inflammation of one or more lymph nodes usually caused by a primary focus of infection elsewhere in the body.[4][5]

Reportable if:

1. Enlargement of one or more lymph nodes, > 1.5 cm in diameter;[4][6][7][8]

   AND/OR

2. Draining sinus over a lymph node. [4][6][7][8]

   AND

3. Onset is within 7 days following immunization with an inactivated vaccine, or occurs between 5 and 30 days following immunization with a live vaccine, or occurs between 0 and 30 days following immunization with a mRNA COVID-19 vaccine.

Discussion:

For the purpose of AEFI reporting, adenopathy of the lymph nodes that drain the injection site or muscle group is of most significance. Adenopathy of a lymph node in a limb other than the limb where the injection was given is unlikely to be related to the immunization. However, any adenopathy in any location within 0-30 days after COVID-19 immunization should be reported.

Adenopathy can occur with any immunization. If the injection site is contaminated with bacteria, adenitis may occur as part of the resulting infection. With infections of injection sites, the lymph nodes draining the injection site will be affected. BCG (Bacillus Calmette–Guérin) can cause local ulceration at the injection site with lymphadenitis up to six months post-immunization.[9][10][11]

Adenopathy was noted as a reaction following receipt of the adjuvanted pH1N1 (2009) vaccine. The adjuvant produces transient chemokine and cytokine stimulation, enhanced local activity of antigen presenting cells, and uptake by regional lymph nodes. This expected axillary or supraclavicular lymph node tenderness does not require reporting unless it meets the reporting criteria.[4][6][7]

Allergic Reaction

Definition:

Allergic reactions constitute a continuum, the extreme end of which is anaphylaxis. An allergy is an immune complex mediated reaction most commonly involving the respiratory tract or the skin. When reported as an adverse event, inquire about possible exposure to other allergens during the same time period if the patient has a history of allergies.[4][6][7]

Reportable if:

One or more of the following signs/symptoms are present within 48 hours of immunization or tuberculin skin testing:

- Skin/mucosal manifestations (hives or itching);
- Local or generalized edema;
- Respiratory (stridor, wheezing).

See *AEFI Descriptors for Anaphylaxis.* In a less severe form these manifestations are applicable for allergic reactions.

Include these descriptors in the AEFI form comments section to describe the event. (Adapted from *Reporting Adverse Events Following Immunization in Canada – User Guide to completion and Submission of the AEFI Reports* (Public Health Agency of Canada) www.phac-aspc.gc.ca/im/pdf/AEFI-ug-gu-eng.pdf – Section 9.

Severe blistering or ulceration resulting from a tuberculin skin test should be reported under *Other severe or unusual events.*

Discussion:

An allergic reaction is an acquired hypersensitivity considered to be related to either the vaccine components or the antigen itself. If triggered by non-antigenic vaccine components (such as gelatin or neomycin) the reaction may present following administration of the first dose of the vaccine.[9] Antigen-antibody complexes stimulate the release of chemicals, such as histamine, which produce signs and symptoms of hypersensitivity. Allergies are more likely related to immunization if the reaction occurs between 0 to two hours after immunization; most occur within 12 hours after immunization.

Additionally, type IV delayed hypersensitivity reactions have also been reported. These start 48 hours after immunization and peak between 72 and 96 hours post-immunization. They are typically observed with vaccines containing thimerosal in sensitized children and adults, and the occurrence of such an event is not a contraindication to further immunization. This reaction is becoming less frequent as mercury is being removed from modern vaccines.[9]

Anaesthesia/Paraesthesia

Definition:

Anaesthesia: The loss of normal feeling or sensation.[5]

Paraesthesia: Abnormal physical sensation such as tingling, burning, or prickling.[5]

Reportable if:[4][6]

1. Physician-diagnosed anaesthesia or paraesthesia lasting 24 hours or more;

   AND[4][6][7][8]

2. Occurring up to 15 days following administration of inactivated vaccines, up to 30 days following MMR, or up to 42 days following a varicella containing vaccine.

Note: Include physician's notes or summary with AEFI report.

Discussion:

The cause of anaesthesia/paraesthesia is often unknown. It can be related to deposition of the vaccine close to a nerve, with subsequent pressure causing symptoms. Inadvertent "nicking" of a nerve could also cause these symptoms. Properly localizing the injection site is important, although unusual pathways for nerves in individuals can account for some of these reactions. [5][6]

Anaphylaxis

Definition:

Anaphylaxis is a clinical syndrome, which presents acutely and leads to a marked change in an individual's previous stable condition. It typically affects multiple body systems (e.g., skin/mucosa/respiratory/cardiovascular/gastrointestinal) at the same time or sequentially but most often occurs over a short period of time (i.e., multiple systems involved within 1 hour from the onset of the first symptom and/or sign).

Report anaphylactic-like reactions (i.e., similar reactions that do not meet the reporting requirements for anaphylaxis) under Allergic reaction.

.

Reportable[12] if:

1. Rapid progression of signs or symptoms affecting multiple body systems

AND

2. Meets clinical diagnostic certainty levels 1, 2, or 3 as defined below.

Use the MAJOR and MINOR criteria met for skin, respiratory, cardiac, gastrointestinal systems, and laboratory results from the table below to determine the highest level of diagnostic certainty (with level 1 > level 2 > level 3).	
Level 1 Definitive case	MAJOR skin/mucosal system involvement AND ≥ 1 MAJOR system involvement including respiratory and/or cardiac and/or gastrointestinal and/or laboratory results
Level 2 Probable case	≥2 MAJOR system involvement including respiratory and/or cardiac and/or gastrointestinal and/or laboratory results (excludes skin/mucosal involvement and must be from different systems)
Level 3 Possible case	Only 1 MAJOR system involvement (skin or respiratory or cardiac or gastrointestinal or laboratory results) and ≥1 MINOR sign/symptom from a different system (respiratory and/or skin)

Major and minor signs or symptoms involving the following systems		
	Major	**Minor**
Skin and/or conjunctival mucosa	• **Urticaria** (hives) at a location other than the vaccine administration site • **Angioedema** (swelling) of the skin at a location other than the vaccine administration site • **Generalized** (widespread) **erythema** (redness) of the skin with itch	• New onset bilateral **red and/or itchy eyes** • **Generalized** (widespread) **erythema** (redness) of the skin without itch

Respiratory	• **Expiratory wheeze** - documented by healthcare professional with or without stethoscope
	• **Inspiratory stridor** - documented by healthcare professional with or without stethoscope
	• **Angioedema of the mucosa of the upper airway** - swelling of the tongue, pharynx, uvula, and/or larynx - unequivocally documented by a healthcare professional - this does not include isolated lip swelling.
	• **≥ 2 indicators of respiratory distress**:
	  • Tachypnoea
	  • Cyanosis
	  • Measured hypoxia with oxygen saturations <90%
	  • Grunting
	  • Chest wall retractions
	  • Increased use of accessory
		• New onset and persistent **Cough and/or sneezing and/or runny nose**

Cardiovascular	• **Measured hypotension** • **Loss of consciousness** • other than the brief, self-resolving loss of consciousness typical of a vasovagal reaction	• None
Gastrointestinal	• New onset **vomiting** • New onset **diarrhea**	• None
Laboratory results	• Elevated mast cell tryptase	• None

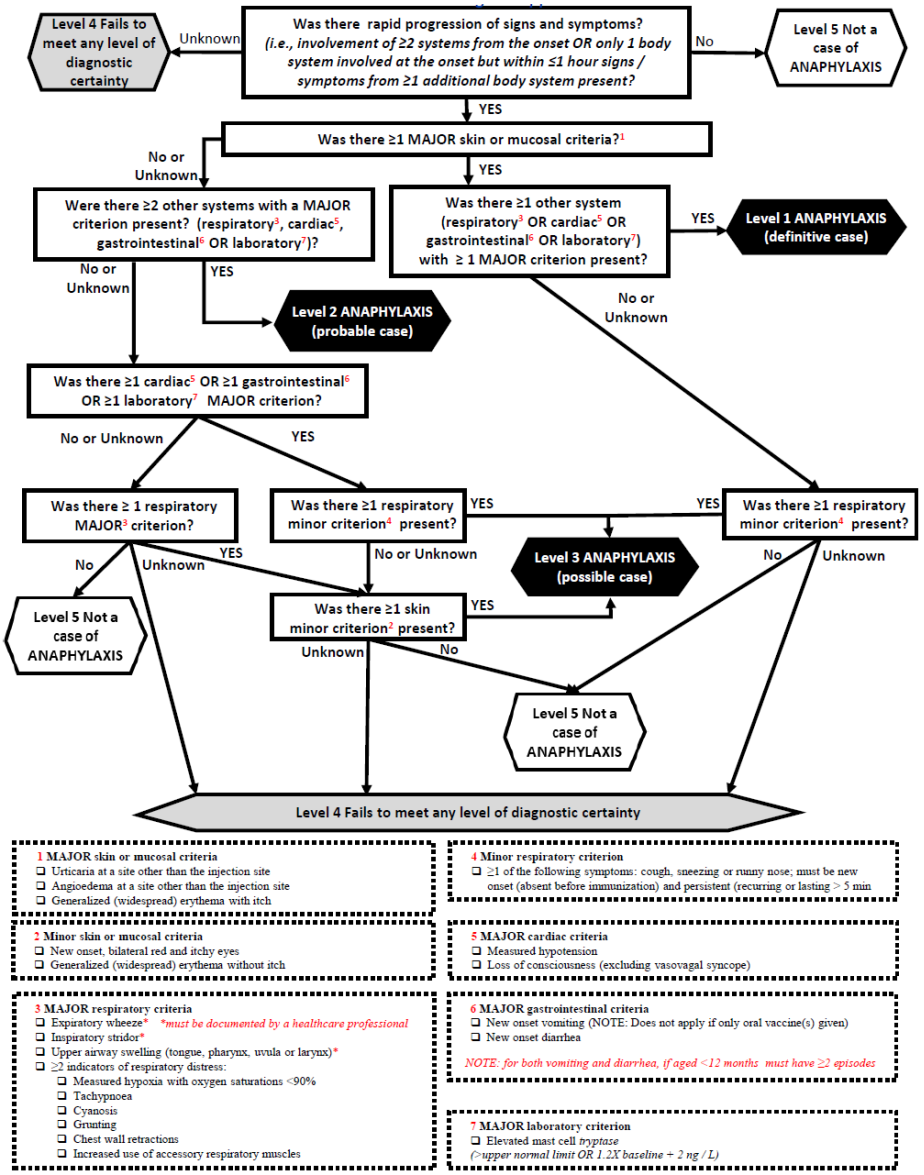
Notes
1. Rapid progression does NOT define the time from immunization to the onset of the first sign or symptom. Rather rapid progression specifically refers to the time from the onset of a sign or symptom in one system to a sign or symptom in at least one other system.
2. If two or more signs or symptoms present in the same system, count system only once. Examples: if urticaria and angioedema present, count as major skin system involvement once; if wheeze and tongue swelling present, count as major respiratory system involvement once; if hypotension and loss of consciousness present, count as cardiovascular system involvement once; and if vomiting and diarrhea present, count as gastrointestinal system involvement once.
3. MAJOR and/or MINOR criteria must be from different systems – count system only once: i.e., one major respiratory sign or symptom and one minor respiratory sign or symptom do not fulfil this criterion.
4. New onset implies that the sign or symptom was not present prior to immunization.
5. Oxygen saturations measured by an oximeter should, if possible, be verified on an oximetry trace.
6. Persistent (for cough/sneezing/runny nose) implies that these symptoms recur and/or last for 5 minutes or longer.

7. Children 10 years of age and younger: systolic BP less than (70 mm Hg + [2 x age in years]) and children 11 years of age and older and adults: decrease of >30% from that person's baseline systolic BP or less than <90 mm Hg or a diastolic BP < 60 mm Hg.
8. Only following administration of an injected/intranasal vaccine. This does not apply to orally administered vaccines.
9. In infants (< 12 months of age) a single non-forceful episode of vomiting (or spilling/reflux) may occur in the context of a painful injection, and this should not be regarded as a major criterion. In addition, a single episode of diarrhea in this age group should not be regarded as a major criterion.
10. Greater than upper normal limit for laboratory doing test or >1.2 x baseline mast cell tryptase + 2 ng/L. If feasible a second post-event level should be measured and shown to be within the normal range.

Additional reporting criteria:

Atypical anaphylaxis can be reported with only sudden hypotension or respiratory tract obstruction (wheeze/stridor) present in the context of exposure to a known or highly probable allergen for a particular patient.

Brighton Anaphylaxis Case Definition flow chart



Discussion:

Anaphylaxis following immunization is a serious, but rare occurrence; estimates are in the range of 1–10 cases per 1 million doses distributed, depending on the vaccine studied, but accurate estimates are hampered by limited data and lack of standard case definitions.(12)

Anaphylaxis refers to a collection of symptoms affecting multiple systems in the body. The most dangerous are breathing difficulties or a drop in blood pressure, which are potentially fatal. Anaphylaxis must be distinguished from fainting (vasovagal syncope), breath-holding spells and anxiety, which are not to be reported. The cascading nature of the symptoms, i.e., symptoms that are progressive or increasing in severity, are more likely to represent anaphylaxis.(4)(6)

The mechanism involved in this type of reaction is generally considered to be a classical type I hypersensitivity reaction involving an IgE-mediated response, causing urticaria, angioedema and anaphylaxis.[13] IgE-mediated reactions to vaccines are more often caused by vaccine components, such as gelatin or egg protein, rather than the immunizing agent itself.[9][13] Gelatin is added to some vaccines as a stabilizer and has been shown to be responsible for anaphylactic reactions to MMR, varicella, and Japanese encephalitis vaccines.[3]

When a patient experiences an apparently IgE-mediated reaction after an immunization, the patient is often labelled as being "allergic" to the vaccine and advised against receiving future doses without further investigation. However, this approach should be avoided because it may leave patients inadequately immunized if they unnecessarily avoid vaccines to which they are not allergic or if the vaccine could be administered safely despite their allergy. In addition, not knowing the particular component of a vaccine to which the patient is allergic may pose a risk with future immunization that contain the same ingredient.[13] Therefore, each case of anaphylaxis warrants further investigation with an allergist.

Arthralgia/Arthritis

Definition:

Arthralgia: Joint pain[14]

Arthritis: Joint inflammation as manifested by joint swelling, redness, and/or warmth.

Arthritis is usually associated with arthralgia, but arthralgia may occur without obvious arthritis. Rubella vaccine-associated arthritis involves, in order of decreasing frequency, the joints of the fingers, knees, wrists, elbows, ankles, hips and toes.[4]

Reportable if:

1. Arthralgia or arthritis occurs between 5 to 30 days following immunization;

   AND

2. Lasts ≥ 24 hours.[4][6][8]

Note: Note in the comment section whether the event involves arthralgia alone or if arthritis is also included.

Discussion:

Arthritis and arthralgia can be manifestations of natural rubella infection in adults. Because the rubella vaccine is a live virus vaccine, the same mechanism is thought to occur with vaccine-associated arthralgia or arthritis.[2] The exact pathophysiology is unknown. It may be due to direct viral infection of the synovial membrane or to the deposition of immune complexes. These reactions are uncommon in children, but the frequency and severity increase with age.[15] They are more common in adolescent and adult females. Arthralgia occurs in 25% and arthritis-like signs and symptoms in 10% of adolescent females after immunization with rubella-containing vaccines.[4][6] It can also occur in children and adolescent and adult men, but at much lower rates. Joint symptoms are almost always transient.[2]

Arthralgia/arthritis has been associated with rubella immunization and is listed as a possible reaction following Rabies Vaccine. The frequency and severity of these adverse reactions are less following immunization than when associated with natural rubella disease.[15]

Bell's Palsy

Definition:

Bell's palsy is a unilateral paralysis or weakness of facial muscles. 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.[4]

Reporting criteria:

Physician-diagnosed Bell's palsy occurring within 3 months of immunization.[4][6]

Discussion:

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.[4][6]

Cellulitis

Definition:

An acute, infectious, expanding inflammatory condition of the skin, located in subcutaneous tissue, fat, fascia or muscle at the vaccine injection site. Characterized by edema, redness, pain and interference with function usually caused by infection with streptococci, staphylococci or similar organisms.[16][17]

Reportable if:

Onset within 7 days of immunization:

1. Physician-diagnosed cellulitis;[17]

   AND

2. Characterized by *at least* three of the following local signs or symptoms:[17]
   - Pain or tenderness to touch
   - Erythema
   - Induration or swelling
   - Warm to touch.

   AND

3. Reaction is at the injection site.

Exclusion criteria are spontaneous rapid resolution.

Note: Include physician's notes or summary with AEFI report.

Convulsion (febrile and afebrile)

Definition:

Episodes of hyperactivity in the brain resulting in sudden, involuntary muscle contractions, abnormal behavior, and/or loss or impairment of consciousness. A generalized convulsive seizure is an episode of unconsciousness accompanied by generalized motor manifestations that may be tonic, clonic, tonic-clonic or atonic.[18]

Reportable if:

1. Seizures (febrile or afebrile) with generalized, tonic, clonic, tonic-clonic, or atonic motor manifestations, occurring within 72 hours of inactivated vaccines,[14] 5-14 days after MMR, MMRV, or Varicella.[19]

   AND

2. History or report of loss of consciousness.[18]

Note: If the child is febrile, this and the recorded temperature must be reported as an event in addition to convulsion/seizure. If the child is afebrile or a temperature was not recorded, this information must be placed in the comment section.

Discussion:

Seizures are episodes of neuronal hyperactivity most commonly resulting in sudden, involuntary muscular contractions. In vaccine safety studies it is the diagnostic certainty, whether a seizure was truly present or not, and whether fever was present immediately prior to the onset of seizure, that are of greatest significance.[18]

Febrile seizures are the most common seizure type in infants and children. Simple febrile seizures have an excellent prognosis without residual sequelae and remit on their own as the child ages. There are no long-term sequelae, such as permanent brain damage, associated with simple febrile seizures.[3][18]

Febrile seizure after MMR or MMRV is associated with development of a protective immune response to measles and patients can be reassured that febrile seizures are not expected to recur following the second dose. Previous history of seizure is not a contraindication to receiving vaccines.[19]

Because vaccines containing acellular pertussis vaccine are less frequently associated with moderate to high fever compared to whole cell pertussis vaccine, fewer febrile convulsions are seen with the current vaccines and the incidence of seizures decreased following the introduction of acellular pertussis vaccine.[3]

Seizure details:

Tonic: Sustained increase in muscle contraction lasting a few seconds to minutes.[18]

Clonic*:* Sudden, brief (<100 milliseconds) involuntary contractions of the same muscle groups, regularly repetitive at a frequency of about 2 to 3 contractions/second.[18]

Tonic-clonic*:* A sequence consisting of a tonic followed by a clonic phase.[18]

Atonic*:* Sudden loss of tone in postural muscles, often preceded by a myoclonic jerk and precipitated by hyperventilation (in the absence of HHE, syncope, or myoclonic jerks).[18]

Encephalitis

Definition:

Encephalitis is defined as inflammation of the parenchyma of the brain.[1] It is an illness, diagnosed by a physician, in which there is at least one listed indicator of central nervous system inflammation[a] AND either > 24 hours of depressed or altered consciousness with one or more signs of reduced responsiveness[b] OR one or more signs of focal or multi-focal central nervous system abnormality[c]. The term "encephalopathy" refers to a state of being, in which consciousness or mental status is altered, whereas "encephalitis" refers to the specific neuropathologic state of cerebral parenchymal inflammation.[1]

Reportable if:

Onset within 42 days following inactivated vaccines, 5 to 30 days following MMR vaccine, and 5 to 42 days following Varicella vaccine:

1. Physician diagnosed encephalitis;

AND

2. At least one listed indicator of central nervous system inflammation*;[1]

AND

2.Greater than 24 hours of depressed or altered consciousness with one or more signs of reduced responsiveness**; [1]

OR

3.One or more signs of focal or multi-focal central nervous system abnormality***.[1]

**Indicators of central nervous system inflammation*

- fever ≥ 38.0°C
- CSF pleocytosis (> 15 WBC/mm^3 if < 2 months old; > 5WBC/mm^3 if ≥ 2months)
- 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

****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)

Note: Include physician's notes or summary with AEFI report.

Discussion:

Demonstration of CNS inflammation, regardless of the underlying cause, is considered confirmatory in the diagnosis of encephalitis/myelitis. Most cases of encephalitis are thought to be infectious in nature, and may be attributed to a number of different agents.[1]

Encephalitis/encephalopathy have been reported approximately once for every three million doses of MMR vaccine It has not been shown that reactions were actually caused by this vaccine.The risk of such serious neurological disorders following live measles virus vaccine administration remains far less than that for encephalitis and encephalopathy with wild-type measles (one per two thousand reported cases).[3]

Erythema Multiforme

Definition:

An acute, self-limited inflammatory disorder of the skin and mucous membrane, characterized by a specific rash (macular, papular, or urticarial) that occurs no sooner than five days after immunization.[20]

Reportable if:

Onset of rash five days or more after immunization or tuberculin skin testing.

Note: **Must be diagnosed by a physician.** Include physician notes or summary, and description of character and timing of erythema multiforme with the AEFI report.

Discussion:

The etiology of erythema multiforme is idiopathic in more than half of the cases. However, infection, drugs, and occasionally immunizations have been associated with this extremely rare reaction.[9][20]

Type IV hypersensitivity reactions such as Stevens Johnson syndrome should be reported under Erythema Multiforme.

Guillain-Barré Syndrome (GBS)

Definition:

An illness that includes acute onset of bilateral flaccid weakness/paralysis of the limbs with decreased or absent deep tendon reflexes and electrophysiologic findings consistent with GBS. GBS is characterized by various degrees of weakness, sensory abnormalities, and autonomic dysfunction due to damage to peripheral nerves and nerve roots. CSF test results, if available, must either be normal, or, have <50 WBC/mm^3. The evolution of illness is monophasic with a maximum degree of weakness reached from 12 hours to 28 days after onset, followed by a clinical plateau and then either improvement or death.[21]

Reportable if:

1. Physician-diagnosed GBS;

   AND

2. Occurs within six weeks[19] following immunization.

Note: Include physician's notes or summary with the AEFI report.

Discussion:

Although the underlying etiology and pathophysiology of GBS are not completely understood, it is believed that immune stimulation plays a central role in its pathogenesis. Studies in developed countries have suggested an incidence of 1–2 per 100,000 population per year.[21]

GBS has been reported sporadically in temporal association with a number of vaccines but no evidence of a causal relationship has been found. It can appear as sequelae to a variety of infections after an interval of one to six weeks.[21]

There is limited evidence of an association between tetanus toxoid and GBS, and oral polio vaccine and GBS,[4][6][7] in addition to a swine influenza vaccine (1976) that is no longer in use.[21] While cases of GBS have been reported temporally associated with other vaccines (e.g., Menactra®), there is no evidence of a causal relationship.

Hypotonic Hyporesponsive Episode (HHE)

Definition:

HHE is characterized by sudden onset of reduced muscle tone, hyporesponsiveness (i.e., less responsive than usual to verbal or other sensorial stimuli) and change of skin colour (pallor or cyanosis).[22] HHE usually occurs between one and 12 hours following immunization. Children may be initially irritable and may have fever, then become pale, limp and unresponsive or hyporesponsive (sometimes described as "a rag doll" reaction). Respirations are shallow and cyanosis may appear (may be reported as stopped breathing/turned blue). Episodes are usually transient (lasting a few minutes) and self-limited, with no long-term sequelae.

Do not report fainting episodes in adults as HHE, nor children who are pale and quiet after a session of crying or vomiting. These are not hypotonic hyporesponsive episodes.

Reportable if:

Sudden onset within 72 hours of immunization, in a child aged less than 2 years of age and includes:[22]

1. Hypotonia (muscle limpness);

AND

2. Either hyporesponsiveness or unresponsiveness;

AND

3. Either pallor or cyanosis.

Note: Pallor, shallow respiration, and quiet behaviour without muscle hypotonicity, and especially following periods of crying or vomiting, are not HHE.

Discussion:

Most reported cases of hypotonic-hyporesponsive episodes (HHEs) have followed administration of pertussis -containing vaccines, and are associated more often with whole-cell pertussis-containing vaccines compared to acellular pertussis-containing vaccines. HHE has been observed most frequently during the primary immunization series.[23][14][22]

The cause of HHE is not known. HHE is not associated with any lasting or long term sequelae.[22]

Infected Abscess

Definition:

A confirmed localized collection of pus in a cavity formed by the disintegration of tissue, usually caused by microorganisms that invade the tissues.[16]

Reportable if:

Onset within 7 days of immunization:

The localized collection must be confirmed in one of two ways:

Spontaneous or surgical drainage of purulent* material from the mass;[5]

OR

Demonstration of material by an imaging technique (such as ultrasound, CT or MRI); or fluctuance (wavelike motion on palpation due to liquid contents);[5]

AND

1. Localized sign(s) of inflammation, which would include one of the following: erythema, pain to light touch, swelling, and warmth to touch;[5]

   AND

2. Evidence of resolution/improvement temporally related to antimicrobial therapy.[5]

* Purulent is defined as containing or consisting of pus, which may be cloudy in appearance and/or foul-smelling.[5]

Discussion:

Infection and abscess formation are usually caused by microorganisms that invade the tissue. An abscess at an injection site involving a localized soft tissue collection of material is a rare local reaction.[5]

Intussusception

Definition:

Intussusception is the prolapse of one part of the intestine into the lumen of an immediately adjacent part, causing partial or complete intestinal obstruction. It is an acute condition, diagnosed by a physician, in which there is evidence of intestinal obstruction and/or invagination and/or vascular compromise.(5)

Reportable if:

Onset within 42 days of immunization:

1. Physician-diagnosed intussusception following rotavirus vaccine receipt;

   AND

2. Evidence of intestinal obstruction[a] and/or invagination[b] and/or vascular compromise[c].

If only one of these three is present, at least three of the following predisposing factors must also be present: <1 year old male, abdominal pain, lethargy, pallor, hypovolemic shock, non bile-stained vomiting, non-specific gas pattern on a plain abdominal radiograph.

[a] History of bile-stained vomiting **AND** either examination findings of acute abdominal distension and abnormal or absent bowel sounds **OR** plain abdominal radiograph showing fluid levels and dilated bowel loops.

[b] Presence of: ≥ 1 of: abdominal mass, rectal mass, intestinal prolapse, visible intussusceptum or soft tissue mass shown on plain abdominal radiograph **OR** abdominal ultrasound **OR** abdominal CT scan.

[c] Presence of ≥ 1 of: passage of blood per rectum, passage of a stool containing “red currant jelly” material, blood detected on rectal examination.

Discussion:

Intussusception is the most common cause of acute intestinal obstruction in infants and young children. Untreated, intussusception is a potentially life-threatening condition; however, diagnosis and non-surgical reduction has resulted in a significant reduction in morbidity and mortality. Intussusception is an uncommon but naturally occurring event.(24) Reports of intussusception following immunization are not expected to exceed the number of cases that would be seen by chance alone.

Meningitis

Definition:

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.[25]

Reportable if:

Physician-diagnosed aseptic meningitis occurring within 15 days of administration of inactivated vaccines, 5 to 30 days following MMR, or 0 to 42 days following a varicella containing vaccine, for which no other cause has been identified.[4][6][7][8]

Note: Include results of any cerebral spinal fluid (CSF) investigations, and physician notes or summary with AEFI report.

Discussion:

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 virus vaccines, including oral polio, combined measles–mumps–rubella (MMR),[9] varicella, yellow fever and smallpox vaccines. There is no causal relationship between non-live vaccines and meningitis. Aseptic meningitis following immunization usually is benign and resolves without sequelae.[25]

Myelitis

Definition:

Myelitis is inflammation of the parenchyma of the spinal cord. It is an illness, diagnosed by a physician, in which there is clinical evidence of myelopathy accompanied by at least one indicator of spinal cord inflammation.[1]

Reportable if:

Onset within 42 days following inactivated vaccines and 5 to 42 days following live vaccines.

1. Physician-diagnosed myelitis;

   AND

2. Two or more indicators suggestive of spinal cord inflammation*.

   **Indicators suggestive of spinal cord inflammation:*

   - fever ≥ 38.0°C
   - CSF pleocytosis (> 15 WBC/mm^3 if < 2 months old; > 5WBC/ mm^3 if ≥ 2months
   - Neuroimaging demonstrates acute inflammation (± meninges), or spinal cord demyelination.

Note: Include any relevant lab / diagnostic reports, and physician's notes or summary with AEFI report.

Discussion:

Demonstration of CNS inflammation, regardless of the underlying cause, is considered confirmatory in the diagnosis of encephalitis/myelitis. Most cases of encephalitis are thought to be infectious in nature, and may be attributed to a number of different agents.[1]

Encephalitis/encephalopathy have been reported approximately once for every three million doses of MMR vaccine distributed. It has not been shown that reactions were actually caused by this vaccine. The risk of such serious neurological disorders following live measles virus vaccine administration remains far less than that for encephalitis and encephalopathy with wild-type measles (one per two thousand reported cases).[3]

Nodule

Definition:

A dermal or subcutaneous firm, well-defined lesion at the injection site in the absence of abscess formation, erythema and warmth.[26]

Reportable if:

Onset within 7 days of immunization:

1. Firm nodule is at the injection site;[26]

   AND

2. Persists for > 1 month.[4][6][7]

Discussion:

Primarily associated with the aluminum-adsorbed vaccines. Sterile abscesses or nodules[14] may take up to one year to resolve, but most commonly resolve within two to three months.[4][6][7] They are believed to be the result of irritation from components of the vaccine, especially the adjuvant.[15] Nodules may also result if a vaccine intended for intramuscular injection was inadvertently given subcutaneously.[23][15] No intervention is recommended; in particular, sterile abscesses or nodules should not be lanced or drained as this practice opens the tissue to the possibility of infection and does not assist in the resolution of the nodule.

Oculo-Respiratory Syndrome (ORS)

Definition:[5][27]

Oculo-respiratory syndrome (ORS) is a set of signs and symptoms of both the eyes and respiratory system following immunization with influenza vaccine.

Reportable if:

Occuring within 24 hours of immunization:

1. Onset of bilateral red eyes;

   AND

2. One or more of the following respiratory symptoms:

   Cough, wheeze, chest tightness, difficulty breathing, difficulty swallowing, hoarseness, sore throat;

   WITH or WITHOUT

3. Facial edema.

Note: Submit initial AEFI report to Alberta Health within one week for all cases of ORS.

Discussion:

During the 2000-2001 influenza season, an increased number of reports of vaccine- associated symptoms and signs that were subsequently described as ORS were reported nationally. The pathophysiologic mechanism underlying ORS remains unknown, but it is considered distinct from IgE-mediated allergy.[28]

Approximately 5% to 34% of patients who have previously experienced ORS may have a recurrence attributable to the vaccine, but these episodes are usually milder than the original one. Persons who have a recurrence of ORS upon re-immunization do not necessarily experience further episodes with future immunizations. Data on clinically significant AEFI do not support the preference of one vaccine product over another when re-immunizing those who have previously experienced ORS.

Orchitis

Definition:

Inflammation of one or both of the testes, characterized by swelling and pain.[4][7]

Reportable if:

Physician-diagnosed orchitis occurring between 5 and 30 days following immunization with a mumps-containing vaccine.[7][8]

Note: Include supporting documentation (physician's notes or summary) with the AEFI report.

Discussion:[3][29][30][31]

Orchitis is a relatively common complication of wild-type mumps infection; it is considered a very rare complication associated with mumps immunization. Post-vaccine orchitis is thought to be due either to direct invasion of testicular cells by the virus or, in some cases, an immune-mediated phenomenon in vaccinees previously exposed to mumps virus.[29] Post-vaccine orchitis is transient and self-limited.

Paralysis

Definition:

Loss of muscle tone and function with or without loss of sensation.

Reportable if:

1. Physician-diagnosed paralysis with no other cause identified;[4][7][8]

   AND

2. Occurring within 15 days following inactivated vaccine receipt, 5 to 30 days following MMR or oral polio vaccine (OPV), or 5 to 42 days after a varicella containing vaccine and lasting more than 24 hours.[6][7]

Note: Include physician's notes or summary with AEFI report.

Discussion:

OPV is the only vaccine known to cause paralysis. This vaccine contains attenuated strains of poliovirus and it has been associated with causing vaccine-associated paralytic polio. The estimated risk of OPV causing paralysis is one case in 2.7 million doses of OPV.[9] The estimated risk of OPV causing paralysis is one case in 750,000 FIRST dose of OPV.[32] The use of OPV was discontinued in Alberta in 1994 and replaced with the inactivated polio vaccine. [33] The last reported case of vaccine-associated paralytic polio (VAPP) in Alberta was in 1979.[34] The last reported case of VAPP in Canada was in 1995.[23]

Parotitis

Definition:

Parotitis is the inflammation of one or both of the parotid salivary glands with pain or tenderness.[5]

Reportable if:

Physician-diagnosed parotitis occurring between 5 and 30 days following immunization with a mumps-containing vaccine.[4][6][7][8]

Note: Include physician's notes or summary with the AEFI report. Do not report submandibular gland swelling as parotitis.

Discussion:

Parotitis is associated with mumps disease. Since mumps-containing vaccines contain a live virus, low-grade infection following immunization can occasionally produce the same manifestation. One of the most common adverse reactions to mumps vaccine is parotitis. Vaccine-associated parotitis occurs most commonly 10 to 14 days after immunization. It is transient and self-limited.[4][6][7]

Rash

Use this section to capture rash related to varicella, measles, or other rash not allergic in nature.

- For rash localized to injection site, capture in Local Reaction at the Injection Site (Event Infective Abscess, Swelling, or Cellulitis)
- For rash allergic in nature, including hives, capture in Event Allergic reaction.

Definition:

A skin or mucosal change that followed immunization and that is either new or an exacerbation of a previous condition.[35]

Reportable if:

1. Varicella-like rash onset within 42 days of varicella immunization with ≥ 50 lesions,[23][15] or requiring hospitalization;[4][6][7][8]

   OR

2. Rashes or eruptions on the skin that are not expected, with an onset within 7 days of immunization and lasts ≥ 4 days;

   AND either

3. Generalized rash: Systemic eruption in two or more parts of the body;

   OR

   Localized at non-injection site; eruption localized at another part of the body, away from the injection site;

   OR

4. Requires hospitalization.[23]

Note: Describe character, location and timing of rash and severity, i.e., approximate number of lesions, in the comments section.

While a morphologic description of the rash is not required it is preferred when possible, using standard terms. See terminology below:

Mucocutaneous lesions: [35]

- ***Bulla****:* a fluid-filled cavity or elevation ≥ 1 cm in diameter. Fluid can be clear, serous, hemorrhagic, or pus-filled.
- ***Cyst:*** a closed cavity or sac containing fluid or semisolid material. A cyst may have an epithelial, endothelial or membranous lining.
- ***Macule:*** a flat, generally < 0.5 cm area of skin or mucous membranes with different color or texture from surrounding tissue.
- ***Nodule:*** a dermal or subcutaneous, firm, well-defined lesion.
- ***Papule:*** a discrete, solid, elevated body usually < 0.5 cm in diameter. Papules are further classified by shape, size, color and surface change.
- ***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, color and surface change.
- ***Pustule*****:** a superficial vesicle containing a cloudy or purulent fluid. Pustules are usually < 0.5 cm in diameter.
- ***Vesicle:*** fluid filled cavity or elevation < 1 cm diameter. Fluid may be clear, serous, or hemorrhagic.
- ***Wheal (hive):*** an edematous transitory papule or plaque.

Secondary mucocutaneous changes: [35]

- ***Erosion*****:** a localized loss of the epidermal or mucosal epithelium.
- ***Crusting*****:** dried exudates of plasma.
- ***Scaling*****:** whitish scales or flakes present on the skin.
- ***Atrophy*****:** thinning or absence of the dermis or subcutaneous fat.
- ***Fissures*****:** linear, wedge-shaped cracks in the epidermis which may extend down to the dermis.
- ***Ulcer*****:** a circumscribed loss of the epidermis or mucosa extending to dermis.
- ***Excoriations*****:** oval or linear depressions in the skin with complete removal of the epidermis, exposing a broad section of red dermis.

Discussion:

Approximately 3% of individuals experienced a varicella-like rash either at the injection site or more generalized following varicella immunization. Most varicella-like rashes occurring within the first two weeks after immunization are due to wild-type virus disease. The varicella-like rash consists of pruritic, vesicular or maculopapular lesions usually appearing five to 26 days after immunization. The rash may be moderate or severe and may occur at the injection site or it may be generalized.[23][4][6][7]

With the exception of rash related to measles-containing vaccines or varicella vaccine, most rashes occurring in children are caused by an intercurrent viral illness. A generalized rash is more likely to be vaccine-associated if it is accompanied by a local reaction at the injection site. The absence of a local reaction weakens the likelihood of a relationship between the reaction and the vaccine.[4][6][7]

Screaming Episode/Persistent Crying

Definition:

Crying in infants and children that is continuous, unaltered (i.e., the quality of crying does not change throughout the episode) and lasts for more than three hours.[36]

Reportable if:

1. Presence of screaming or crying (continuous and unaltered) > 3 hours;[36]

   AND

2. Onset within 72 hours following immunization and lasting for three or more continuous hours.[4][6][7][8]

Discussion:

The term persistent crying implies the apparent discomfort of the child, a prolonged duration of the episode as well as various futile attempts to comfort the child. 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.[15]

Little is known about the pathophysiology of these types of crying, though the reaction has been historically associated with whole cell pertussis-containing vaccines. It has also been reported after receipt of vaccines other than pertussis containing vaccines.[3]

Severe Diarrhea and/or Vomiting

Definition:

Diarrhea: Abnormally frequent discharge of loose and/or watery fecal matter from the bowel.[5]

Vomiting: Ejection of the contents of the stomach through the mouth.[5]

Reportable if:[37]

Onset within 72 hours of immunization of:

1. Three or more episodes of vomiting or diarrhea within a 24-hour period,

   AND

2. Vomiting and/or diarrhea is severe, i.e. projectile vomiting or explosive, watery diarrhea.

Note: Provide details in the comment section and indicate if the event involves diarrhea, vomiting or both.

Discussion:

Diarrhea is a commonly reported AEFI in both passive surveillance systems and clinical trials, for both oral and non-oral vaccines.[37] These events could be a manifestation of low-grade infection after immunization with live vaccines, a physiological response to a foreign substance or a symptom of an underlying intercurrent illness.

Sterile Abscess

Definition:

An abscess at the injection site whose contents are not caused by pyogenic bacteria. Sterile abscesses are typically not accompanied by fever and/or regional lymphadenopathy.[5]

Reportable if:

Onset within 7 days of immunization:

The localized collection is confirmed in one of two ways:[5]

1. Spontaneous or surgical drainage of non-purulent* material from the mass:

   OR

2. Demonstration of material by an imaging technique (such as ultrasound, CT, MRI, or other modality) or fluctance (wavelike motion on palpation due to liquid content).

   AND

   Absence of localized signs of inflammation such as erythema, pain to light touch, and warm to touch at the injection site;

   OR

   Failure to resolve or improve on antimicrobial therapy;

* Purulent defined as containing or consisting of pus, which may be cloudy in appearance and/or foul-smelling

Discussion:

Primarily associated with the aluminum-adsorbed vaccines sterile abscesses.[14] They are believed to be the result of irritation from components of the vaccine, especially the adjuvant.[15] Sterile abscesses may also result if a vaccine intended for intramuscular injection was inadvertently given subcutaneously.[23][15] No intervention is recommended; in particular, sterile abscesses or nodules should not be lanced or drained as this practice opens the tissue to the possibility of infection and does not assist in the resolution of the nodule.

Subacute Sclerosing Panencephaltis (SSPE)

Definition:

A rare, degenerative central nervous system disease occurring as a late complication of measles disease (up to 10 years later).[3] It can also occur after rubella disease, with most of those cases occurring in children with congenital rubella syndrome. SSPE is characterized by behavioural and intellectual deterioration and convulsions due to inflammation of brain tissue.[3] Seizures, blindness and dementia can occur. Remission occurs in only four per cent of cases; otherwise it is fatal and only supportive treatment exists. As with cases related to measles disease, occurrence could be years following immunization for vaccine-associated cases.[4][7]

Reportable if:

1. Physician-diagnosed SSPE;[4][7][8]

AND

2. Occurring up to ten years following immunization with measles-containing vaccine.

Note: Include serology and measles culture results, and physician notes or summary with the AEFI reporting form.

Discussion:

There have been reports of SSPE in children who did not have a history of infection with wild-type measles but did receive measles vaccine. Some of these cases may have resulted from unrecognized measles in the first year of life or possibly from the measles immunization.[4][7]

Successful measles immunization programs directly and indirectly protect against SSPE. Both epidemiological and virological data suggest that measles vaccine does not cause SSPE.[38] There has been a dramatic decline in the incidence of SSPE since the introduction of widespread measles immunization. No vaccine-strain viruses have been isolated from these patients to date.[3]

Swelling and/or Pain

Definition:

Swelling is a visible enlargement of an injected limb with or without objective measurements.[39] Large, localized reactions may be characterized by swelling, pain, induration and redness at the injection site and may involve the entire limb.[39] Such reactions usually begin two to 12 hours following immunization and develop gradually over a period of hours or over several days.[32][40]

Reportable if: [4][6][7][8]

1. Onset of swelling is within 48 hours following immunization;

   AND

2. Swelling extends past the nearest joint;[14]

   OR

3. Severe pain that interferes with the normal use of the limb lasts > 4 days;[4][6][7][8]

   OR

4. Reaction requires hospitalization.

Discussion:

Many vaccines can cause localized swelling and/or pain, which may sometimes be severe. Irritation of tissues through the process of injection, as well as the introduction of foreign material into tissues can produce an inflammatory response.[15][41] A cell mediated immune response to the antigens may also contribute to the local reaction.[9][10] Swelling at the injection site is a frequently reported AEFI.[15][39] As an AEFI, it is diagnosed clinically as an enlargement surrounding the injection site with possible extension to the entire limb.[39]. Swelling is typically caused by fluid infiltration in tissue and may be either soft (typically) or firm (less typical) to touch, depending on the space available for the fluid to disperse.[39]

Overall, local reactions tend to be more common after the fourth and fifth dose of a diphtheria, tetanus, pertussis containing vaccine.[23][42][43]

Occurrence varies by type of antigen. Reported commonly with whole cell pertussis (>10%) and less so with acellular pertussis 1 to 10%.[23][11]

Arthus Reactions: Severe arthus-type injection site reactions are occasionally reported following receipt of diphtheria toxoid or tetanus toxoid-containing vaccines. There may be extensive painful swelling around the injection site, often involving the arm from shoulder to elbow and generally beginning 2 to 8 hours after injection. Such reactions are most often reported in adults, particularly those who have received frequent doses of diphtheria or tetanus toxoid-containing vaccines or both. Persons experiencing severe injection site reactions usually have very high serum antitoxin concentrations and should not receive further routine doses of tetanus containing vaccine for at least 10 years.[23][3]

A large local reaction with the initial dose of this vaccine in an infant less than four months of age is probably due to high levels of maternal antibody in the child's blood.[4][7] and also have been observed following repeat doses of pneumococcal polysaccharide vaccine.[23][7]

Generalized arthus reactions are rare with current vaccines, as they contain small amounts of antigen.[40]

Thrombocytopenia

Definition:

An abnormal hematological condition in which the number of platelets is reduced to less than 150 X 10^9/L (150,000/mm^3).[44] Although haemorrhagic complications can occur, it is usually mild and transient in children.

Reportable if:

1. Physician-diagnosed platelet count of less than 150 X 10^9/L.[44]

   AND

2. Occurs within 6 weeks of immunization.[19]

Note: Include supporting documentation (i.e., laboratory report with the lowest recorded value for platelets, physician's notes or summary) and information regarding the duration of condition with the AEFI report.

Discussion:

Thrombocytopenia after immunization is rare. The cause of vaccine-associated thrombocytopenia is unknown. It occurs after approximately 1 in 25,000 to 1 in 40,000 doses of measles-mumps-rubella (MMR) vaccine[44] and less frequently after other vaccines.[45] Despite the addition of varicella vaccine to the routine schedule with increased uptake since 2005, there has been no increase in the number of cases of thrombocytopenia per year.[45] Approximately 70 percent of cases occur following viral illnesses, often in children.[44] It can also occur as a complication associated with a variety of medications and after other viral infections.[46]

Other Severe or Unusual Events

Definition:

Any other severe or unusual events of unknown etiology, temporally linked with immunization should be reported in the event.[23] The event must be of epidemiological significance or clinically intriguing, usually requiring medical intervention, occurring within four weeks of immunization and not covered by other categories. Also report events that require medical attention, and particularly events that are (i) fatal, (ii) life-threatening, (iii) require hospitalization, or (iv) result in residual disability.[4]

Reportable if:

1. Occurs within four weeks of immunization or tuberculin skin testing;
   AND
2. Not clearly covered by other reporting categories and fits description above;
   OR
3. Requires emergency room visit within 72 hours of immunization for which there is no other known cause;
   OR
4. Any death of a vaccine recipient temporally linked (within 30 days) to immunization where no other clear cause of death can be established.

Narcolepsy should be reported under severe/unusual event. Narcolepsy is characterized by excessive daytime sleepiness and episodes of muscle weakness brought on by emotions. See www.who.int/vaccine_safety/initiative/BC_Narcolepsy_case_definition.pdf for complete Brighton Collaboration case definition.[47]

SIRVA (Shoulder injury related to vaccine administration)
Includes both pain and reduced range of motion AND these are limited to the shoulder in which the intramuscular vaccine was administered; and

- No history of pain, inflammation or dysfunction of the affected shoulder prior to intramuscular vaccine administration that would explain the alleged signs, symptoms, examination findings, and/or diagnostic studies occurring after vaccine injection; including no other condition or abnormality is present that would explain the patient's symptoms.
- Lasting longer than 4 days

Type IV hypersensitivity reactions such as Stevens Johnson syndrome should be reported under Erythema Multiforme.

Note: Report details of the severe/unusual event, attaching or submitting medical summaries when appropriate. .

VI. Non-Reportable adverse events following immunization

Fever

Fever, by itself, is no longer reportable. It is an expected reaction following immunization. Fever is also a common occurrence in children with illnesses unrelated to immunization. Do not report the occurrence of fever unless it accompanies one or more reportable AEFI.

Local inflammation, swelling, and/or pain (moderate severity)

Do not report less severe local reactions. Mild or moderate local reactions are expected reactions to immunization. See Swelling with/ without pain to see if reaction meets reporting requirements.

High pitched unusual crying

This reaction was almost exclusively related to whole cell pertussis vaccine, which is no longer used; this category is no longer reportable. Unusual crying episodes should be considered under Screaming episode/persistent crying.

Screaming episode/persistent crying (less severe)

Do not report an episode of consolable but persistent screaming or crying with duration between one and three hours. This is likely related to discomfort from the injection. It is considered an expected reaction in children less than two years of age.

Allergic reaction (mild)

Do not report using this code. Mild and severe allergic reactions have been combined into one category: Report allergic reactions meeting the criteria Allergic reaction.

Excessive somnolence

Excessive somnolence or prolonged sleeping with difficulty rousing is not considered to be an adverse reaction.

Irritability

Responses to pain and the assessment of the level of irritability are highly variable. Irritability is considered to be an expected response of infants to fever, discomfort, or disruptions in schedule. It may also be an indication of an intercurrent condition or illness, unrelated to immunization.

Coma

Do not report coma using this code. Please use code Other Unusual Events (if appropriate).

Apnoea

Do not report apnoea.

VII. Interpretation of Diphtheria Antitoxin (DAT) Levels and Tetanus Antitoxin (TAT) Levels

Interpretation of DAT Levels

Antitoxin level testing is recommended for large local reactions occurring following the first, second or third dose of a diphtheria-containing vaccine. For atypical reactions following immunization with a diphtheria containing vaccine, antitoxin level testing may also be recommended. In rare instances, sensitivity testing may be important. In such cases, adsorbed toxoid will be provided for testing to physicians experienced in its use and interpretation.

Although a diphtheria antitoxin titre of 0.1 IU/mL or greater is the accepted protective level, no degree of immunity is absolutely protective in the face of a severe challenge. Improved protection is associated with increasing antitoxin levels between 0.2 and 1.0 IU/mL: however, above that level, incremental protection is minimal. Testing before administering another dose is not recommended. The only risk of proceeding without testing is a repeat adverse local reaction.

Interpretation of DAT Levels

Titre Result	Interpretation	Immunization direction
Less than 0.1 IU/mL	No protection	Continue with routine immunization or reinforcing dose of vaccine (serological testing 4 to 8 weeks after completion of series or booster).
0.1 IU/mL to 1.0 IU/mL	Short-term immunization protection present	Reinforcing dose of vaccine recommended.
Greater than 1.0 IU/mL to 1.5 IU/mL	Long-term immunization protection present	Reinforcing vaccine dose or serological testing recommended after 5 years minimum.
Greater than 1.5 IU/mL to 2.0 IU/mL	Long-term immunization protection present	Reinforcing vaccine dose or serological testing recommended after 7 years minimum.
Greater than 2.0 IU/mL	Long-term immunization protection present	Reinforcing vaccine dose or serological testing recommended after 10 years minimum.

If the DAT level is less than 0.1 IU/mL and the TAT level is greater than 0.5 IU/mL, do not immunize, as the risk of diphtheria disease in Canada is low. dTap booster or serology is recommended after 3 years if TAT level is greater than 0.5 IU/mL to 1.0 IU/mL.

Interpretation of TAT Levels

Antitoxin level testing is recommended for large local reactions occurring following the first, second or third dose of a tetanus-containing vaccine. For atypical reactions following immunization with a tetanus containing vaccine, antitoxin level testing may also be recommended. In rare instances, sensitivity testing may be important. In such cases, adsorbed toxoid will be provided for testing to physicians experienced in its use and interpretation.

Although levels of greater than 0.1 IU/mL of tetanus antitoxin indicate protection, no degree of immunity is absolutely protective in the face of a severe challenge. Testing before administering another dose is not recommended. The only risk of proceeding without testing is a repeat adverse local reaction (i.e., reinforcing doses given with antibody concentrations of greater than 0.5 IU/mL could lead to unwanted side effects).

Interpretation of TAT Levels

Titre Result	Interpretation	Immunization direction
Less than 0.1 IU/mL	No protection	Continue with routine immunization or reinforcing dose of vaccine (serological testing 4 to 8 weeks after completion of series or booster).
0.01 IU/mL to 0.1 IU/mL	Immunization uncertain	Reinforcing dose of vaccine required with serological testing 4 to 8 weeks later.
Greater than 0.1 IU/mL to 0.5 IU/mL	Short-term immunization protection present	Reinforcing dose of vaccine recommended.
Greater than 0.5 IU/mL to 1.0 IU/mL	Immunization protection present	Reinforcing dose of vaccine or serological testing recommended after 3 years minimum.
Greater than 1.0 IU/mL to 5.0 IU/mL	Long-term immunization protection present	Reinforcing dose of vaccine or serological testing recommended after 5 years minimum.
Greater than 5.0 IU/mL to 10.0 IU/mL	Long-term immunization protection present	Reinforcing dose of vaccine or serological testing recommended after 8 years minimum.
Greater than 10.0 IU/mL	Long-term immunization protection present	Reinforcing dose of vaccine or serological testing recommended after 10 years minimum.

If the TAT level is less than or equal to 0.5 IU/mL and the DAT is greater than 1.0 IU/mL, continue with immunization, as the risk of tetanus exposure is significant.

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