



**SECTION IX – VACCINE ASSOCIATED ADVERSE EVENTS
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INTRODUCTION

An adverse event following immunization is defined as an untoward event temporally associated with immunization that may or may not have been caused by the vaccine or the immunization process. Adverse reactions following immunization are generally mild; severe events resulting in permanent sequelae are extremely rare. The benefits of preventing disease far outweigh the risks of immunization. Even when adverse events occur following immunization, they may not have been caused by the immunization or the vaccine components. Because of the large number of vaccine doses administered, there will be some temporal and merely coincidental association between adverse events and vaccine administration (1).

Most reported adverse events occur in children, not because they are necessarily at greater risk of adverse events, but because of several other factors:

- Children receive the vast majority of immunizations
- Infants are seen frequently by health practitioners in the first year of life when they receive several immunizations, providing opportunities for reporting adverse events
- Viral and bacterial illnesses are very common in children and can result in signs and symptoms similar to those which may occur following immunization

The last point may be the most important, and vaccinators should be reminded to consider intercurrent illness and other potential causes when interpreting adverse reactions following immunization.

PURPOSE

The purpose of this document is to assist the Medical Health Officer and other health practitioners who administer vaccines with the interpretation of adverse events and their implications for subsequent immunization. Consultation with Communicable Disease Epidemiology Services at the BC Centre for Disease Control will continue to be available at the request of the Medical Health Officer for serious or unusual events.

An understanding of the basic mechanisms by which adverse events following immunizations occur will aid in the timely and accurate management of these adverse events. Deferral of subsequent immunization because of incorrect or over cautious interpretation of an adverse event may leave an individual at greater risk from the natural disease than from continued immunization.



FORMAT

The framework used for this document corresponds to the framework of the "Adverse Event (Reaction) Following Immunization" form (HLTH 2319 Rev. 94/09). The same format and adverse event categories and descriptions are used. Each category of event includes the definition and criteria for reporting, the significance and possible cause(s), management and implications regarding the continuance, deferral or discontinuation of future immunizations. It is recommended that the *Canadian Immunization Guide*, 6th edition, 2002, The U.S. National Institute of Medicine texts: "*Adverse Events Associated with Childhood Vaccines, Evidence Bearing on Causality, 1994*" and "*Adverse Effects of Pertussis and Rubella Vaccines, 1991*" be used as a references to augment this paper.

The definitions for vaccine-associated adverse events and the temporal criteria were developed by a large group of experts at the Health Canada and World Health Organization co-sponsored workshop held in Ottawa on October 30-31, 1991. The proceedings were published in the Canada Communicable Diseases Report (CCDR) Supplement, October 1992, Vol. 18S2. Since that time the same temporal criteria and definitions have been published by Health Canada and are detailed in the Appendices of the annual national report titled Adverse Events Temporally Associated with Vaccines. BC Centre for Disease Control (BCCDC) Society, Communicable Disease Epidemiology Services uses Health Canada's criteria and definitions, as do the other provinces. In 1994, BCCDC, in consultation with the Division of Immunization at Health Canada, revised the format of the HLTH 2319 form and made the adverse event descriptions more specific. The temporal criteria was not revised.

1.0 Fever

Definition/Criteria for Reporting:

Reportable if equal to or greater than 39° C, occurring anytime within the temporal criteria for the particular vaccine, i.e. 5-30 days following MMR or 0-72 hours following DaPT/IPV, DT/IPV, Act-Hib, Td/IPV, Td, or hepatitis B.

Cause/Significance:

Fever is a common reaction following immunization. In BC in 1992, fever following immunization was reported at a rate of 54 events per 100,000 doses of vaccine distributed compared to the 1992 Canadian reported rate of 14 per 100,000 doses distributed. This difference is probably due to the commendably high rate of adverse event reporting in BC compared to other provinces. These rates were based on immunization programmes using whole-cell pertussis vaccines. While fever $\geq 40.5^{\circ}\text{C}$, has been reported rarely after administration of DaPT, fever occurs less frequently among children administered DaPT than among children administered whole-cell pertussis (2).

Fever following immunization with live vaccines (e.g. MMR) results from the lowgrade infection produced by the live viruses. Following inactivated vaccines (e.g. DaPT) the body's response to injected proteins can affect heat regulation and produce fever. Fever that does not **begin** until ≥ 24 hours after vaccination with inactivated vaccines such as Act-Hib or persists for more than 24 hours after vaccination should not be assumed to be due to the vaccine. These new or persistent fevers should be evaluated for other causes unrelated to immunization so treatment is not delayed for serious conditions such as otitis media or meningitis (3).

While fevers are usually benign, an abrupt rise in temperature is a risk factor for febrile convulsions in susceptible children. Febrile convulsions are the most common seizure disorder of childhood, but are age-dependant. They are rare prior to 9 months of age and after 5 years of age, with peak onset at 14-18 months of age. Incidence in this age group approaches 3-4%, with greater risk in those with a family history. While they 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 (4).

Management:

Antipyretics, e.g. acetaminophen (15-20 mg/kg/dose) are recommended for children who develop fever following immunization or for fever prophylaxis in children who are at increased risk for febrile seizures following immunization. Included in the last category are children with a history of febrile seizures, a history of high fever ($>39^{\circ}\text{C}$) following a previous dose of any pertussis-containing vaccine, or children with other seizure disorders. The acetaminophen may be given at intervals of 4 to 5 hours if fever persists, not to exceed five

doses in 24 hours. Tepid sponge baths, extra fluids, extra cuddling and rest will aid in fever management.

Although 20 mg/kg is higher than the dose recommended by manufacturers, it is commonly used by clinicians including those at the Hospital for Sick Children in Toronto for fever management, and will not increase the risk of toxicity when used appropriately.

Because of the lower incidence of fever and febrile convulsions associated with acellular pertussis vaccines, routine use of prophylactic acetaminophen, other than the groups mentioned above, is less justified and therefore not recommended by Communicable Disease Epidemiology Services.

Products containing acetylsalicylic acid (ASA) should **not** be given to children because of their association with Reye syndrome.

Implications:

Fever is not a contraindication to further doses of vaccine. Recurrence risk with the same vaccine is moderate. Fever occurs more frequently with increasing doses of DaPT (5). Acetaminophen should be given in appropriate doses with subsequent vaccinations of the same type to treat fevers if they occur.

2.0 Local Reaction at Injection Site

2.1 Minor

Definition/Criteria for reporting:

Redness and swelling at the injection site which is at least 5 cm in diameter and begins within 48 hours of immunization. Smaller reactions may also be reported if they are painful and persist for at least four days or are felt to be clinically significant by the reporter.

Cause/Significance:

The injection of foreign material into the tissues and irritation of the tissues by the process of injection can produce an inflammatory response.

Whole-cell pertussis vaccines were discontinued in BC in the summer of 1997. Local reactions associated with the primary series of whole-cell DTP were due primarily to the whole-cell pertussis component of the vaccine. These reactions were more common at older ages, with up to 70% of children receiving a booster dose of DTP at 4 to 6 years of age developing local redness and/or swelling \geq 5 cm in diameter. Administering acellular pertussis vaccine for the fifth dose results in much lower rates of local reactions (6). Large local reactions at this age may also be associated with the diphtheria component of the vaccine (7). Because local reactions are more common and severe with increasing age, persons \geq 7 years of age are not given pertussis vaccine and receive a lower dose of

diphtheria toxoid. Using acellular pertussis vaccine, local reactions are reduced by 50% or more (8)(9)(10).

Rabies vaccine (human diploid cell vaccine) often results in local reactions such as pain, erythema, swelling or itching at the injection site. They may occur in 30% to 74% of recipients.

Management:

Cold compresses and acetaminophen, if required. Avoid pressure on the injection site. Products containing acetylsalicylic acid (ASA) should **not** be given to children because of their association with Reye syndrome.

Implications:

Not a contraindication to further doses of vaccine. Recurrence risk with same vaccine is moderate, and declines with the length of interval between doses.

2.2 Major (Arthus-reaction)

Definition/Criteria for Reporting:

A large, localized reaction characterized by pain, swelling, induration and edema. It usually begins 2 to 12 hours following immunization and develops gradually over a period of hours. It must begin within 48 hours of immunization to be reportable. It may develop over several days, producing a more generalized reaction consistent with serum sickness, with symptoms such as fever and arthritis.

Cause/Significance:

The formation of immune (antigen-antibody) complexes due to the presence of a large amount of circulating antibody prior to injection of the antigen. Because antibody must be present at the time of antigen injection, it is not usually seen following the initial dose in a vaccine series. The immune complexes deposit in the walls of blood vessels, resulting in intense mobilization and leakage of white blood cells. Red blood cells also leak into the surrounding tissues. This results in massive swelling at the injection site which may involve the entire limb.

If a large local reaction occurs with the initial dose of vaccine in an infant less than 4 months of age, it is probably due to high levels of maternal antibody in the child's blood. Generalized Arthus reactions (serum sickness) are rare with modern vaccines because they contain very small amounts of antigen. These reactions were common when horse serum was widely used in vaccine production, because of the often repeated injections of large amounts of foreign protein.

Arthus reactions can occur with overly frequent boosters of tetanus toxoid because circulating antitoxin levels may be very high. Severe Arthus reactions

have been observed very occasionally following repeat doses of pneumococcal vaccine after short intervals (less than or equal to 3 years).

Management:

Cold compresses, acetaminophen and limb elevation. Most Arthus reactions resolve within one week.

Products containing acetylsalicylic acid (ASA) should **not** be given to children because of their association with Reye syndrome.

Implications:

If the reaction occurs with the initial dose in the primary infant series in a child <6 months of age, deferral of subsequent doses of the same vaccine for several months may be recommended to await decline of passive maternal antibody levels. If the child will be <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 greater than 6 months of age because circulating maternal antibody will be greatly reduced.

If an Arthus reaction occurs with a tetanus toxoid booster, future boosters may need to be spaced at longer intervals and anti-toxin levels may require monitoring to determine when boosting is needed (11). Consultation with Communicable Disease Epidemiology Services, BCCDC is recommended in these cases.

Pneumococcal vaccines should only be given once to most recipients to avoid Arthus reactions. This applies even to those who have received the 14-valent vaccine in the past (8). There are exceptions including asplenic persons, persons with renal problems and persons with HIV in whom a one-only revaccination is recommended after the initial immunization; immunity wanes with time in these groups, and they have a significant risk of serious consequences from pneumococcal infection. (*Refer to Canadian Immunization Guide for details on revaccination and to Pneumococcal vaccine in the CD Immunization Manual*).

If elderly patients cannot recall having received the pneumococcal vaccine in the past and there is no record of immunization, the vaccine can be given; even if it represents a repeat dose, it will likely have been more than three years since the previous dose.

2.3 Infected abscess

Definition/Criteria for Reporting Infected abscess:

Existence of swelling at the vaccination site with one or both of:

- i) purulence and inflammatory signs, usually well demarcated;
- ii) positive gram stain or culture

2.4 Sterile abscess:

Sterile abscess/nodule:

A nodule occurring at the vaccination site **without** evidence of bacterial infection as defined in i) and ii) above. Reportable if persists for >1 month, is >2.5 cm in diameter and/or drainage is evident.

Cause/Significance:

Nodules are mainly associated with aluminum-adsorbed vaccines, particularly if the dose is deposited subcutaneously rather than intramuscularly as a result of an error in injection technique.

Contamination of multidose vials (re-entering vial with a used needle, improper cleaning or improper storage) can result in infection and abscess formation.

Sterile nodules can take up to 1 year or more to resolve, and rarely are permanent. Sterile abscesses/nodules are the tenth most frequently reported vaccine-related adverse events in Canada. The 1992 reported rate in Canada was 0.8/100,000 vaccine doses distributed and 0.5/100,000 vaccine doses distributed in BC

BCG vaccination commonly results in skin ulceration and/or keloids at the site of immunization.

Management:

Analgesics, e.g. acetaminophen, ice to injection site, incision and drainage of infected abscess. Products containing acetylsalicylic acid (ASA) should **not** be given to children because of their association with Reye syndrome.

Implications:

No deferral of subsequent vaccines is necessary. Use an alternate site for the next dose. Use the correct length of needle for I.M. injections and ensure sterile technique.

3.0 Systemic Reactions

3.1 Adenopathy

Definition/Criteria for Reporting:

Enlargement of at least one lymph node, ≥ 1.5 cm in diameter, or a draining sinus over a lymph node.

Cause/Significance:

Live vaccines produce a low-grade infection which can include adenopathy. Following BCG, which can cause local ulceration at the site of immunization, lymphadenitis may occur. 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.

Although adenopathy can commonly occur following immunization with live agents, it is only when it becomes severe, as defined above, that it is considered an adverse event. Severe adenopathy is almost exclusively caused by BCG and is generally seen 2 to 6 months following the injection on the same side as the vaccination.

Management:

For suppurative lymphadenitis associated with BCG immunization, treatment with antibiotics such as isoniazid (INH) may be required. The decision to treat such cases may be made by a private physician or by referral to the Division of Tuberculosis Control, BCCDC. Lymphadenitis associated with other injection-site infections may also require antibiotic treatment.

Implications:

Continue with further immunizations at a different injection site.

3.2 Allergic Reaction

Definition/Criteria for Reporting:

An immune complex mediated reaction characterized by one or more of the following:

- i) skin manifestations (hives),
- ii) bronchospasm (wheezing),
- iii) local or generalized edema

To be reportable, it must occur within 72 hours of immunization. Most instances begin within 12 hours of immunization.

Cause/Significance:

An allergic reaction is an acquired hypersensitivity to an antigen that does not normally produce such a reaction. It is essentially a disorder of the immune system, where antigen-antibody complexes stimulate the release of chemicals, such as histamine, which produce overt signs and symptoms of hypersensitivity. It 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. Therefore, allergic reactions are rarely seen following the first dose in a vaccine series, but may be seen with the second dose or any subsequent dose.

Allergic reactions are reported at a rate of 2.5-3.0/100,000 doses of all vaccine distributed in BC. It has been estimated by experts that the true rate may be ten times higher due to underreporting.

Management:

Antihistamines such as Benadryl® to control hives and itching. For severe reactions, epinephrine may be required. Bronchodilators such as Ventolin® or other medications may be needed if wheezing or respiratory symptoms occur.

Implications:

1. Hives occurring from 0 to 2 hours after immunization: (cause and effect likely):

If **generalized** hives occur within 2 hours of immunization, refer to an allergist for assessment prior to further doses of the same vaccine or its components.

2. Hives occurring ≥ 2 hours of immunization: (cause and effect link less likely):

Continue with subsequent immunizations but observe the patient for one to two hours after the next immunization with the same antigens. In such cases, the Medical Health Officer may wish to recommend that the next dose of vaccine be given in a physician's office or in an emergency room. If there is no reaction with the subsequent dose, further immunization can be given in the routine setting. If a hive-like rash reappears with the next dose of the same vaccine, particularly a generalized rash appearing within 48 hours of vaccination dose, refer to an allergist for assessment prior to further doses of the same vaccine or its components.

3. **Hives occurring ≥ 48 hours after immunization: (cause and effect link unlikely):**

Subsequent immunizations can be given under normal conditions. Other potential causes of the hives should be considered, particularly if there was no reaction at the injection site.

3.3 Rash

Refer to

Definition/Criteria for Reporting:

A generalized rash occurring within 7 days of immunization for all vaccines except MMR; rashes occurring 5-30 days following MMR immunization meet the temporal criteria for reporting. There are two categories for reporting; one for transient rashes (lasting 1 to 3 days) and one for more persistent rashes (lasting longer than 4 days). Any rash requiring hospitalization or treatment in an emergency room is reportable if it meets the temporal criteria. **Note:** A rash diagnosed as hives should be reported as an allergic reaction (*refer to Section 3.2*).

Cause/Significance:

Most rashes occurring in children are caused by intercurrent viral illness, even those temporally related to immunization. The exception are rashes related to MMR vaccine, which produces 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 to 10 days after vaccination. It is much less common following the second dose of MMR. Petechial rashes are rare and warrant investigation for thrombocytopenia, a rare complication of MMR vaccination.

Rashes that are macular or papular appearing hours or days after a dose of DPT are frequently the manifestation of antigen-antibody reactions of little consequence (3). 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.

Management:

Good skin care, antihistamines for itching, mitts on children to prevent scratching.

Implications:

Rashes other than petechial rashes are not a contraindication to further doses of a vaccine. Petechial rashes should be referred for consultation to determine if further doses of a vaccine can be given. (*For management of hives, refer to Section 3.2.*)

3.4 Anaphylaxis

Refer to Section V - Anaphylaxis

3.5 Hypotonic-Hyporesponsive (HH) Episodes

Definition/Criteria for Reporting:

A HH episode can occur following immunization with any whole-cell pertussis-containing vaccine and most commonly are reported in children under 2 years of age. The incidence of HH episode using acellular pertussis vaccine is similar to the incidence when diphtheria and tetanus alone are used (10). It is the most misdiagnosed and thereby misreported of all vaccine-associated adverse events.

A HH episode is an unusual reaction consisting of an acute diminution in sensory awareness or loss of consciousness accompanied by pallor and muscle hypotonicity in infants receiving pertussis-containing vaccines. 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, although it may be as long as 36 hours before the child returns to normal (16). To meet the criteria for reporting, the HH episode must occur between 0 and 72 hours following vaccination and must be diagnosed by a physician.

Cause/Significance:

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 (16). They are not associated with any lasting sequelae.

Follow-up of children who have had hypotonic-hyporesponsive episodes or convulsions has demonstrated complete recovery without persistent neurologic or developmental defects (8).

The 1992 Canadian rate for reported HH episodes was 2.4/100,000 doses of whole-cell pertussis vaccine distributed. The B.C. rate using whole-cell pertussis was 3.2/100,000 doses distributed. Rates reported in the literature, based on passive and active surveillance, range from 3.5-291/100,000 injections using whole-cell pertussis vaccine. HH episodes have been reported rarely after administration of DaPT, and occur much less frequently among children administered DaPT than among children administered whole-cell DTP (2).

Management:

No treatment is necessary. If the HH episode does not resolve spontaneously, other underlying problems should be sought and ruled out or treated.

Implications:

In most cases a HH episode has to be marked enough to be brought to the attention and substantiated by a health care professional for it to be considered to have been significant enough to affect recommendations regarding future immunizations.

HH episode is NOT a contraindication or relative contraindication for the use of acellular pertussis vaccine. Again, because the incidence of HH episode appears similar between DaPT recipients and DT recipients, it is difficult to attribute causation of HH episodes in recipients of DaPT to the pertussis components; therefore continued immunization with all antigens is recommended. There is no deferral of acellular pertussis for children with a history of HH episodes (8).

3.6 Excessive Somnolence

Definition/Criteria for Reporting:

Prolonged sleeping with difficulty rousing in a child < 2 years of age. To meet the temporal criteria for reporting, it must occur between 0 and 72 hours following pertussis-containing immunizations.

Cause/Significance:

Unknown. It may be a response to fever and crying, a disruption of the infant's schedule, or from some other factor.

Management:

No treatment is required.

Implications:

No deferral or deletion of pertussis required for subsequent immunizations.

4.0 Neurologic Symptoms/Diagnosis

4.1 Screaming/persistent crying

Definition/Criteria for Reporting:

Inconsolable crying for at least 3 continuous hours or cry of unusual quality (high-pitched). To meet the criteria for reporting, it must occur between 0 and 72 hours following DaPT immunization.

Cause/Significance:

Screaming or persistent crying is thought to be a normal response to pain. It is a very common occurrence following immunizations. It is **not** a neurological reaction, although it has been included in this grouping on the reporting form.

Treatment:

Analgesics e.g. acetaminophen in doses of 15-20 mg/kg every 4-6 hours as needed to control the pain. Products containing acetylsalicylic acid (ASA) should **not** be given to children because of their association with Reye syndrome. Extra cuddling may help comfort the child.

Implications:

Persistent, inconsolable crying and unusual high-pitched crying after pertussis vaccination are not associated with any long-term sequelae and may simply be a pain response at the site of injection in young infants. Pertussis **should not be deleted from future immunizations** (12). Persistent crying lasting at least 3 hours has been only rarely reported after the administration of DaPT; it occurs less frequently among children administered DaPT than among children administered whole-cell pertussis (2).

4.2 Convulsion/seizure

Definition/Criteria for Reporting:

Paroxysms of generalized tonic skeletal muscle contractions and generalized clonic jerking, usually associated with decreased level of consciousness. They must be distinguished from vasovagal or fainting episodes, in which isolated muscle contractions may occur. Seizures may last for several minutes or more.

They may or may not be associated with fever. To meet the temporal criteria for reporting, they must occur within 0 to 72 hours following immunization (with the exception of MMR; the time period for which is 5 to 30 days following immunization).

Cause/Significance:

Febrile convulsions may be more likely in a susceptible child who develops high fever (*refer to Section 1.0 Fever*) following any immunization. Because DaPT is less frequently associated with moderate to high fever compared to whole cell pertussis containing vaccine, immunization with DaPT causes less febrile convulsions (2). Seizures may be one of the manifestations of acute encephalopathy but are never the sole manifestation.

The 1992 Canadian rate of reported convulsions temporally associated with immunization was 1.5/100,000 doses of all vaccines distributed and 2.9/100,000 doses of vaccine distributed for B.C. Febrile convulsions occur less frequently among children administered DaPT than among children administered whole-cell DTP (2).

Management:

A child with a history of febrile convulsions following a DPT-containing vaccine (both whole-cell and acellular pertussis) should be given acetaminophen in doses of 15-20 mg/kg prior to or at the time of subsequent DaPT immunization and every 4 hours, not to exceed five doses in 24 hours. Products containing acetylsalicylic acid (ASA) should **not** be given to children because of their association with Reye syndrome.

Implications:

There are no long-term sequelae, such as permanent brain damage, associated with uncomplicated febrile convulsions. Pertussis vaccine should not routinely be deleted from future immunizations in children with a history of febrile convulsions. However, if the febrile convulsions were multiple or prolonged (status epilepticus), there should be discussion between the parents and a physician about the parents' ability to manage future episodes should they occur.

4.3 Acute Encephalopathy

Definition/Criteria for Reporting:

Encephalopathy is a term used to describe a constellation of signs and symptoms reflecting a generalized disturbance in brain function. It should be distinguished from the term encephalitis (*refer to Section 4.4*) which is used when there are signs and symptoms of brain dysfunction with evidence of inflammation of the brain i.e. proteins and white blood cells in the cerebrospinal fluid.

For the purposes of adverse event reporting, acute encephalopathy is defined as an acute 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 fontanelle as described by a parent to a nurse rather than observed by a physician, is **not** sufficient to diagnose increased intracranial pressure. Often intense crying can cause a bulging, pulsating fontanelle.
 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.

The following clinical features alone or in combination do not qualify as evidence of an acute encephalopathy: sleepiness, irritability (fussiness), high-pitched and unusual screaming, persistent inconsolable crying, and bulging fontanelle. Seizures in themselves are not sufficient to constitute a diagnosis of encephalopathy.

The temporal criteria for reporting varies with the vaccine administered. For DaPT, DaPTP, and Td the time of onset for a reportable event is 0 to 7 days following immunization; for MMR it is 5 to 30 days following immunization and for IPV, hepatitis B and Hib vaccines it is 0 to 15 days following immunization. Please refer to the temporal criteria chart on the back of the HLTH 2319 form when deciding if an adverse event could be temporally linked to the vaccine.

Encephalopathy must be diagnosed by a physician and appropriate medical documentation, including physicians' assessments and test results, must accompany the HLTH 2319 form. All reported cases of this severe but rare adverse event are reviewed by the Advisory Committee on Causality Assessment, which is coordinated by Health Canada in Ottawa.

Cause/Significance:

The following discussion pertains to whole cell pertussis vaccines. Acellular vaccines are much less likely to cause serious adverse events. Encephalopathy is sometimes discussed in relation to whole-cell pertussis-containing vaccines. There is no biologically plausible explanation for pertussis vaccine to cause encephalopathy. The physiological reason for encephalopathy occurring with natural occurring pertussis disease is that anoxia from the cough causes encephalopathy. Since there is no cough following the receipt of the pertussis vaccine, there is no known biologically plausible reason for encephalopathy to occur following vaccination (17).

Recent epidemiological studies have indicated that DPT (whole-cell pertussis) vaccine may be associated with acute encephalopathy, albeit rarely. The largest and best of these studies is the National Childhood Encephalopathy Study (NCES), which was initiated in Britain in 1976 in response to concerns about pertussis vaccine. This large case-control study was designed to assess the risks of certain serious neurological disorders associated with immunization in early childhood and to identify factors that might cause or predispose to such



disorders. The study included 1,182 children ages 2 to 35 months with acute neurological illnesses, including encephalopathy, encephalitis and encephalomyelitis. The results of the study indicated that the attributable risk of acute encephalopathy in previously normal children in the week following DPT (whole-cell pertussis) immunization was 2.7 cases per million immunizations (95% confidence interval 0-10.5 cases per million vaccinations). This study and other evidence reviewed by the U.S. Institute of Medicine (IOM) has led to the conclusion that the available evidence is consistent with a causal relation between DPT (whole-cell pertussis) vaccine and acute encephalopathy, primarily in the first three days after vaccination, with the range of risk being 0.0 to 10.5 cases per million immunizations.

The IOM further concluded, based on NCES follow-up data, that there is evidence of an association between DPT, containing whole-cell pertussis and chronic nervous system dysfunction in children who had had a serious acute neurologic illness after vaccination with DPT containing whole-cell pertussis.

They proposed three possible explanations for this association:

1. The acute neurologic illness and subsequent chronic nervous system dysfunction might have been caused by DPT containing whole-cell pertussis.
2. DPT containing whole-cell pertussis, might trigger an acute neurologic illness and subsequent chronic nervous system dysfunction in children who have underlying brain or metabolic abnormalities. Such children might experience similar chronic dysfunction in the absence of DPT containing whole-cell pertussis vaccination, if other stimuli (e.g. fever or infection) are present.
3. DPT containing whole-cell pertussis might cause an acute neurologic illness in children who have underlying brain or metabolic abnormalities that would inevitably have led to chronic nervous system dysfunction even if the acute neurologic illness had not developed.

The IOM concluded that the NCES data does not support one of the three explanations over another, but that the balance of evidence was consistent with a causal relationship between DPT containing whole-cell pertussis and some forms of chronic nervous system disorders in children who had developed an acute neurologic disorder after receiving DPT containing whole-cell pertussis. However, they further concluded that the results were insufficient to determine whether DPT containing whole-cell pertussis increases the overall risk for chronic nervous system dysfunction in children.

In the past, encephalopathy was thought to occur after measles immunization, because it is a known complication of natural measles infection. However, encephalopathy and encephalitis have been reported at a rate of less than one case per million doses of measles vaccine administered, which is lower than the background rate of encephalitis of unknown etiology in the same age group. This

suggests that severe neurologic reactions may be only temporally rather than causally related to measles vaccination (18).

In 1992 in Canada encephalopathy following immunization was reported at a rate of 0.1/100,000 doses of all vaccines distributed. In B.C. in 1992, the rate reported was 0.06/100,000 doses of vaccine distributed. Onset of encephalopathy temporally related to DPT containing whole cell pertussis or whole-cell pertussis vaccination does not necessarily indicate that the vaccine was the cause.

Management:

Supportive therapy in hospital.

Implications:

Encephalopathy itself is not a contraindication to further vaccination, and is less likely following DaPT than DPT whole- cell vaccine. Deferral of pertussis immunization may be considered until the neurologic condition has been diagnosed or is stable. If no other cause is found and the encephalopathy meets the temporal criteria for the vaccine, refer to a paediatric neurologist and consult with Communicable Disease Epidemiology Services, BCCDC, to determine which components of the vaccine may be continued.

Deferral of pertussis immunization for children with progressive, evolving or unstable neurological conditions (such as poorly controlled convulsions, central nervous system malformations, or neurodegenerative diseases) **is no longer necessary** because of the availability of acellular pertussis vaccines. Specific data using these vaccines are not available in individuals with neurologic diseases and must await post-marketing surveillance. However, since the incidence of adverse events including fever and seizures was no different in recipients of DaPT or DT, it makes little sense to defer the pertussis component of the vaccine (8).

4.4 Meningitis/Encephalitis

Reporting:

Meningitis:

An infection or inflammation of the membranes covering the brain and spinal cord. It is characterized by severe headache, vomiting, and pain and stiffness in the neck.

Encephalitis:

An inflammatory condition of the brain characterized by headache, neck pain, fever, nausea, and vomiting. Neurologic disturbances may occur, including seizures, personality change, irritability, lethargy, paralysis, weakness, and coma. Severe inflammation with destruction of nerve tissue may result in a

seizure disorder, loss of a special sense or other permanent neurologic problem, or death. Usually, the inflammation involves the spinal cord and brain.

The temporal criteria for reporting for these conditions varies by vaccine. For DaPT/IPV, DaPT, Td/IPV, Td, Hib, hepatitis B and IPV the time of onset for reporting is 0 to 15 days following immunization. The time period following MMR immunization is 5 to 30 days. Meningitis/encephalitis must last 24 hours or more to be reportable. Please refer to the temporal criteria chart on the back of the HLTH 2319 form when deciding if an adverse event could be temporally linked to the vaccine.

Meningitis/encephalitis must be diagnosed by a physician and documentation must accompany the HLTH 2319 form. Reports of this major, severe but rare adverse event are subsequently investigated by the Advisory Committee on Causality Assessment at Health Canada.

Cause/Significance:

For mumps vaccine and other live virus vaccines, an association with meningitis has been postulated because such an association has been seen with natural mumps infection. The postulated mechanism is infection of the meninges with the vaccine virus. Such a causal relationship has been established with the Urabe strain of mumps virus (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, or with any of the other routinely used live virus vaccines.

There is no causal relationship between non-live vaccines and meningitis. Studies which have included cases of acute encephalitis and acute encephalopathy have identified a causal relationship with whole-cell DPT (*refer to Section 4.3*).

Encephalitis has occurred rarely following Yellow Fever immunization in young infants and thus this vaccine is not recommended for infants less than 4 months of age.

Management:

Supportive therapy in hospital.

Implications:

Defer further vaccines until a diagnosis is made as to the cause of the meningitis or encephalitis (*refer to Section 4.3*).

4.5 Anaesthesia/Paraesthesia

Definition/Criteria for Reporting:

Anaesthesia:

The absence of normal sensation, especially sensitivity to pain, in an area of nerve distribution.

Paraesthesia:

Numbness or a tingling feeling in an area of nerve distribution.

To be reportable, both must last 24 hours or more and must occur between 0 to 15 days following administration of DaPT/IPV, DaPT, Td, Hib, or hepatitis B vaccine or 5 to 30 days following MMR (it may occur earlier if related to injection technique). Both events must be diagnosed by a physician and supporting documentation of the diagnosis be included with the HLTH 2319 form.

Cause/Significance:

The cause of anaesthesia or paraesthesia following vaccination is often not determined. An obvious cause could be accidental injection of vaccine into a nerve, but this is ruled out in most reported cases.

There are anecdotal reports of peripheral neuropathy associated with tetanus toxoid administration that are felt to be related to immune complex formation. Rubella vaccine may be rarely associated with peripheral neuropathy.

Management:

No specific treatment. Investigation by a neurologist should be done to rule out permanent nerve damage.

Implications:

If the cause is related to injection technique, avoid the site for future injections. In most cases immunizations can continue.

4.6 Paralysis

Definition/Criteria for Reporting:

A condition characterized by the loss of muscle tone and function with or without the loss of sensation. To be reportable it must occur within 0 to 15 days following DaPT/IPV, DaPT, Td/IPV, Td, Hib, or hepatitis B immunization, and must occur within 5 to 30 days following MMR and after OPV. It must last over 24 hours and be diagnosed by a physician.

Cause/Significance:

Infection with a live virus vaccine. A causal relationship has been established only with oral polio vaccine (OPV). OPV has been associated with paralytic disease in vaccine recipients and their close contacts. Contacts can be infected because recipients excrete the virus in their stool for 3-4 weeks after

immunization, and transmission can occur with such activities as changing diapers. The greatest risk of paralysis occurs with the first dose of OPV. 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. B.C. has used IPV exclusively since June 1, 1994, but OPV is still used in several jurisdictions in North America.

Management:

Supportive therapy.

Implications:

The decision to continue immunization must be made on a case-by-case basis. All cases should be evaluated by a neurologist and reported to Communicable Disease Epidemiology Services, BCCDC.

4.7 Guillain-Barre Syndrome

Definition/Criteria for Reporting:

Guillain-Barre syndrome (GBS) is also called acute febrile polyneuritis or acute idiopathic polyneuritis. It is a subacute, usually symmetrical ascending paralysis, with associated sensory disturbances. It occurs due to segmental demyelination of peripheral nerves that is associated with lymphocytic infiltration. It can appear as a sequelae to a variety of infections after an interval of 1 to 6 weeks and has been reported to occur sporadically in temporal association with a number of vaccines.

To be reportable it must occur within 0 to 31 days after immunization for all vaccines and must be diagnosed by a physician. However, GBS beginning less than 4 to 5 days following immunization is not generally related to vaccination because the time interval is too short. It takes longer than 4 to 5 days following antigen exposure for GBS to develop (17). Health Canada requires documentation and additional reports substantiating the diagnosis.

Cause/Significance:

Unknown. It is postulated that the injection of an antigen might induce in the susceptible host an autoimmune response with activation of T cells directed against myelin proteins. It is thought that this might occur if there are sequence similarities of proteins in the vaccine to host proteins such as those of myelin.

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



U.S. national surveillance for GBS was established in 1976 in association with the National Immunization Program against swine influenza. A definitive study of approximately 1,300 reported cases of GBS undertaken by the Centers for Disease Control (CDC) identified the risk as 4.9 to 5.9/million up to 8 weeks after vaccination with swine influenza vaccine (11). No other influenza vaccines have been associated with an increased risk of GBS.

Management:

Supportive care. May require ventilatory support.

Implications:

If GBS occurs in temporal relationship to vaccination and other potential causes have been ruled out, the recipient should generally not receive further doses of the same antigen, as they may have a greater risk of GBS than other persons undergoing immunization. This should be assessed on a case-by-case basis after consultation with Communicable Disease Epidemiology Services, BCCDC. There is no contraindication to immunization in persons with a previous history of GBS unrelated to vaccination.

4.8 Subacute Sclerosing Panencephalitis (SSPE)

Definition/Criteria for Reporting:

A rare, degenerative central nervous system disease occurring as a late complication of measles (can be up to 10 years later) and 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 there is no treatment. For vaccine-associated cases there is no temporal criterion for reporting; as with cases following infection, the occurrence would be years following immunization. SSPE requires a physician diagnosis.



Cause/Significance:

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. Identification of the cause of SSPE as wild-type or vaccine-strain measles virus has not been possible.

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 (about 1/1,000,000 persons vaccinated versus 1/100,000 cases of measles) (10). There has been a dramatic decline in the incidence of SSPE since the introduction of widespread measles immunization.

Management:

No effective therapy is known.

Implications:

Anyone with a diagnosis of SSPE should **not** receive measles immunization. However, because SSPE occurs many years after infection, it would not likely affect routine immunization schedules.

5.0 Miscellaneous

5.1 Parotitis

Definition/Criteria for Reporting:

Inflammation or infection of one or both of the parotid salivary glands. These glands lie at the side of the face just below and in front of the external ear. Temporal criteria for reporting is 5 to 30 days following MMR, although it is usually seen 10 to 14 days after vaccination. It must be diagnosed by a physician.

Cause/Significance:

Parotitis is a common manifestation of mumps infection. Since the mumps vaccine is a live virus vaccine, low-grade infection following immunization can occasionally produce the same manifestation. It is transient and self-limiting.

Management:

Antipyretics/analgesics, as required, and adequate fluid intake.

Implications:

Continue with further doses of MMR if required.

5.2 Orchitis

Definition/Criteria for Reporting:

Inflammation of one or both of the testes, characterized by swelling and pain. It must be diagnosed by a physician.

Cause/Significance:

Usually associated with mumps vaccination. Since the mumps vaccine is a live virus vaccine, orchitis can occur following immunization as it can with natural infection.

Management:

Support and elevation of the scrotum, cold packs, and analgesics.

Implications:

Continue with future doses of MMR vaccine if required.

5.3 Thrombocytopenia

Definition/Criteria for Reporting:

An abnormal haematologic condition in which the number of platelets is reduced to less than 150,000/mm (normal platelet counts are 150-450,000/mm). Thrombocytopenia can occur in persons of all ages. Approximately 70 percent 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. It must occur within 31 days following vaccination to be considered temporally associated and reportable as an adverse event. It must be diagnosed by a physician. Laboratory reports should accompany the HLTH 2319.

Cause/Significance:

The cause of vaccine-associated thrombocytopenia is unknown. It is postulated that live virus in vaccine suppresses the bone marrow and hence production of platelets.

Thrombocytopenia is a known complication of measles vaccination, occurring in 1 per 30,000 to 40,000 children following vaccination with the first dose of measles vaccine. It may also occur following the second dose, even in persons who did not have a reaction after the first dose. However, thrombocytopenia after the first dose may increase the risk for recurrence with the second dose.

Management:

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. Transfusion of platelets may be required.

Implications:

Children with a history of thrombocytopenia may be at increased risk for developing clinically significant 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. The exception is persons who develop thrombocytopenia temporally related to their first dose of MMR; they should **not** receive further MMR vaccine.

5.4 Severe Vomiting/Diarrhea

Definition/Criteria for Reporting:

At least 3 episodes of either vomiting or diarrhea must occur within a 24 hour period to meet the criteria for reporting. The vomiting and/or diarrhea must be severe, i.e. projectile vomiting or explosive, watery diarrhea.

The temporal criteria for reporting is vaccine-dependent; for DaPT/IPV, DaPT, Td/IPV, and Td vomiting/diarrhea must occur within 0 to 72 hours following immunization; for MMR, within 5 to 30 days and for Hib and hepatitis B vaccine within 0 to 7 days.

Cause/Significance:

Not specifically related to a particular vaccine. It could be a manifestation of low-grade infection after immunization with live vaccines or a physiological response to a foreign substance.

Nausea and vomiting have been particularly associated with oral typhoid vaccine, human diploid cell rabies vaccine (HDCV), and Japanese B encephalitis vaccine. Following oral typhoid vaccine, nausea and vomiting is the most commonly reported adverse event.

Management:

Symptomatic treatment to prevent dehydration and electrolyte imbalance.

Implications:

Continue with further doses of vaccine, as required, once patient recovered.

5.5 Arthralgia/Arthritis

Definition/Criteria for Reporting:

Arthralgia: Joint pain.

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. The arthralgia or arthritis must last at least 24 hours to be reportable. Temporal criteria for reporting is 5 to 30 days following MMR vaccination. Arthralgia/arthritis has only been associated with rubella immunization.

Cause/Significance:

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 felt to occur with vaccine-associated arthritis.



The exact pathophysiology is unknown. It may be due to direct viral infection of the synovial membrane or to the deposition of immune complexes. Acute arthritis or arthralgia has been shown to occur 7-21 days post immunization in 13% to 15% of adolescent and adult women immunized with the RA 27/3 strain of rubella (the strain in use in the MMR vaccine currently available in Canada). It can also occur in children and adolescent and adult men, but at much lower rates. Joint symptoms are almost always transient, but chronic arthritis has occurred rarely.

There have been a limited number of case reports of rheumatoid arthritis following hepatitis B vaccination in Canada. There were five reports of swollen joints following immunization during the first year (1992-3) of the grade six hepatitis B programme in BC which were temporally but not causally related to the vaccine.

Management:

Analgesics/anti-inflammatories 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.

Implications:

If the arthritis/arthralgia resolves, further doses of rubella-containing vaccine can be given, if required. Since the arthritis is likely related to seroconversion, the risk following a second dose is lower than following the first dose. Cases of persistent arthritis require consultation with Communicable Disease Epidemiology Services, BCCDC, to determine if further doses of vaccine should be given.

5.6 Other Severe or Unusual Events

Definition/Criteria for Reporting:

Other severe and unusual events occurring within 4 weeks of immunization and not covered under the existing categories described on the HLTH 2319 should be reported in this category. It may also include events occurring later if there is evidence of a link to vaccination. These must be clinically intriguing or epidemiologically interesting and usually require medical intervention to meet the criteria for reporting. Health Canada requires additional documentation of the unusual event. The “comments” section of the HLTH 2319 form is provided for the detailed documentation of such adverse events.

Any death of a vaccine recipient temporally linked (within 4 weeks) to immunization where no other clear cause of death can be established should be reported. Autopsy reports must accompany the HLTH 2319 form.



Cause/Significance:

Depends on the reported event. The cause may not be known. An example of a severe event not listed on the form is disseminated infection occurring within 1 to 12 months after BCG vaccination and confirmed by isolation of *Mycobacterium bovis* BCG- strain.

Another example is osteitis/osteomyelitis, an inflammation or infection of the bone, either due to BCG immunization (occurring within 8 to 16 months after immunization) or caused by other bacterial infection.

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. An example is the concern following reports of sudden infant death syndrome (SIDS) cases occurring in temporal association with whole-cell DPT vaccination.

An extensive review of available studies has indicated that there is no causal relation between whole-cell DPT vaccination and SIDS. Rates temporally related to immunization are no different than background rates (16).

Management:

Treatment is specific for each event.

Implications:

The severity of the adverse event and the plausability of a causal association with vaccination will determine whether further doses of the implicated vaccine will be continued. For these unusual cases, consultation with Communicable Disease Epidemiology Services, BCCDC, is recommended.



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