Yukon Immunization Program Manual

Section 13- Adverse Event Following Immunization (AEFI)

SECTION 13 – ADVERSE EVENT FOLLOWING IMMUNIZATION (AEFI)

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1.0 INTRODUCTION

An **adverse event following immunization** (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). Temporal association alone (i.e., onset of an event following receipt of vaccine) is not proof of causation.

Vaccine safety is a focus of pre-licensure studies. An acceptable safety profile must be observed in order for vaccines to progress to phase III (clinical) trials in humans. These studies provide frequency data on the occurrence of common adverse events such as local reactions at the injection site or systemic events, and grading of the severity of these events.

Uncommon and rare adverse events are usually not identified in pre-licensure studies and reliance is placed on phase IV studies or post-marketing surveillance; this is especially important in the first year following introduction of a vaccine (see Canadian Immunization Guide, Part 2 – Vaccine Safety) (2).

The Canadian Immunization Guide outlines the importance of AEFI reporting 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.

- 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.

- 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.

2.0 PURPOSE

The Yukon Immunization Program monitors AEFIs that involve vaccines and biologicals; this is an important component of evaluating the territorial program. Reporting and monitoring AEFI's is important because:

- Increases public confidence in vaccine programs;
- Essential to vaccine safety surveillance;
- Confirms results of pre-licensure clinical trials;
- 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. AEFI's are reported to PHAC and data is stored in the Canadian Adverse Events Following Immunization Surveillance System (CAEFISS) (3). CAEFISS has the following objectives:

1. To monitor the safety of vaccines in Canada;
2. To identify vaccine related reaction frequency and severity;
3. To identify unknown or unexpected AEFIs;
4. To identify areas of further investigation and or research; and
5. To provide AEFI reporting profiles for vaccines marketed in Canada which informs immunization related decisions.

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.

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

3.0 REPORTING ADVERSE EVENTS

A health professional who is aware of an adverse event following immunization must report the event to the Yukon Immunization Program. The Yukon Immunization Program reviews all AEFIs and submits these to the Chief Medical Officer of Health (CMOH) for review and recommendation(s).

3.1 WHEN TO REPORT

An AEFI must be reported to the Yukon Immunization Program **within 3 days** of determining or being informed that a client has experience an adverse event following immunization.

3.2 WHAT TO REPORT

Events that **must be reported** include the following:

a) follows immunization
b) cannot be attributed to a pre-existing condition, and
c) meets one or more of the following criteria:
    - 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;
    - the health occurrence is unusual or unexpected, including, without limitation, an occurrence that
        - has not previously been identified (i.e., Oculo-Respiratory Syndrome was first identified during the 2000/2001 influenza season), or
        - has previously been identified but is being reported at increased frequency (i.e., extensive local reactions);
    - 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.
    - Clusters of events: known or new events that occur in a geographic or temporal cluster (i.e., 6 in a week, or 6 in a Health Service Delivery Area) that require further assessment, even if the total number of AEFIs may not be higher than expected.

When an AEFI follows the administration of a passive immunizing agent (i.e., immune globulin) do not complete an AEFI, instead please follow the established procedures for reporting an adverse drug reaction to the Canadian Adverse Drug Reaction Monitoring Program (4).

When an AEFI follows the administration of an active immunizing agent (i.e., vaccine) that is administered simultaneously with a passive immunizing agent (i.e., immune globulin) and/or a diagnostic agent (i.e. tuberculin skin test), complete the AEFI form in Panorama.

3.3 HOW TO REPORT

1. The AEFI report is to be completed in Panorama by the health care provider immediately upon knowledge of an adverse reaction. If unsure or if you have questions, contact the Yukon Immunization Program.

2. Notification of the completed AEFI report is to be sent to the Yukon Immunization Program by emailing or calling with the client's Panorama ID number and message that an AEFI has been documented.

3. Yukon Immunization Program nurse reviews the AEFI report and adds the Unique Episode Number. The nurse identifies if further information is required prior to sending the file on for review. Once the AEFI report is complete it is then forwarded to Yukon CMOH/MOH who will make public health recommendations regarding the future use of vaccine product(s) associated with the AEFI.

4. The CMOH/MOH will review the AEFI report, document the recommendations, and notify the Yukon Immunization Program. Any recommendations are recorded on the client's immunization record in Panorama under the section titled *public health recommendations*.

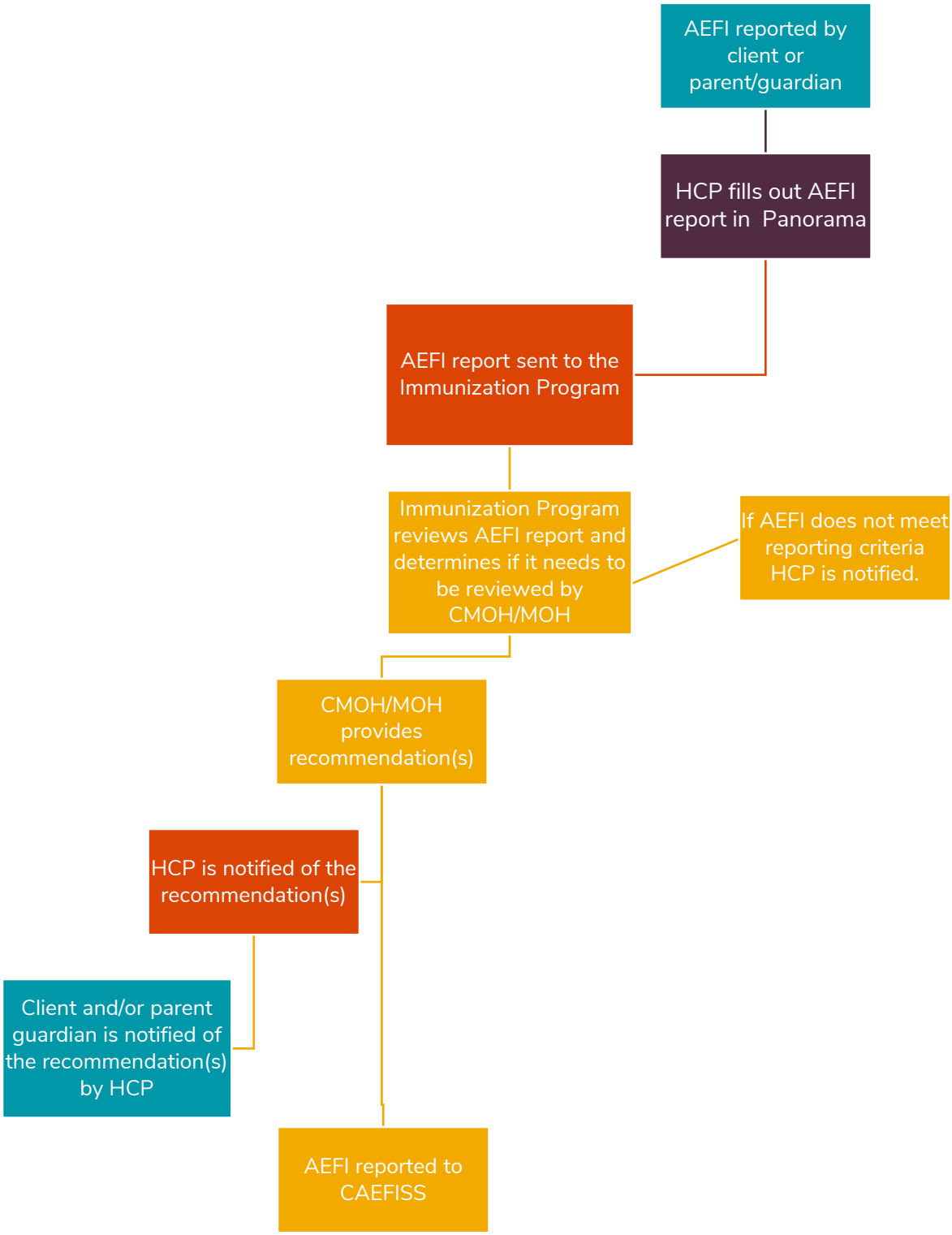
5. The reporting healthcare provider will be notified by e-mail once the recommendations have been entered into Panorama and will be responsible for follow up with the client advising of the public health recommendations. COVID-19 immunization follow a different process; the Immunization Program nurse follows up with the client directly to inform them of public health recommendations. Refer to Appendix B-E for COVID-19 AEFI reporting based on immunizing facility.

6. The completed AEFI will be sent by the Immunization Program to PHAC to be stored in the CAEFISS database for ongoing national surveillance to ensure continued safety of vaccine.

***Documentation is to be completed by the practitioner who becomes aware of the adverse reaction following the vaccine. If Panorama access is not available, please complete the AEFI Case Report Form and submit to the Immunization Program for upload and review.**

See Appendix A, B, C, D for the COVID-19 vaccine AEFI reporting flow for each facility (i.e. Health Centres, ER, Continuing Care, Mass Clinic)

Figure 3.3.1 Adverse Event Information Flow (Routine Vaccines)



3.4 WHAT NOT TO REPORT

Local injection site reactions and non-specific systemic reactions (e.g. headache, myalgia) should not be reported as an AEFI **unless these are more frequent or severe than expected based on clinical trial findings (rates and severity are typically found in the product monograph).**

- Always counsel clients about expected reactions following immunization and how to manage these reactions.
- Events which have another obvious cause (e.g. co-existing conditions).

3.4.1 Non-Reportable Adverse Events Following Immunization

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 to 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: Report using code OTHER SEVERE OR UNUSUAL EVENTS.

Apnoea: Do not report apnoea.

3.5 HEALTH INFORMATION PRIVACY MANAGEMENT ACT (HIPMA)

Inform the client that the information is collected will be reported to the Yukon Immunization Program, CMOH and reported to the Public Health agency of Canada (after the removal of personal health identifiers). The information will be handled confidentially, stored safely and not disclosed without authority as per the HIPMA regulation. As well, inform the client of whom to call for more information about HIPMA issues.

4.0 RECOMMENDATIONS FOLLOWING AN ADVERSE EVENT

It is within an immunizer's scope of practice to assess adverse events following immunization and determine a course of action that may include decision-making about subsequent doses of the vaccine(s).

The following are **recommended** criteria for events to be reviewed by the Chief Medical Officer of Health:

- events which the client's health care provider considers to confer precautions, contraindications or a reason to postpone a future immunization
- all events managed as anaphylaxis
- all neurological events including febrile and afebrile convulsions
- allergic events
- all events where medical attention is required, and
- all events that are serious (resulting in hospitalization, residual disability, death, or congenital malformation)
- all major reactions

Upon receiving recommendations from the Chief Medical Officer of Health, discuss with the client. Any questions or consults for the Chief Medical Officer of Health are to be directed to the Immunization Program. Do not contact the Chief Medical Officer directly.

5.0 SUMMARY OF REPORTING CRITERIA

Adverse Event Following Immunization	Reporting Criteria	Temporal Criteria❶	
		Inactivated Vaccines	Live Attenuated Vaccines
Local Reaction at Injection Site			

Abscess, Infected	• Material from abscess known to be purulent (positive gram stain or culture)
	OR
	• There are one or more signs of localized inflammation (erythema, pain to light touch, warmth) **AND**
	  ○ Evidence of improvement on antimicrobial therapy **OR**
	  ○ Physician-diagnosed
		0-7 days	

Abscess, Sterile	Physician-diagnosed **AND** any of the following: • Material from mass is known to be non-purulent • Absence of localized inflammation • Failure to improve on antimicrobial therapy	0-7 days	
Cellulitis	Physician-diagnosed **AND** characterized by at least 3 of the following: pain or tenderness to touch, erythema, induration or swelling, warmth	0-7 days	
Nodule	• Is more than 2.5 cm in diameter **AND** • Persists for more than 1 month	0-7 days	
Pain or Redness or Swelling	• Pain or redness or swelling that extends past the nearest joint **AND/OR** • Pain or redness or swelling that persists for 10 days or more	0-48 hours	

❶ The length of time between vaccine administration and onset of events is an important consideration in causality assessment. Temporal criteria guidelines in this table are generally agreed upon approximate timelines.

Adverse Event Following Immunization	Reporting Criteria	Temporal Criteria❶	
		Inactivated Vaccines	Live Attenuated Vaccines
Systemic Reactions			
Adenopathy/ Lymphadenopathy	• Enlargement of 1 or more lymph nodes, ≥ 1.5 cm in diameter **AND/OR** • Draining sinus over a lymph node	0-7 days	MMR: 5-30 days Varicella: 5-42 days
Fever	Fever ≥ 38°C that occurs in conjunction with another reportable adverse event	Timing in conjunction with the other reportable adverse event(s)	
Hypotonic-Hyporesponsive Episode (HHE)	Physician-diagnosed **AND** • Reduced muscle tone **AND** • Hyporesponsiveness or unresponsiveness **AND** • Pallor or cyanosis **AND** • Child < 2 years of age	0-48 hours	
Parotitis	Physician-diagnosed parotitis following immunization with a mumps-containing vaccine	N/A	MMR: 5-30days
Orchitis	Physician-diagnosed orchitis following immunization with a mumps-containing vaccine	N/A	MMR: 5-30days
Rash	• Inactivated vaccines: generalized rash for which medical attention is sought, when the rash is believed to be caused by the vaccine, and for which no alternative cause has been identified **OR** • Live vaccines: an expected rash following a live vaccine that requires hospitalization	0-7 days	MMR: 0-30 days Varicella: 0-42 days
Screaming/ Persistent Crying	• Crying is continuous/unaltered **AND** • Lasting for 3 or more hours	0-72 hours	
Severe Vomiting/ Diarrhea	• 3 or more episodes of vomiting or diarrhea in a 24-hour period **AND** • Symptoms are severe, i.e., projectile vomiting or explosive, watery diarrhea	0-72 hours	0-72 hours **0-7 days for rotavirus vaccine

❶ The length of time between vaccine administration and onset of events is an important consideration in causality assessment. Temporal criteria guidelines in this table are generally agreed upon approximate timelines.

Adverse Event Following Immunization	Reporting Criteria	Temporal Criteria❶	
		Inactivated Vaccines	Live Attenuated Vaccines
Allergic Reactions			
Anaphylaxis	Any event managed as anaphylaxis following immunization	0-24 hours	
Oculo-respiratory syndrome (ORS)	• Bilateral red eyes **AND** • Respiratory symptoms • Following influenza vaccine	0-24 hours	
Other allergic reactions	• Skin **OR** • Respiratory **OR** • Gastrointestinal manifestations	0-48 hours	
Neurological Events			
Anaesthesia/ Paraesthesia	Physician-diagnosed anaesthesia or paraesthesia lasting 24 hours or more	0-15 days	MMR: 0-30 days Varicella: 0-42 days
Bell's palsy	Physician-diagnosed Bell's palsy	0-3 months	
Convulsion/seizure	• Seizures (febrile or afebrile) • Include temperature if febrile seizure reported	0-72 hours	MMR: 5-30 days Varicella: 5-42 days
Encephalopathy or Encephalitis or Acute Disseminated Encephalomyelitis (ADEM)	Physician-diagnosed encephalopathy or encephalitis or ADEM	0-42 days	MMR: 5-30 days Varicella: 5-42 days
Guillain-Barre syndrome (GBS)	Physician diagnosed GBS	0-56 days	
Meningitis	Physician-diagnosed meningitis for which no other cause has been identified	N/A	MMR: 5-30 days Varicella: 5-42 days
Sub-acute sclerosing panencephalitis (SSPE)	Physician diagnosed SSPE	N/A	Up to 10 years following immunization with a measles containing vaccine
Vaccine-Associated Paralytic Poliomyelitis	Physician diagnosed paralysis	N/A	OPV: 5-30 days

❶ The length of time between vaccine administration and onset of events is an important consideration in causality assessment. Temporal criteria guidelines in this table are generally agreed upon approximate timelines.

Adverse Event Following Immunization	Reporting Criteria	Temporal Criteria❶	
		Inactivated Vaccines	Live Attenuated Vaccines
Other Events of Interest			
Arthritis	Physician-diagnosed arthritis **AND** • Lasting 24 hours or more	0-30 days	MMR: 5-30 days Varicella: 5-42 days
Intussusception or hematochezia	Physician-diagnosed intussusception or hematochezia	N/A	Rotavirus vaccine: 0-42 days
Syncope with injury	Syncope with injury following immunization	0-30 minutes	
Thrombocytopenia	Physician-diagnosed thrombocytopenia	0-30 days	
Other severe or unusual events❷		Variable based on event	

❶ The length of time between vaccine administration and onset of events is an important consideration in causality assessment. Temporal criteria guidelines in this table are generally agreed upon approximate timelines.

❷ Other serious or unusual events may include those events which:

- are life threatening or result in death; require hospitalization
- result in a residual disability; are associated with a congenital malformation
- require urgent medical attention
- have:
    - not been identified previously (e.g., Oculo-Respiratory Syndrome (ORS) was first identified during the 2000/2001 influenza season), or
    - been identified before but is occurring with greater frequency in the population (e.g., extensive local reactions)
- are clusters of events: known or new events that occur in a geographic or temporal cluster (e.g., 6 in a week, or 6 in a Health Service Delivery Area) that require further assessment, even if the total number of AEFIs may not be higher than expected.

6.0 LOCAL REACTIONS AT INJECTION SITE

6.1 ABSCESSES AT INJECTION SITE

Definitions (5)**:**
Infected abscess: a confirmed localized collection of pus in a cavity formed by the disintegration of tissue, usually caused by microorganisms that invade the tissues. The abscess may be confirmed by spontaneous or surgical drainage of material from the mass, or imaging techniques (e.g., ultrasound, CT or MRI).

Sterile abscess: an abscess whose contents are not caused by pyogenic bacteria.

Reporting Criteria:
a) Infected Abscess:

- Material from the abscess is known to be purulent (positive gram stain or culture) OR
- There are one or more signs of localized inflammation (erythema, pain to light touch, warmth) AND
- Evidence of improvement related to antimicrobial therapy OR
- Physician-diagnosed

b) Sterile Abscess:
Physician-diagnosed AND any of the following:

- Material from the mass is known to be non-purulent
- Absence of signs of localized inflammation (erythema, pain to light touch, warmth)
- Failure to improve on antimicrobial therapy

Discussion: An abscess is a fluctuant (i.e., there is a wave-like motion on palpitation due to liquid content) or draining fluid – filled lesion at the injection site, with or without fever, and generally seen within 7 days of vaccine receipt. An abscess at the injection site is a rare local reaction. Contamination of multi-dose vials (re-entering vial with a used needle, improper cleaning or improper storage) can result in infection and abscess formation. Sterile abscesses are typically not accompanied by fever. Sterile abscesses are primarily associated with aluminum-adsorbed vaccines and may occur when these vaccines are injected into subcutaneous tissue instead of muscle. They are believed to be the result of irritation from components of the vaccine, especially the adjuvant. Manage abscesses with analgesics (e.g., acetaminophen, and ice to injection site). Incision and drainage of infected abscess and antimicrobials may be required.

Recommendations: Abscesses are not a contraindication to further doses of vaccine. Use an alternate site for the next dose. Ensure aseptic technique is used, and the correct needle length for an intramuscular injection.

6.2 CELLULITIS

Definition:
Cellulitis (6): an acute, infectious, expanding inflammatory condition of the skin, located in subcutaneous tissue, fat, fascia or muscle at the vaccine injection site.

Reporting Criteria:
Physician-diagnosed AND

- Characterized by at least 3 of the following local signs or symptoms:
  - pain or tenderness to touch
  - erythema
  - induration or swelling
  - warmth

Laboratory culture results would confirm the diagnosis, but such results are seldom available.

Discussion: Cellulitis is a rare adverse event following immunization. It is distinguished from the expected local reactions by its intense erythema, tenderness to light touch, presence of induration, and substantial local warmth. Cellulitis is usually caused by infection with streptococci, staphylococci, or similar organisms. It can result from bacterial contamination of the vaccine during the manufacturing process, contamination of a vaccine vial or injection equipment, or can be due to introduction of surface bacteria into the deeper layers of the skin. Injection site cellulitis is generally seen within 7 days of vaccine receipt. Cellulitis is commonly treated with antimicrobials as it is generally a bacterial infection.

Recommendation: Cellulitis is not a contraindication to further doses of vaccine. Use an alternate site for the next injection. Ensure aseptic technique is used.

6.3 NODULE

Definition:
Nodule (7): a firm, small mass of tissue at the injection site with discrete or well demarcated borders in the absence of abscess formation, erythema and warmth.

Reporting Criteria:

- Nodule is more than 2.5 cm in diameter AND
- Nodule persists for more than 1 month

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

Recommendation: Nodules are not a contraindication to further doses of vaccine. Use an alternate site for the next dose. Use the correct length of needle for intramuscular injections

6.4 PAIN, REDNESS AND SWELLING

Definition (7-9):
Swelling: a visible enlargement of a limb at the site of the injection(s).

Reporting Criteria:
One or both of the following:

- Pain or redness, or swelling extends past the nearest joint
- Pain or redness, or swelling persists for 10 days or more

Discussion: Pain, redness and swelling at the injection site are common reactions to vaccine. These reactions tend to occur within 48 hours of vaccination. The injection of foreign material into the tissues and irritation of the tissues by the process of injection can produce an inflammatory response. These local reactions are well reported in clinical trials.

An Arthus reaction is a large, localized reaction characterized by pain, swelling, induration and edema. The reaction usually begins 2-12 hours following immunization and develops gradually over a period of hours. The reaction is due to circulating antigen-antibody complexes formed when there is a large amount of circulating antibody prior to injection of the antigen. This results in extensive swelling at the injection site which may involve the entire limb. Most Arthus reactions resolve within one week. An Arthus reaction in a young infant is probably due to high levels of maternal antibody in the child's blood. Arthus reactions may be seen with too frequent boosters of tetanus-containing vaccines, and have been observed following repeat doses of pneumococcal polysaccharide vaccine after short intervals.

Manage pain and swelling with cold compresses at the injection site, and acetaminophen, if required. Avoid pressure on the injection site.

Recommendations: Local reactions are not a contraindication to further doses of vaccine.
If an Arthus reaction occurs with the initial dose of the primary infant series defer subsequent doses of the same vaccine for several months to await decline of maternally-acquired antibodies. If the infant will be less than 6 months of age for the scheduled second dose, it should be deferred until 6 months of age and the third dose given 2 months later. Deferral is not necessary if the next dose of the vaccine is due when the child is ≥ 6 months of age because circulating maternal antibody will be greatly reduced.If an Arthus reaction occurs with a tetanus-containing booster, future boosters can be spaced at longer intervals and anti-toxin levels may be monitored to determine when boosting is needed. As anti-toxin testing is no longer routinely available, specify the reason why the test is required on the laboratory requisition.

7.0 SYSTEMIC REACTIONS

'Systemic Reactions' is not a defined reporting section in Panorama. The following reactions can be found under the sections 'Local reaction at or near injection site' or 'Other defined events of interest', and should be reported under those respective sections.

7.1 ADENOPATHY/LYMPHADENOPATHY

Definitions:
Adenopathy or **lymphadenopathy** can include:

- Enlargement of one or more lymph nodes.
- 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).
- Draining sinus over a lymph node.
- 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.

Reporting Criteria:
Physician-diagnosed AND

- Enlargement of one or more lymph nodes, ≥ 1.5 cm in diameter AND/OR
- Draining sinus over a lymph node.

Discussion: Live vaccines produce a low-grade infection which can include adenopathy. With any vaccine injection, if bacteria contaminate the injection site, adenitis may occur as part of the resulting infection. Adenitis in injection site-associated infections would usually occur first in the lymph nodes draining the injection site. The adjuvanted pH1N1 (2009) vaccine was known to be associated with axillary or supraclavicular lymph node tenderness.

Recommendation:
Adenopathy is not a contraindication to further doses of vaccine. Continue with further immunizations at a different injection site. Use aseptic technique.

7.2 FEVER

Definition:
Fever (10): elevation of temperature above the normal body temperature (37°C; 98.6°F).

Reporting Criteria:

- Fever ≥ 38°C that occurs **in conjunction with** another reportable adverse event.

Discussion: Fever is a common expected systemic reaction that generally occurs within 72 hours of immunization with inactivated vaccines. Injected protein can affect the body's heat regulation. Fever following immunization with a live vaccine may occur at a later time (e.g., commonly 5-14 days after MMR or varicella vaccines). These delayed fevers result from a low-grade non-transmissible infection produced by the live vaccine viruses.

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. Evaluate fevers for other causes unrelated to immunization so treatment is not delayed for serious conditions. Consider intercurrent illness and other potential causes when interpreting an adverse event following immunization.

Physician evaluation is advised when:

- an infant < 3 months of age has a fever
- infants 3-12 months of age have a fever ≥ 39°C
- a child < 2 years has a fever lasting longer than 24-48 hours
- an older child has a fever lasting more than 72 hours, or
- there are signs of dehydration, refusal to eat food or drink, irritability, listlessness, unresponsiveness or any other worrisome signs or symptoms.

Antipyretics [e.g., acetaminophen (10-15 mg/kg/dose)] are recommended for children who develop fever following immunization. See **Section 6 – Administration of Biological Products, 15.1 Fever Management**. Tepid sponge baths and extra fluids will also aid in fever management. Products containing acetylsalicylic acid (ASA) should not be given to children because of their association with Reye syndrome.

Recommendation: Fevers are not a contraindication to further doses of vaccine.

7.3 HYPOTONIC-HYPORESPONSIVE EPISODE (HHE)

Definition (11):
HHE: the sudden onset, in a child under 2 years of age, of reduced muscle tone, AND either hyporesponsiveness or unresponsiveness, AND either pallor or cyanosis.

Reporting Criteria:
Physician-diagnosed HHE in a child < 2 years of age.

Discussion: With a hypotonic-hyporesponsive episode, there is an acute decrease in sensory awareness or loss of consciousness, accompanied by pallor and muscle hypotonicity. Most reported episodes occur between 1 and 12 hours after immunization. Children are initially irritable and may be febrile. They then become pale, limp, and unresponsive or hyporesponsive. Respirations are shallow and cyanosis is frequently noted. As a result, parents may report that the child was not breathing. These episodes are usually transient (lasting a few minutes) and self-limiting.

HHE has been documented to occur after immunization with diphtheria, tetanus, Haemophilus influenzae type b, and hepatitis B vaccines. Most reported episodes have followed administration of pertussis containing vaccines; there has been a decline in these reports with the use of acellular pertussis vaccines (12).

HHE has 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. Some HH episodes may represent atonic seizures, consisting of sudden loss of postural tone and consciousness, perhaps triggered by fever. Other cases have been confused with anaphylaxis or hypoglycemia. Follow-up of children who have had hypotonic-hyporesponsive episodes has demonstrated complete recovery without persistent neurologic or developmental defects. No treatment is necessary. If the HH episode does not resolve spontaneously, other underlying problems should be sought and ruled out or treated.

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

7.4 PAROTITIS

Definition:
Parotitis: inflammation of one or both parotid salivary glands with accompanying pain and tenderness.

Reporting Criteria:
Physician-diagnosed parotitis occurring 5-30 days following immunization with a mumps-containing vaccine.

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. Vaccine associated parotitis occurs most commonly 10-14 days after vaccination. It is transient and self-limiting, and can be managed with analgesics as required and adequate fluid intake.

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

7.5 ORCHITIS

Definition (13, 14):
Orchitis or inflammation of the testes rarely occurs in pre-pubertal males. Primary orchitis is uncommon except with certain viral diseases, with mumps being the most common. Less frequently, enterovirus or rarely adenoviruses, varicella-zoster virus, or West Nile virus is the causative agent. Orchitis can also be caused by bacterial infections.

When caused by mumps virus, orchitis usually occurs 4-8 days after parotitis but can develop up to 6 weeks later with or without parotitis. Viral orchitis can begin gradually but onset is usually abrupt when associated with mumps and preceded by fever, chills, nausea, and lower abdominal pain. The mumps virus can be detected in the semen for 14 days and mumps RNA can be detected for up to 40 days after wild type mumps infection. Identification of the virus following vaccine is less frequent. Laboratory testing can differentiate the wild type virus from the vaccine strain mumps virus. A recent publication of 3 cases following MMR receipt in Australia hypothesizes an immune mediated mechanism for mumps vaccine associated orchitis.

Discussion: Mumps is a live attenuated virus vaccine therefore it is biologically plausible for orchitis to be associated with mumps vaccine. Case reports in the literature are rare (15-17). There are also rare reports of higher rates of orchitis following use of mumps vaccine attributable to a mutated vaccine strain (18) or inadequately attenuated vaccine (19), in both instances in association with the Leningrad-Zagreb strain of the vaccine.

Reporting Criteria:
Physician-diagnosed. This event is no longer reportable in its own category. If it occurs, report under “Other severe or unusual events”.

Recommendation: A history of orchitis temporally associated with mumps vaccine is not a contraindication to further doses of the vaccine. Wild type mumps virus orchitis rarely causes infertility, even when bilateral, and infertility as a complication of mumps vaccination has not been described. Management of viral orchitis is supportive with symptomatic management of pain with analgesics and bed-rest. Corticosteroid treatment is not recommended. Early treatment of mumps orchitis with interferon-α2B in a single randomized trial suggested that it may lead to earlier symptom resolution and return to normal sperm count and motility (14).

7.6 RASH

Definition (20):
Rash: a temporary eruption of the skin.

Reporting Criteria:

- Generalized rash, for which medical attention is sought, when the rash occurs within 7 days of immunization with an inactivated vaccine, is believed to be due to the vaccine, and for which no alternative cause has been identified OR
- An expected rash following MMR (up to 30 days) or varicella vaccine (up to 42 days) that requires hospitalization.

Notes: A rash diagnosed as hives should be reported as an allergic reaction (refer to Part 8.0 Allergic Reactions). If consultation on a rash is planned to be sought from a secondary provider who will be unable to assess the client in person, it is recommended that photos be taken of the rash with client consent to further inform the consultation and recommendation.

Discussion: MMR vaccine may produce a mild, non-transmissible measles-like illness which can be manifested by a generalized rash and fever. It occurs in 5-10% of persons following the first dose of MMR, usually 7-12 days (range 5-30 days) after vaccination. It is much less common following the second dose of MMR.

An erythematous, maculopapular, measles-like rash should be distinguished from a petechial rash. Petechiae are small, purplish, hemorrhagic spots on the skin that do not blanch with pressure. Petechial rashes should be referred for consultation to determine if further doses of the vaccine should be administered (see 10.4 Thrombocytopenia).

A localized varicella-like rash occurs at the injection site in 3%-5% of individuals after a first dose of varicella vaccine, and in 1% of individuals after a second dose. A similar proportion of individuals will develop a small number of generalized varicella-like papules or vesicles. Lesions usually appear within 5- 26 days of immunization. A varicella-like rash is rarely transmissible.

Most rashes occurring in children, even those temporally related to immunization, are caused by 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.

Recommendation: Rashes other than petechial rashes are not a contraindication to further doses of a vaccine.

7.7 SCREAMING/PERSISTENT CRYING

Definition (21):
Crying of infants and children that is continuous and unaltered.

Reporting Criteria:

- Screaming or persistent crying [continuous, unaltered (i.e., the quality of the crying does not change throughout the episode)] AND
- Onset within 72 hours of vaccine receipt and lasting for 3 or more hours

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. Use analgesics (e.g., acetaminophen in doses of 10-15 mg/kg every 4-6 hours) as needed to control pain. Products containing acetylsalicylic acid (ASA) should not be given to children because of their association with Reye syndrome.

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

7.8 SEVERE VOMITING/DIARRHEA

Definitions:
Vomiting: ejecting stomach contents through the mouth.
Diarrhea (22): abnormally frequent discharge of loose or watery fecal matter from the bowel.

Reporting Criteria:

- 3 or more episodes of vomiting or diarrhea in a 24-hour period AND
- Vomiting or diarrhea is severe (i.e., projectile vomiting or explosive, watery diarrhea).

Discussion: Nausea and diarrhea have been particularly associated with oral typhoid vaccine, human diploid cell rabies vaccine (HDCV), and Japanese B encephalitis vaccine. In clinical trials, diarrhea was not more frequent in infants following receipt of rotavirus vaccines compared to placebo.

Treat severe vomiting/diarrhea symptomatically to prevent dehydration and electrolyte imbalance.

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

8.0 ALLERGIC REACTIONS

8.1 ANAPHYLAXIS

Definition (23):

Anaphylaxis: a rare but potentially life threatening allergic reaction. It is characterized by sudden onset, rapid progression of signs and symptoms and is set apart from simple allergic reactions by the simultaneous involvement of several organ systems.

Following appropriate clinical management of suspected anaphylaxis, the Worksheet for Treatment of Anaphylaxis (Section 12) should be completed by the health care professional who observed and treated the anaphylaxis episode. The information should be added to the AEFI report in Panorama to allow the Immunization Program Manager and CMOH to assess the event, and will allow for application of the Brighton anaphylaxis case definition. The Brighton Collaboration defines anaphylaxis according to diagnostic certainty, not clinical severity of the event. The highest level of diagnostic certainty, Brighton Level 1, is defined as:

- ≥ 1 major dermatological
  AND
- ≥ 1 major cardiovascular or ≥ 1 major respiratory criterion.

A minority of cases reported as anaphylaxis will meet Level 1 degree of certainty. This may be because when suspected anaphylaxis is managed appropriately and promptly, escalation of symptoms and progression to a severe outcome is avoided.

Anaphylaxis must be distinguished from fainting (vasovagal syncope), breath-holding spells and anxiety, which are not reportable and which, when misdiagnosed as anaphylaxis, can result in failure to complete immunization in individuals without a valid contraindication. Symptoms that are progressive or increasing in severity are more likely to represent anaphylaxis. For management of anaphylaxis including differentiation from events such as fainting and pain reaction, refer to Section 12: Anaphylaxis.

Reporting Criteria:

- Managed as anaphylaxis at the time of occurrence AND
- Occurs within 24 hours of immunization.

Recommendation: A true anaphylactic reaction to a vaccine is a contraindication to receipt of further doses of the same vaccine or to a component of a vaccine. Referral to the primary health care provider for consultation with an allergist may be sought to identify the component to which the client has hypersensitivity. It is important to avoid leaving clients inadequately immunized if they unnecessarily avoid vaccines to which they are not hypersensitive. In addition, not knowing the particular component of a vaccine to which the client is allergic may pose a risk from future vaccines that contain the same component.

8.2 OCULO-RESPIRATORY SYNDROME (ORS)

Definition:
ORS: the onset of bilateral red eyes and respiratory symptoms (cough, wheeze, chest tightness, difficulty breathing, difficulty swallowing, hoarseness or sore throat) with or without facial edema, following influenza vaccine.

Reporting Criteria:

- Bilateral red eyes AND respiratory symptoms AND
- Onset within 24 hours of influenza vaccine receipt.

Recommendation: Most people who have had ORS after a previous dose of influenza vaccine do not experience it again. The event recurs in about 5% to 34% but it is usually milder. Most people who have experienced ORS can be safely revaccinated.

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

8.3 OTHER ALLERGIC REACTIONS

Discussion: Allergic reactions constitute a spectrum, the extreme end of which is anaphylaxis. Milder forms of allergic reactions may involve only dermatologic/mucosal, respiratory or gastrointestinal systems.

An allergic reaction is an acquired hypersensitivity to an antigen that does not normally produce such a reaction. Antigen-antibody complexes stimulate the release of chemicals, such as histamine, that produce overt signs and symptoms of hypersensitivity. An allergic reaction can occur in response to a component of a vaccine in a person previously sensitized (i.e., antibodies must be present from a previous exposure to the antigen). When reported as an adverse event, enquire about history of allergies and possible exposure to other allergens during the same time period.

Allergic reactions may be limited to one system only:

i. Skin manifestations: urticaria (hives), erythema, pruritus, or prickle sensation, and localized or generalized edema (in the deeper layers of the skin, subcutaneous tissues or mucosa lining the throat, airways and gut). Refer to Section 12: Anaphylaxis for specific management of hives and swelling at the injection site only.
ii. Respiratory manifestations: sneezing, wheezing, stridor, sensation of throat closure, sore throat, rhinorrhea, hoarse voice, dry cough, tachypnea, grunting, difficulty breathing, difficulty swallowing, indrawing/retractions, chest tightness or cyanosis.
iii. Gastrointestinal symptoms: nausea, vomiting, or abdominal pain.

Practically, the vast majority of recognized 'other allergic reactions' following immunization are dermatological. Isolated gastrointestinal reactions are uncommon and/or difficult to differentiate from other causes such as gastroenteritis, and respiratory manifestations such as wheezing more commonly occur in those with a pre-existing diagnosis of asthma and are difficult to differentiate from an exacerbation of asthma. Therefore, the recommendations below are based on the temporal relationship between vaccination and the onset of dermatological manifestations. The presence of hives at the injection site is considered important in the assessment of the likelihood that event was associated with the vaccine, as an IgE mediated reaction due to the deposition of the vaccine along the needle track indicates hypersensitivity to the product component(s).

Reporting Criteria:

- Allergic reactions occurring within 48 hours of immunization.

Note: If consultation on a rash is planned to be sought from a secondary provider who will be unable to assess the client in person it is recommended that photos be taken of the rash with client consent to further inform the consultation and recommendation.

Recommendation:

1. Generalized hives occurring from 0-2 hours after immunization (cause and effect likely): Refer to primary health care provider with a recommendation for further assessment by an allergist prior to further doses of the same vaccine or its components.
2. Hives occurring from 2-48 hours following immunization (cause and effect less likely): Consider providing next dose of the vaccine in a physician's office or an emergency setting and observe the patient for 1-2 hours following immunization. If there is no reaction following this dose, further immunization can be given in the routine setting. If a hive-like rash reappears with this dose, particularly a generalized rash appearing within 48 hours of vaccination dose, refer to primary health care provider with a recommendation for further assessment by an allergist prior to further doses of the same vaccine or its components.
3. Hives occurring ≥ 48 hours after immunization (cause and effect link unlikely): Consider giving next vaccine dose under routine conditions. Consider other potential causes of the hives, particularly if there was no reaction at the injection site.

9.0 NEUROLOGICAL EVENTS

9.1 ANAESTHESIA/PARAESTHESIA

Definitions:
Anaesthesia: the loss of normal feeling or sensation; numbness.
Paraesthesia: abnormal physical sensation such as tingling, burning or prickling.

Reporting Criteria:

- Physician-diagnosed anaesthesia or paraesthesia lasting 24 hours or more.
- Beginning up to 15 days following administration of inactivated vaccines, up to 30 days following MMR, or up to 42 days following varicella vaccine. Supporting documentation of the diagnosis should be included with the adverse event report.

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

Recommendation: 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.

9.2 BELL'S PALSY

Definition:
Bell's palsy: a unilateral paralysis or weakness of facial muscles.

Reporting Criteria: Physician-diagnosed Bell's palsy occurring within 3 months of immunization.

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

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

Bell's palsy has only once been definitively linked to immunization. An intranasal inactivated influenza vaccine used only in Switzerland was removed from the market after an increase in cases of Bell's palsy was noted (24).

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

9.3 CONVULSION/SEIZURE

Definition (25):
Seizure(s): Episode(s) of hyperactivity in the brain resulting in sudden, involuntary muscle contractions and abnormal behaviour, loss or impairment of consciousness.

Reporting Criteria:

- Seizures (febrile or afebrile) that occur within 72 hours of inactivated vaccines, 5-30 days after MMR, or 5-42 days following varicella vaccine.

Specify in the reporting whether the seizure was afebrile or febrile; if febrile, include the temperature.

Discussion: Seizures include paroxysms of generalized tonic skeletal muscle contractions and generalized clonic jerking, usually associated with decreased level of consciousness. Seizures may last for several minutes or more.

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-dependant. They are rare prior to 6 months of age and after 5 years of age, with peak onset at 14-18 months of age. Incidence in this age group approaches 2-5%, with greater risk in those with a family history. While simple febrile seizures are disturbing for the child and parents, they have a uniformly excellent prognosis without residual sequelae and remit on their own as the child ages. There are no long-term sequelae, such as permanent brain damage, associated with simple febrile seizures. Remind parents that children susceptible to febrile seizures may have a recurrence following immunization or following other events, such as viral infections. Pre-emptive treatment with antipyretics such as acetaminophen has not been shown to prevent febrile seizures in such children.

Recommendations: Uncomplicated febrile seizures are not a contraindication to further doses of a vaccine. Refer to the primary health care provider with a recommendation for a consultation with a neurologist when the febrile seizures are multiple or prolonged (complex seizures, status epilepticus), or, when the seizures are afebrile, to rule out an underlying disorder.

9.4 ENCEPHALOPATHY/ENCEPHALITIS, MYELITIS/TRANSVERESE MYELITIS, ADEM AND SSPE

9.4.1 Encephalopathy/Encephalitis

Definitions:
Encephalopathy: a term used to describe a constellation of signs and symptoms reflecting a generalized disturbance in brain function.
Encephalitis: inflammation of the brain.
Reporting Criteria:

- Encephalopathy or encephalitis diagnosed by a physician.

Include appropriate documentation, physicians' assessments and test results, with the AEFI report. All reports are investigated by the Advisory Committee on Causality Assessment.

Discussion: Acute **encephalopathy** is the sudden onset of major neurological illness temporally linked with immunization and characterized by two of the following:

1. Severe alteration in level of consciousness or unresponsiveness, with or without generalized or focal convulsions. The symptoms must persist for more than a few hours, with failure to recover completely within 24 hours.
2. Increased intracranial pressure (as measured and diagnosed by a physician). A bulging fontanel as described by a parent to a nurse rather than observed by a physician is not sufficient to diagnose increased intracranial pressure. Intense crying can cause a bulging, pulsating fontanel.
3. Distinct change in behaviour or intellectual functions lasting one day or more and felt by a physician to indicate an alteration in neurological function.

Encephalitis includes 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 multifocal central nervous system abnormality.

Immunizations may very rarely lead to acute encephalitis, particularly in the setting of live-attenuated viral vaccines. The risk of encephalitic complications from viral infections (1/1000 cases of measles; 1/6000 cases of rubella) is greater than the risk following vaccination (1/1,000,000 following MMR). Encephalitis has occurred rarely following yellow fever immunization in young infants and thus this vaccine is not recommended for infants less than 9 months of age.

Recommendation: Encephalitis/encephalopathy are not a contraindication to further vaccination. Deferral of immunization may be considered until the neurologic condition has been diagnosed or is stable. Individuals who experience encephalitis following MMR vaccine may be tested for immunity, as further immunization is not required if serologically immune. If no other cause is found and the encephalopathy is temporally related to a combination vaccine, refer to a paediatric neurologist to determine which components of the vaccine may be continued.

9.4.2 Myelitis/Transverse Myelitis

Definitions:
Myelitis: inflammation of the parenchyma of the spinal cord.
Transverse Myelitis (TM): an abrupt onset inflammatory demyelinating condition of the spinal cord that affects almost the entire thickness of the cord but spans only one or a few vertebral segments. Both of these conditions have multiple underlying causes similar to those associated with encephalitis/ADEM, and include infectious, toxic, neoplastic, autoimmune, and metabolic etiologies but the most common are viral and post-viral, as well as multiple sclerosis or other autoimmune disease. Myelitis may occur in conjunction with encephalitis and transverse myelitis in conjunction with ADEM.

Reporting Criteria:
Physician-diagnosed transverse myelitis with no other cause identified AND

- Occurring within 6 weeks of vaccine receipt.

Supporting documentation of the diagnosis should accompany the report.

Discussion: In a 2009 systematic review of the relationship between transverse myelitis (TM) and vaccination, 43 cases of post-vaccination TM were identified in the literature between 1970 and 2009 (27, 28). In 73% of cases, onset was within the first month post-vaccination and the age of patients ranged from several months to 50 years. Thirteen cases followed hepatitis B vaccination, 6 MMR, 4 DTP, 4 rabies, 3 OPV, 2 influenza, 1 typhoid vaccine, 1 pertussis, 1 Japanese B encephalitis and 2 in recipients of multiple vaccines.

In its recently published safety review of a number of vaccines, the Institute of Medicine (IOM) concluded that there is evidence of TM association to several of the diseases, with rare occurrences following wild type mumps, reactivated varicella zoster, and influenza; as well, measles and rubella can cause myelitis. However, the small number of case reports of TM associated with the vaccines reviewed by the IOM did not contain sufficient evidence of mechanisms such as autoantibodies, T cells, or molecular mimicry at play in such cases. The 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.

Recommendation: The decision to continue immunization must be made on a case-by-case basis. All cases should be evaluated by a neurologist (46).

9.4.3 Acute Disseminated Encephalomyelitis (ADEM)

Definition:
ADEM: A uniphasic syndrome of brain inflammation and demyelination, occurring in temporal association with an antecedent immunologic challenge, which may rarely include immunization. ADEM is distinguished from acute encephalitis by (a) a predominance of demyelinating, rather than cytotoxic injury and (b) a temporal association with a specific inciting immunogenic challenge (29).

Reporting Criteria:
Physician-diagnosed monophasic ADEM with no other cause identified. Monophasic nature of ADEM must be assessed after monitoring for 3 months from clinical nadir.

Discussion: Clinically, ADEM may be difficult to distinguish from acute encephalitis in the early phase of the disease, presenting with global cerebral dysfunction, multifocal neurologic findings, and meningismus. The key distinguishing feature between these two conditions is the presence of acute demyelination, confirmed on MRI or by histopathology.

Various immunizations have been temporally associated with ADEM, including Japanese encephalitis, yellow fever, measles, influenza, smallpox, anthrax and others. However, the only epidemiologically and pathologically proven association of an antecedent event is with antirabies vaccination using the Semple rabies vaccine [a vaccine derived from sheep/mouse brains (not used in Yukon)]. There has been no observed association with modern rabies vaccines. For most vaccines incidence rates are low (0.1-0.2 per 100,000 doses administered) compared to the reported 1 in 1000 incidence of post-infectious ADEM following infection with the measles virus.

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

9.4.4 Subacute Sclerosing Panencephalitis (SSPE)

Definition:
SSPE (30, 31): a rare, degenerative central nervous system disease occurring as a late complication of measles infection (up to 10 years later).

Reporting Criteria:
Physician-diagnosed SSPE.

Discussion: SSPE is caused by persistence of defective measles virus in the central nervous system through means that are as yet unknown (32). It is characterized by behavioural and intellectual deterioration and convulsions due to inflammation of brain tissue. Seizures, blindness and dementia can occur. Remission occurs in only 4% of cases; it is otherwise fatal, and only supportive treatment exists. For vaccine-associated cases there is no temporal criterion for reporting; as with cases following infection, the occurrence would be years following immunization.

The association between natural measles infection and SSPE has led to concern that live attenuated measles vaccine virus could also cause a persistent infection of the central nervous system. Genetic sequencing of viruses from the brains of patients with SSPE including those without a history of measles disease has only identified wild type measles virus.

Some reported cases of SSPE had history of measles vaccination and lacked a history of natural measles infection. If the vaccine indeed is associated rarely with SSPE, the risk following vaccination, if it exists, is estimated to be approximately one tenth or less of that noted after natural infection (less than 1/1,000,000 persons vaccinated versus 1/100,000 cases of measles). The results of a retrospective case control study by the Centers for Disease Control and Prevention indicate that the overall effect of measles vaccination has been to protect against SSPE by preventing measles disease. There has been a dramatic decline in the incidence of SSPE since the introduction of widespread measles immunization.

Recommendation: A diagnosis of SSPE is a contraindication to receipt of a measles-containing vaccine.

9.5 GUILLAIN-BARRE SYNDROME (GBS)

Definition (33):
Guillain-Barré syndrome: an illness that includes acute onset of bilateral flaccid weakness/paralysis of the limbs with decreased or absent deep tendon reflexes. CSF test results, if available, must either be normal, or have < 50 WBC/mm (6).

Reporting Criteria:
Physician-diagnosed GBS AND

- Occurring within 8 weeks after immunization.

Provide documentation confirming the diagnosis. GBS cases are reviewed by the Advisory Committee on Causality Assessment.

Discussion: Guillain-Barré syndrome 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 1-8 weeks; approximately two-thirds of patients with GBS report an antecedent infectious illness, most commonly a diarrhoeal or respiratory illness, prior to the onset of neurologic signs; Campylobacter jejuni is the most commonly reported pathogen in adults. A maximum degree of weakness is reached from 12 hours to 28 days after onset, followed by a clinical plateau and then either improvement or death. Overall, approximately 5-15% of patients die, and continued disability after 1 year has been estimated to be seen among 20% of patients. Studies in developed countries have suggested an incidence of 1-2 per 100,000 population per year.

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

Recommendation: 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 if vaccine is given. There are no contraindications to immunization in persons with a previous history of GBS unrelated to vaccination.

9.6 MENINGITIS

Definition:
Meningitis: an infection or inflammation of the membranes covering the brain and spinal cord. It is characterized by sudden onset of fever, intense headache, nausea and vomiting, and pain and stiffness in the neck.
Aseptic meningitis (34): a syndrome characterized by acute onset of signs and symptoms of meningeal inflammation, cerebrospinal fluid pleocytosis and the absence of microorganisms on Gram stain and/or on routine culture.

Reporting Criteria:
Physician-diagnosed meningitis for which no other cause has been identified AND

- Occurring within 15 days of inactivated vaccines, 5-30 days following MMR, or 0-42 days following varicella vaccine.

Include medical documentation. Reports of this major, severe but rare adverse event are subsequently investigated by the Advisory Committee on Causality Assessment.

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 vaccines, including oral polio, MMR vaccine, varicella, yellow fever and smallpox. The postulated mechanism for aseptic meningitis following attenuated live virus vaccines is infection of the meninges with the vaccine virus. Such a causal relationship was established with the Urabe strain of mumps virus32 (1 case reported per 62,000 vaccinations), which is no longer used in vaccines in Canada. There is no evidence of a causal association with the Jeryl Lynn strain of mumps used in MMR, nor with any of the other routinely used live virus vaccines. Aseptic meningitis following immunization typically resolves without sequelae.

Recommendation: Defer further vaccines until a determination is made as to the cause of the meningitis.

9.7 VACCINE ASSOCIATED PARALYTIC POLIOMYELITIS

Definition:
Paralysis: loss of muscle tone and function with or without loss of sensation.

Reporting Criteria:
Physician-diagnosed paralysis with no other cause identified AND

- Occurring within 5-30 days following OPV and lasting more than 24 hours.

Supporting documentation of the diagnosis should accompany the report.

Discussion: Cases of paralytic poliomyelitis have been associated with oral polio vaccine (OPV). Yukon has used inactivated polio vaccine (IPV) exclusively since 1995, and OPV has not been used since that time. In Canada from 1965 through 1992, vaccine-associated paralysis occurred in recipients of OPV at a rate of 1 case per 11.7 million doses of OPV distributed, and in contacts of vaccinees at a rate of 1 case per 3.1 million doses distributed.

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

10.0 OTHER EVENTS OF INTEREST

10.1 ARTHRITIS

Definitions:
Arthritis: joint inflammation, with swelling, redness and/or warmth
Arthralgia: joint pain

Reporting Criteria:
Physician-diagnosed arthritis following receipt of a rubella-containing vaccine AND

- Lasting 24 hours or longer and associated with limitation of regular activities.

Discussion: Arthritis is usually associated with arthralgia, but arthralgia may occur without obvious arthritis. Rubella vaccine-associated arthralgia involves, in order of decreasing frequency, the joints of the fingers, knees, wrists, elbows, ankles, hips and toes. Arthritis and arthralgia can be manifestations of natural rubella infection in adults.

Arthritis and arthralgia are recognized complications of rubella immunization. Reporting transient arthralgia is not necessary.

Transient acute arthritis or arthralgia has been shown to occur 7-21 days post immunization in susceptible adolescent and adult women immunized with the RA 27/3 strain of rubella (the strain in the measles-, mumps-, rubella-containing vaccine currently available in Canada). 25% of post-pubertal females develop arthralgia, while 10% develop arthritis-like signs and symptoms. Arthritis/arthralgia can also occur in children and adolescent and adult men, but at much lower rates. Persistence or recurrence of these symptoms is rare (36).

Analgesics or anti-inflammatory medications may be used to reduce inflammation, swelling and joint pain. Products containing acetylsalicylic acid (ASA) should not be given to children because of their association with Reye syndrome.

Recommendation: Transient arthritis or arthralgia is not a contraindication to a further dose of MMR vaccine. Since the joint symptoms are likely related to seroconversion, the risk following a second MMR dose is lower than that following the first dose. It is important to offer rubella vaccine to seronegative women of childbearing age to reduce the risk of Congenital Rubella Syndrome.

10.2 INTUSSUSCEPTION/HEMATOCHEZIA

Definitions:
Intussusception (37): the telescoping of one segment of the intestine with a neighbouring segment, most often the ileum into the colon, causing partial or complete intestinal obstruction. The walls of the two sections of intestine press on each other, causing irritation, swelling and eventually decreased blood flow.
Hematochezia: red blood in the stool, (described as "red currant jelly" material) which may be associated with intussusception.

Reporting Criteria:

- Intussusception or hematochezia occurring within 42 days following rotavirus vaccine receipt.

Discussion: Intussusception is an uncommon event but one that occurs at a background rate in infants. If left untreated, intussusception can cause internal bleeding, severe abdominal infection, and death of intestinal tissue. Intussusception is the most common cause of acute intestinal obstruction in infants and young children.

A rotavirus vaccine used in the United States was withdrawn from the market in 1999 because of the reported temporal association between the development of intussusception and receipt of the vaccine. New rotavirus vaccines have been licensed after undergoing large clinical trials to assess safety with regard to intussusception. Recent large scale post-licensure trials in Mexico and Brazil found an association between rotavirus vaccine and intussusception with an excess of 1 case observed among 51,000 to 68,000 vaccinated infants (38). A study from Australia found no overall increased risk of intussusception but did find some evidence of an elevated risk following the first dose of both rotavirus vaccines within the 1-7 and 1-21 day windows (39). Hematochezia has not been observed in association with the bovine reassortant rotavirus vaccine in use in the USA in the VAERS system, and was not observed at a higher rate in vaccine compared to placebo infants in the clinical trials for the attenuated rotavirus vaccine which is used in the Yukon program.

Recommendation: Reports of intussusception following vaccination are not expected to significantly exceed the number of cases that would be seen by chance alone. Intussusception following rotavirus vaccine is a contraindication to further doses of rotavirus vaccine. Hematochezia is not considered a contraindication to further doses of rotavirus vaccine.

10.3 SYNCOPE WITH INJURY

Definition:
Syncope (vasovagal reaction) or fainting: a temporary unconsciousness caused by diminished blood supply to the brain.

Reporting Criteria:

- Syncope **with injury** following immunization.

Discussion (40, 41): Syncope can be triggered by various stimuli, and is observed to occur following immunization, perhaps triggered by pain or emotional reaction to the immunization process itself. It happens suddenly, before, during, or after immunization. Recovery occurs within 1-2 minutes. Refer to Part 12: Anaphylaxis for signs, symptoms and management of syncope. The risk of fainting is the more common reason to keep vaccinees under observation for 15 minutes post immunization.

Syncope with injury has been reported following HPV vaccine and H1N1 vaccine receipt. These reports include head injuries after syncope-related falls, and motor-vehicle incidents where the individual lost consciousness while driving. Immunizers should be aware of presyncopal manifestations and take appropriate measures to prevent injuries if weakness, dizziness or loss of consciousness occurs. These events are potentially serious and may result in hospitalization, residual disability or death. They are related to the process of immunization, rather than to a specific vaccine.

Recommendation: Syncope is not a contraindication to further immunizations.

10.4 THROMBOCYTOPENIA

Definitions (42-44):
Thrombocytopenia: an abnormal haematological condition in which the number of platelets is reduced to less than 150 x 109 /L, accompanied by clinical signs and/or symptoms of spontaneous bleeding.
Petechiae: small, purplish, hemorrhagic spots on the skin that do not blanch with pressure.

Reporting Criteria:
Physician-diagnosed thrombocytopenia occurring within 30 days following vaccination.

Laboratory results should accompany the report.

Discussion: Normal platelet counts are 150-450,000/mm (6). 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 haemorrhagic complications can occur.

The incidence of thrombocytopenia is estimated to be between 1 in 25,000 to 1 in 40,000 doses of MMR. Most cases occur following vaccination with the first dose of measles-containing vaccine; the risk of recurrence is not known, but is thought to be low. Thrombocytopenia has also been reported following other vaccines/toxoids such as diphtheria, pertussis and tetanus vaccine, and varicella.

Corticosteroids and gamma globulin may be used to treat idiopathic thrombocytopenia. Precautions should be taken, particularly for young children, to avoid the risk and complications of bleeding (e.g., precautions to avoid serious head injuries). Control of bleeding may be necessary and transfusion of platelets may be required.

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

Children who develop thrombocytopenia temporally related to their first dose of MMR should be assessed for immunity to measles; if the child is susceptible, discuss the benefits/risks of revaccination with the parent. If proceeding with vaccination, ensure that the parent is aware of the potential risk of recurrence, watches the child closely for development of petechiae in the 2-3 weeks post-vaccination, and is aware of the need for injury prevention.

10.5 OTHER SEVERE OR UNUSUAL EVENTS

Criteria for Reporting: Report other severe and unusual events with a temporal association to immunization, and for which there is no other known cause, and which are not covered under the categories previously described. These must be clinically intriguing or epidemiologically interesting events and usually require medical intervention to meet the criteria for reporting. Provide all details of the event, and include all necessary documentation with the report. Do not report expected local reactions such as pain, redness, and swelling that do not meet current reporting criteria as "other severe or unusual events".

Report any death (45) of a vaccine recipient temporally linked (within one month) to immunization, where no other clear cause of death can be established. Report fetal death that occurs following the immunization of a pregnant woman and deaths in infants which may be diagnosed as Sudden Infant Death Syndrome when the investigation has concluded. Provide autopsy report when available.

Reporting of severe or unusual events is important not only to identify a possible causal relationship with vaccination, but also to rule out the vaccine as the cause. The severity of the adverse event and the plausibility of a causal association with vaccination will determine whether further doses of the implicated vaccine will be continued.

"Other severe or unusual" events may include those events which: are "severe":

- are life threatening or result in death
- require hospitalization or result in a prolongation of a hospitalization
- result in a residual disability
- are associated with a congenital malformation
- require urgent medical attention

are "unusual":

- have not been identified previously (e.g., ORS was first identified during the 2000/2001 influenza season)
- have been identified previously but are happening with greater frequency in the population
- are clusters of events: known or new events that occur in a geographic or temporal cluster that require further assessment, even if the total number of AEFIs is not higher than expected.

11.0 BACKGROUND ON ADVERSE EVENT SURVEILLANCE

Post-marketing surveillance for AEFIs is an important component of all immunization programs and is conducted at all levels of the public health system including at the global level by the World Health Organization. In Canada post-marketing adverse event surveillance started in 1965 at the Laboratory Centre for Disease Control, and is now the responsibility of the Public Health Agency of Canada (PHAC) and of Health Canada, the regulatory authority for vaccines (46).

The safety profile of vaccines is significantly better than that of other pharmaceutical agents, however, vaccines are not entirely risk free and their safety needs to be monitored (47). The importance of this surveillance is further highlighted by the fact that vaccines are unique amongst pharmaceuticals as these products are intended for use in healthy people, thus the public acceptability of risk associated with vaccines is lower than that for drugs used to treat disease and illness.

Before coming to the market, vaccine safety is assessed in clinical trials which are typically industry funded. As these studies are limited in the number of subjects enrolled, they have limited ability to detect adverse events that are rare, have long onset intervals or occur in populations that were not studied (48, 49). These limitations can be addressed through post-marketing vaccine safety surveillance. A robust and well-rehearsed vaccine safety surveillance system can identify and investigate suspect associations of adverse events with vaccines. Action can then be taken to debunk false associations with well-founded science, modify the use or safety profile of a vaccine, or remove unsafe vaccines from the public market.

Post-marketing vaccine safety surveillance is a key component in instilling confidence among both the public and health care providers about the safety of vaccines which is important to ensure uptake and ultimately disease prevention (50, 51).

11.1 OBJECTIVES OF SURVEILLANCE

The primary objective of the AEFI surveillance system in Yukon is the early detection of clusters or serious adverse events related to use of specific vaccines and their further investigation and response, as well as to share reports with the national vaccine safety surveillance system.

In Yukon a health care provider who suspects that an adverse health event in a patient under their care may have been caused by a vaccine must report it. Reportable events are entered into Panorama, reviewed by the Immunization Program Manager and may be referred to the CMOH for review and recommendation.

Territorial AEFI data with personal identifiers removed are submitted by the Immunization Program to the Public Health Agency of Canada CAEFISS program monthly or more frequently during outbreaks (ie. On a weekly basis during the COVID-19 Pandemic). If an immunization provider becomes aware of unusual clusters of adverse events, these should be reported to the Immunization Program for further investigation. If a suspect cluster is identified at the territorial level, an investigation is started and a notification may be submitted to PHAC and/or through the Canadian Network for Public Health Intelligence (CNPHI) vaccine safety alert module.

Activities include case or cluster verification through collection of confirmatory data and application of the Brighton Collaboration case definition criteria, assessment of the temporal relationship to specific vaccines, and comparison to historical event reporting rates including against available administrative data.

11.2 NATIONAL ROLE IN SURVEILLANCE

In Canada, AEFIs are monitored by the Centre for Immunization and Respiratory Infectious Diseases (CIRID) at the Public Health Agency of Canada using the data in the Canadian Adverse Events Following Immunization Surveillance System (CAEFISS) (52). This surveillance system was renamed in 2005 from the Vaccine Associated Adverse Event Surveillance System (VAAESS) to correspond to terminology used internationally including by the World Health Organization (4).

IMPACT (Immunization Monitoring Program ACTive) is a PHAC funded active surveillance program running in 12 paediatric centres across Canada, and started in 1991 for serious adverse events following immunization (53). A revised national adverse event reporting form, available at Reporting Adverse Events Following Immunization (AEFI) in Canada was developed by the federal/provincial/territorial Vaccine Vigilance Working Group of the Canadian Immunization Committee and is used in provinces without a provincial form (54). The national reporting guide uses information from the Brighton Collaboration for definitions of adverse events, and for levels of diagnostic certainty of events. The Brighton Collaboration is an international voluntary collaboration focussing on vaccine safety and the development of globally accepted case definitions for adverse events following immunization.

If a potential signal is identified, PHAC will work closely with Health Canada's Marketed Health Products Directorate (MHPD) to discuss data extracts from CAEFISS and the Canadian Vigilance Program to enable regulatory action related to vaccines marketed in Canada. Market authorization holders (i.e., the vaccine industry) are required to report serious adverse events following immunization of which they become aware from any source to the MHPD. Following review, the data on these events are incorporated into the online Canada Vigilance Adverse Drug Reaction Data Base. CIRID also shares AEFI data from CAEFISS with MHPD; these data are not incorporated into the Canada Vigilance Adverse Drug Reaction Data Base.

The Canadian National Vaccine Safety Network (CANVAS) is an active vaccine surveillance system that was created in 2009. CANVAS was designed to conduct surveillance for pandemic vaccines (e.g. H1N1 influenza vaccine in 2009), seasonal influenza vaccines (2010-2020) and other new vaccines (e.g. COVID-19 vaccine) in order to inform public health authorities about their safety. Yukon has collaborated with CANVAS in British Columbia to enhance safety monitoring of the COVID-19 vaccines. This is in the form of a voluntary study where CANVAS staff collect data from participants. If collected data meets AEFI reporting criteria this information is shared with the Yukon Immunization Program for further follow up. CANVAS does not replace the AEFI reporting system we currently have in place but is a valuable asset that should be promoted for extra monitoring of vaccine safety.

11.3 INTERNATIONAL ROLE IN SURVEILLANCE

The World Health Organization's International Drug Monitoring Program has been operated by the Uppsala Monitoring Centre in Sweden since 1978. This program collects and aggregates case reports from over 75 countries and uses this global data set to monitor for unusual trends in adverse events (4). The Public Health Agency of Canada (PHAC) contributes to this program as well as being represented on the WHO Global Advisory Committee on Vaccine Safety. The Global Advisory Committee on Vaccine Safety was established in 1999 to "respond promptly, efficiently, and with scientific rigor to vaccine safety issues of potential global importance" (58). The committee is composed of 14 members including experts from around the world in epidemiology, statistics, paediatrics, internal medicine, pharmacology and toxicology, infectious disease, public health, immunology and autoimmunity, drug regulation and safety.

The Brighton Collaboration is an international voluntary collaboration that aims to facilitate the development, evaluation, and dissemination of high-quality information about the safety of human vaccines. The primary aim of the Brighton Collaboration is to develop globally accepted and implemented standardized case definitions of adverse events following immunizations.

Valuable information about vaccine safety is also available from the US Centers for Disease Control and Prevention (CDC) Immunization Safety Office and sourced from the passive surveillance conducted in the US jointly through the CDC and the Food and Drug Administration (Vaccine Adverse Event Reporting System or VAERS) as well as specific analytic initiatives including the Vaccine Safety Datalink (VSD). These have provided evidence regarding associations of a variety of adverse events for vaccines used in both the US and Canada, and research priorities reflect information needs for Canadian immunization programs (59).

12.0 ADVERSE EVENTS OF SPECIAL INTEREST (AESI)

Conventional vaccine safety pharmacovigilance and surveillance systems have been adapted rapidly in the Yukon in the context of COVID-19 vaccine introduction to ensure that the safety of the public is not put at risk.

Definition: AESI is a pre-specified medically-significant event that has the potential to be causally associated with a vaccine product that needs to be carefully monitored and confirmed by further special studies.

AESI detection can only start after the country finalizes the list of events that are considered as AESIs to be monitored in vaccinated and unvaccinated individuals. If we are noticing certain adverse events following immunization from new vaccines then we try to figure out what the rate of these reactions was prior to vaccine introduction to see if its normal or abnormal. If possible, the background rates of these conditions should be known before COVID-19 vaccine introduction.

At the 42nd meeting of the Global Advisory Committee on Vaccine Safety (GACVS) in May 2020, a list of potential AESIs were identified in collaboration with Brighton Collaboration's Safety Platform for Emergency Vaccines (SPEAC). It was recommended that available and newly generated Brighton Collaboration case definitions for AESIs and tools to assess certainty of cases should be shared widely for countries to use and to be aligned.

AEFIs reported to the Yukon Immunization Program are reviewed by program staff to see if they meet reporting criteria for AESIs. These reports are shared with federal partners at PHAC, VVWG and CAEFISS to identify any potential safety signals related to the COVID-19 vaccines.

Table 4 lists the vaccine platform- and COVID-19 disease-related AESI from the May SPEAC list. Details are available at https://brightoncollaboration.us/covid-19/. As new information emerges this list will be updated.

List of AESI's defined for COVID-19 vaccines (May 2020)
AESI Vaccine-associated enhanced disease
Multisystem inflammatory syndrome in children
Acute respiratory distress syndrome
Acute cardiovascular injury (microangiopathy, heart failure, stress cardiomyopathy, coronary artery disease arrhythmia, myocarditis)
Coagulation disorder (thromboembolism, haemorrhage)
Acute kidney injury
Generalized convulsion

Guillain Barré Syndrome
Acute liver injury
Anosmia, ageusia Chilblain – like lesions
Single organ cutaneous vasculitis
Erythema multiforme
Anaphylaxis
Acute aseptic arthritis
Meningoencephalitis
Acute disseminated encephalomyelitis
Thrombocytopenia

13.0 VACCINE INJURY SUPPORT PROGRAM

The Public Health Agency has established a pan-Canadian no-fault Vaccine Injury Support Program (VISP), in consultation with provinces and territories. The program launched in June 2021 is operational and ready to accept claims. The Government of Canada is committed to ensuring that Canadians who support public health by being vaccinated are supported should they experience a serious and permanent injury as a result of vaccination.

Even though serious injuries related to vaccine administration are very rare, having a program like this is important to ensure equitable access to support for all individuals vaccinated in Canada should they be injured by vaccines. This program is based on the model that has been in place in Quebec for more than 30 years. Due to the longevity of Quebec's existing vaccine compensation program, they will be the only province in which this program will not operate.

VISP is PHAC funded but will be operated independently of government, and is currently administered by RCGT (Raymond Chabot Grant Thornton) Consulting. A three-physician committee will adjudicate the claims. Rejected claims can be appealed.

This program applies to:

- all Health Canada approved vaccines administered in Canada
- vaccines administered on or after December 8, 2020
- individuals of all ages
- claims filed within 3 years of vaccination, date of death, or the date the injury becomes apparent

Eligible individuals are those who have suffered a serious and permanent injury resulting in persistent or significant disability or incapacity, or where the outcome is a congenital malformation or death.

The program will operate completely independently of the adverse event following immunization (AEFI) surveillance programs, and information from these surveillance programs will not be sought in the claims or adjudication processes. However, periodic summary information from the injury compensation (e.g., number of claims submitted, types of claims/ events, results of adjudication process, etc.) will be shared with the provinces and territories.
Access to the program is available at this link: https://www.vaccineinjurysupport.ca/en

14.0 REFERENCES

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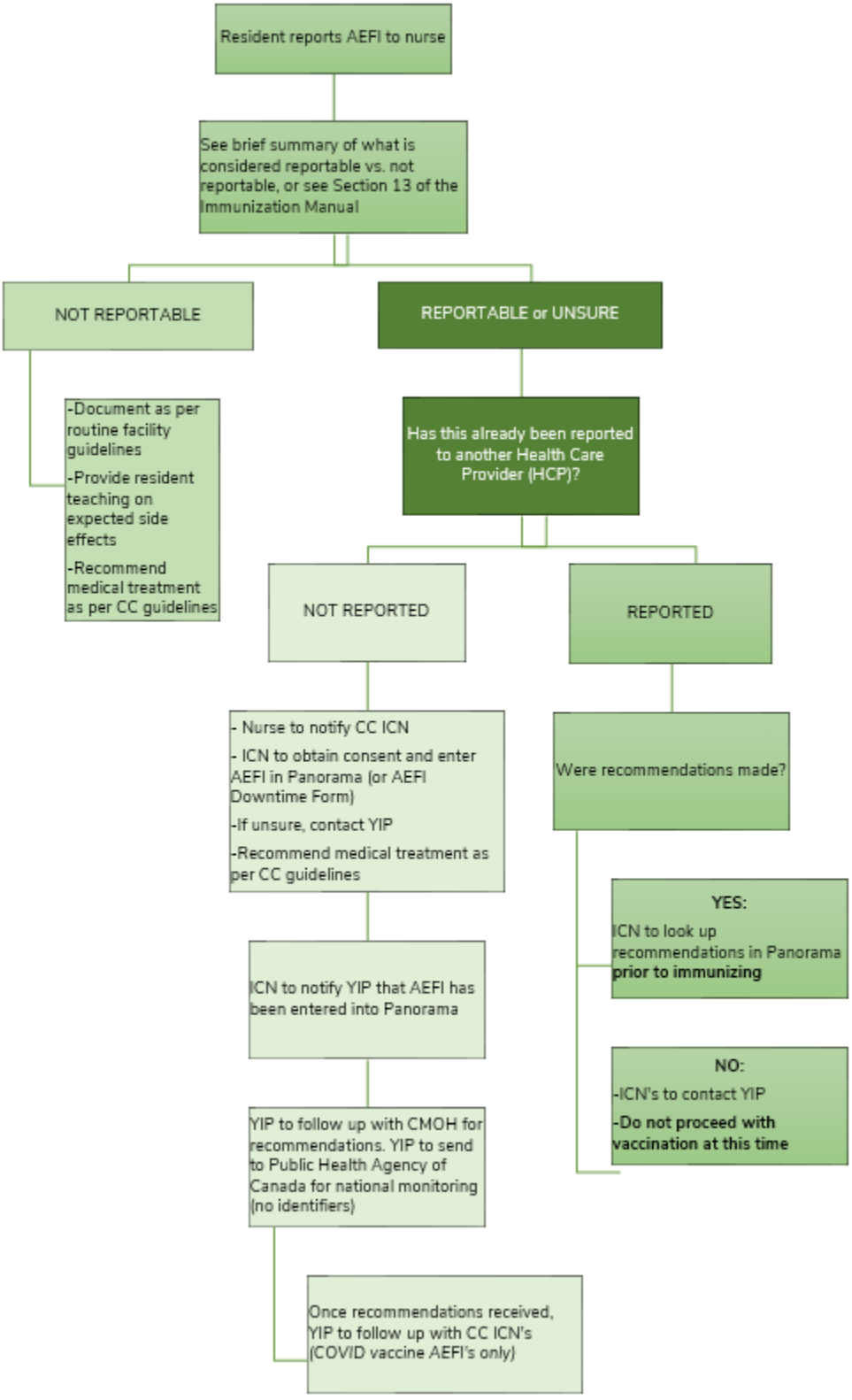
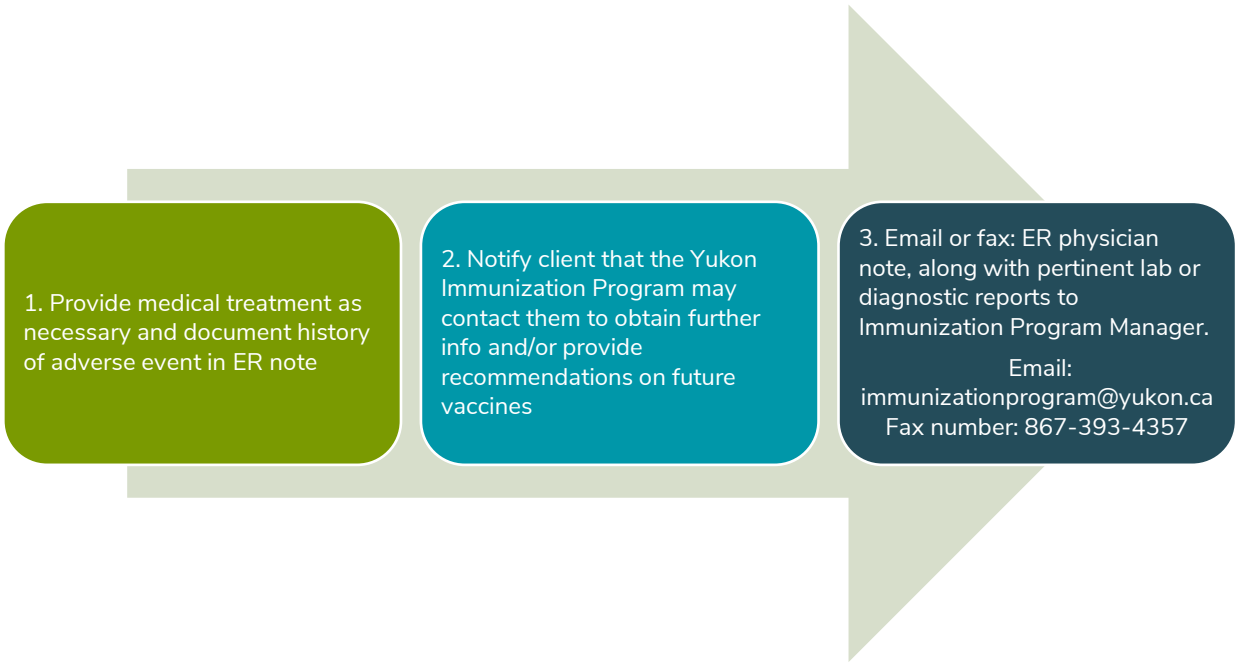
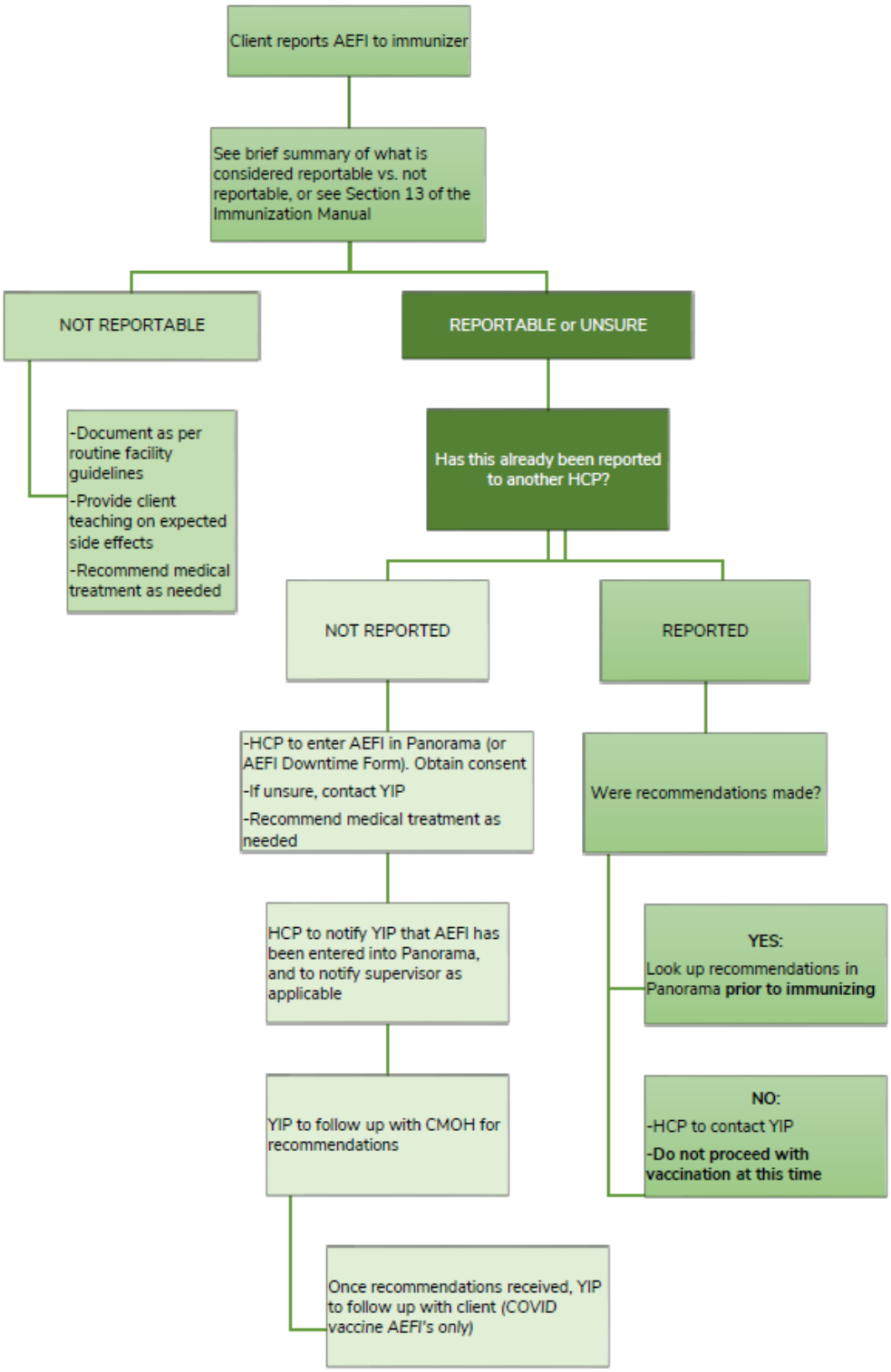
15.0 APPENDIX A: AEFI Continuing Care Process (COVID-19 Vaccine)



16.0 APPENDIX B: AEFI ER Process (COVID-19 Vaccine)



17.0 APPENDIX C: AEFI Health Centre Process (COVID-19 Vaccine)



18.0 APPENDIX D: AEFI Mass Clinic Process (COVID-19 Vaccine)