Vaccine	Age
	18 years of age and older
	OR
HA-HB	H 3 or 4 dose schedule
Inf	[illegible]
Typh-I	J 1 dose + booster doses if at ongoing risk
	OR
Typh-O	J 4 dose schedule + booster doses if at ongoing risk
BCG	K 1 dose
Rab	L 3 dose schedule + booster doses if required

* Refer to *Table 8* for abbreviations and brand names for vaccines.

A. ***Haemophilus influenzae* type b**: adults with increased risk of invasive Hib disease – 1 dose regardless of prior history of Hib vaccination and at least 1 year after any previous dose.
B. **Inactivated polio**: 1 booster dose for adults at increased risk of exposure to polio.
C. **Measles-mumps-rubella**: adults born in 1970 or later - 1 dose, except - travellers to destinations outside of North America, health care workers, students in post-secondary educational settings, and military personnel - 2 doses, at least 4 weeks apart. Adults born before 1970 can be assumed to have acquired natural immunity to measles and mumps and do not need MMR vaccination except - non-immune military personnel or health care workers (2 doses, at least 4 weeks apart), non-immune travellers (1 dose), non-immune students in post-secondary educational settings (consider 1 dose). Rubella-susceptible adults, regardless of age – 1 dose.
D. **Pneumococcal polysaccharide 23-valent**: adults at high risk of invasive pneumococcal disease - 1 dose. Give 1 booster dose if 5 years from first vaccination with Pneu-P-23.

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E. **Meningococcal conjugate quadrivalent**: adults at high risk of invasive meningococcal disease - 2 doses, 8 weeks apart. Re-immunize every 5 years.
F. **Hepatitis A**: adults in high risk groups - 2 doses, 6-36 months apart (depending on vaccine product used).
G. **Hepatitis B**: adults in high risk groups - 3 or 4 dose schedule (depending on vaccine product used). Higher dose of monovalent HB vaccine recommended for certain immune compromising or chronic conditions.
H. **Hepatitis A-hepatitis B**: combined vaccine preferred if both HA and standard dosage HB vaccines are recommended - 3 or 4 dose schedule
I. **Influenza**: adults at high risk of influenza-related complications - 1 dose annually.
J. **Typhoid**: adults with ongoing or intimate exposure to a chronic carrier of *Salmonella typhi* - 1 dose injectable typhoid vaccine or 4 doses oral typhoid vaccine; re-immunization recommended if at continuing risk.
K. **Bacille Calmette-Guérin**: 1 dose may be considered in exceptional circumstances for adults at high risk of repeated exposure to tuberculosis.
L. **Rabies**: adults at high risk of close contact with rabid animals - 3 doses for pre-exposure immunization. Periodic serology testing and booster doses (if required) for those at continuing high risk.

TABLE 8: ABBREVIATIONS AND BRAND NAMES OF VACCINES USED IN IMMUNIZATION SCHEDULES

Abbreviation	Vaccine	Brand names*
BCG	Bacillus Calmette-Guérin	BCG Vaccine
DTaP-HB-IPV-Hib	Diphtheria, tetanus, acellular pertussis, hepatitis B, inactivated polio, *Haemophilus influenzae* type b (pediatric)	INFANRIX hexa™
DTaP-IPV	Diphtheria, tetanus, acellular pertussis, inactivated polio (pediatric)	QUADRACEL®
DTaP-IPV-Hib	Diphtheria, tetanus, acellular pertussis, inactivated polio, *Haemophilus influenzae* type b (pediatric)	PEDIACEL®
HA	Hepatitis A	AVAXIM® AVAXIM®– Pediatric HAVRIX® 1440 HAVRIX® 720 Junior VAQTA®
HAHB	Hepatitis A, hepatitis B	TWINRIX® TWINRIX® Junior
HB	Hepatitis B	ENGERIX®-B RECOMBIVAX HB®
Hib	*Haemophilus influenzae* type b	Act-HIB®
HPV2	Human papillomavirus	CERVARIX™
HPV4	Human papillomavirus	GARDASIL®

Abbreviation	Vaccine	Brand names*
Inf	Influenza	AGRIFLU® FLUAD® FLUMIST® FLUVIRAL® FLUZONE® INFLUVAC® INTANZA® VAXIGRIP®
IPV	Polio (inactivated)	IMOVAX® Polio
MenC-ACYW-135	Meningococcal conjugate quadrivalent	Menactra® Menveo™
MenC-C	Meningococcal conjugate monovalent	Meningitec® Menjugate® NeisVac-C®
MMR	Measles, mumps, rubella	M-M-R® II PRIORIX®
MMRV	Measles, mumps, rubella, varicella	PRIORIX-TETRA®
Pneu-C-13	Pneumococcal conjugate 13-valent	Prevnar® 13
Pneu-P-23	Pneumococcal polysaccharide 23-valent	PNEUMOVAX® 23 PNEUMO 23®
Rab	Rabies	IMOVAX® Rabies RabAvert®
Rot-1	Rotavirus monovalent	ROTARIX™
Rot-5	Rotavirus pentavalent	RotaTeq®
Td	Tetanus, diphtheria (reduced)	Td ADSORBED
Tdap	Tetanus, diphtheria (reduced), acellular pertussis (reduced)	ADACEL® BOOSTRIX®

Abbreviation	Vaccine	Brand names*
Tdap-IPV	Tetanus, diphtheria (reduced), acellular pertussis (reduced), inactivated polio	ADACEL®-POLIO BOOSTRIX®-POLIO
Td-IPV	Tetanus, diphtheria (reduced), inactivated polio	Td POLIO ADSORBED
Typh-I	Typhoid (injection)	TYPHIM Vi® TYPHERIX®
Typh-O	Typhoid (oral)	Vivotif®
Var	Varicella (chickenpox)	VARILRIX® VARIVAX® III
Zos	Herpes zoster (shingles)	ZOSTAVAX®

* Refer to vaccine-specific chapters in Part 4 for brand-specific recommendations.

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PART 1

BASIC IMMUNOLOGY AND VACCINOLOGY

Immunology is the study of the structure and function of the immune system. *Vaccinology* is the science of vaccine development and how the immune system responds to vaccines, but also includes ongoing evaluation of immunization programs and vaccine safety and effectiveness, as well as surveillance of the epidemiology of vaccine-preventable diseases. This chapter provides a brief overview of some of the main concepts of immunology and vaccinology as they relate to immunization. A detailed review of immunology and vaccinology is beyond the scope of the *Canadian Immunization Guide*.

HUMAN IMMUNE SYSTEM

COMPONENT OF THE IMMUNE SYSTEM

An *antigen* is a substance that the body recognizes as foreign and that triggers immune responses. The terms *immunogen* and *antigen* are often used interchangeably.

Antibodies are proteins that are produced in response to antigens introduced into the body. Antibodies protect the body from disease by:

- binding to the surface of the antigen to block its biological activity (*neutralization*)
- binding or coating (*opsonisation*) of the antigen to make it more susceptible to destruction and clearance by phagocytes (*phagocytosis*)
- opsonisation of special receptors on various cells, allowing them to recognise and respond to the antigen
- activation of the complement system to cause disintegration (*lysis*) of the pathogen and to enhance phagocytosis.

IMMUNE REPONSES

Immunity is the ability of the human body to protect itself from infectious diseases. The human immune system is able to react to an enormous number and variety of foreign antigens and provides immunity through two complementary types of responses:

- *Innate immunity* is the body's initial defence mechanism that is not specific to particular antigens and comes into play immediately or within hours of a pathogen's entry into the body. Innate immunity is made up of physical barriers (skin and mucous membranes), physiologic defences (temperature, low pH and chemical mediators), human microbiome (aggregate of microorganisms that reside on and in the human body; these microorganisms may protect from potential pathogens by blocking binding sites and competing for nutrients), as well as phagocytic and humoral inflammatory responses. Innate immunity:
    - does not depend upon previous exposure to the pathogen
    - does not produce immunologic memory
    - does not improve with repeated exposure to the pathogen.

- *Adaptive immunity* is the body's second level of defence, which develops as a result of infection with a pathogen or following immunization. It defends against a specific pathogen and takes several days to become protective. Adaptive immunity:
    - has the capacity for immunologic memory
    - provides long-term immunity which may persist for a lifetime but may wane over time
    - increases in strength and effectiveness each time it encounters a specific pathogen or antigen.

The cells of the adaptive immune system include specialized white blood cells: T cells (T lymphocytes) and B cells (B lymphocytes), which provide *cell-mediated immunity* and *antibody-mediated immunity*, respectively:

- *Cell-mediated immunity* provides protection through activation of specialized T cells to destroy pathogens or to induce the death of cells displaying the foreign antigen on their surface, and stimulation of further immune response.
- *Antibody-mediated (humoral) immunity* is mediated by B cells. The terms *antibody* and *immunoglobulin (Ig)* are often used interchangeably. There are five types of antibodies: IgA, IgD, IgE, IgG and IgM.

Immunologic memory is the immune system's ability to remember its experience with an infectious agent, leading to effective and rapid immune response upon subsequent exposure to the same or similar infectious agents. Development of immunologic memory requires participation of both B and T cells; memory B cell development is dependent on the presentation of antigens by T cells.

IMMUNIZING AGENTS

Immunization refers to the process by which a person becomes protected against a disease with immunizing agents. Immunizing agents are classified as active or passive, depending on the process by which they confer immunity; prevention of disease through the use of immunizing agents is called *immunoprophylaxis*. *Active immunization* is the production of antibodies against a specific agent after exposure to the antigen through vaccination. Active immunizing agents are typically referred to as vaccines. Refer to Part 4 for information on active vaccines. *Passive immunization* involves the transfer of pre-formed antibodies, generally from one person to another or from an animal product, to provide temporary protection, since transferred antibody degrades over time. It can occur by transplacental transfer of maternal antibodies to the developing foetus, or it can be provided by administration of a passive immunizing agent prepared from the serum of immune individuals or animals. Refer to Passive Immunizing Agents in Part 5 for information on passive immunizing agents.

ACTIVE VACCINES

Vaccines are complex biologic products designed to induce a protective immune response effectively and safely. An ideal vaccine is safe with minimal adverse effects, and effective in providing lifelong protection against disease after a single dose that can be administered at birth. Also ideally, it would be inexpensive, stable during shipment and storage, and easy to administer. Some vaccines come closer to fulfilling these criteria than others. Although each vaccine has its own benefits and risks, and indications and contraindications, all vaccines offer protection against the disease for which they were created.

In addition to the active component (the antigen), which induces the immune response, vaccines may contain additional ingredients such as preservatives, additives, adjuvants and traces of other substances necessary in the production of the vaccine. Vaccine antigens include: inactivated (killed) or attenuated (weakened) live organisms; products secreted by organisms that are modified to remove their pathogenic effects (e.g., tetanus toxoid); and components of the organism, some of which some are made in the laboratory through recombinant technology.

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Vaccines are classified according to the type of antigen they contain (refer to Table 1). Most often they are categorized in two groups - live attenuated vaccines and inactivated vaccines:

- *Live attenuated vaccines* contain whole, weakened bacteria or viruses. Since the agent replicates within the vaccine recipient, the stimulus to the immune system more closely resembles that associated with natural infection, resulting in longer lasting and broader immunity than can be achieved with other vaccine types. Because of the strong immunogenic response, live attenuated vaccines, except those administered orally, typically produce immunity in most recipients with one dose; however, a second dose helps to make sure that almost everyone is protected, because some individuals may not respond to the first dose. Live vaccines require careful storage and handling to avoid inadvertent inactivation and are, in general, contraindicated for pregnant women (because of the theoretical risk of effects on the foetus) and for people who are immunocompromised (because of the risk of disease being caused by the live vaccine strains).

- *Inactivated vaccines* contain whole or part of (fractional) killed bacteria or viruses and cannot cause the disease it is designed to prevent, even in an immunocompromised person. Fractional inactivated vaccines can be protein or polysaccharide-based. Antigens of protein-based vaccines include *toxoids* (inactivated bacterial toxin), *subunit* and *split-virus* products.

    - *Subunit* vaccines are highly purified products containing surface antigen only, with most (if not all), of the internal viral or bacterial components removed. Some subunit vaccines are synthesized using *recombinant* technology (e.g. hepatitis B vaccine). Subunit vaccines have excellent safety profiles and are used in a variety of combination products.
    - *Split-virus* vaccines are treated to disrupt the integrity of the virus but contain essentially all viral structural proteins and components.

Polysaccharide vaccines are composed of bacterial capsule and are less immunogenic compared to other vaccines, particularly in children younger than two years of age. However, polysaccharides may be conjugated (chemically joined or linked) to a carrier protein (a protein that is easily recognized by the immune system, such as diphtheria or tetanus) to produce conjugate polysaccharide vaccines that have improved functional activity and are highly immunogenic in young children.

Because the immune response to inactivated vaccines may be less than that induced by live organisms, inactivated vaccines often require multiple doses: the first dose *primes* the immune system and a protective immune response develops after the second or third dose. These initial doses are called *primary vaccination* or *the primary series*. Because protection following primary vaccination may diminish over time, periodic supplemental doses (*booster doses*) may be required to increase or boost antibody levels.

Table 1: Live attenuated vaccines and inactivated vaccines

Live attenuated vaccines
Live attenuated bacterial vaccines
• BCG vaccine • Typhoid vaccine (oral formulation)
Live attenuated viral vaccines
• Live attenuated influenza vaccine (intranasal formulation) • Measles-mumps-rubella containing vaccines • Rotavirus vaccines • Varicella-containing vaccines, including herpes zoster vaccine • Yellow fever vaccine
Inactivated vaccines
Whole inactivated vaccines
• Viruses (e.g., polio, hepatitis A, rabies vaccines) • Bacteria (e.g., cholera vaccine)
Fractional inactivated vaccines
• Protein-based o Toxoid (e.g., diphtheria toxoid, tetanus toxoid) o Subunit (e.g., hepatitis B, acellular pertussis, some influenza vaccines) o Split-virus (e.g., some influenza vaccines) • Polysaccharide-based o Pure polysaccharide (e.g., pneumococcal polysaccharide, parenteral typhoid vaccine) o Conjugate polysaccharide (e.g., pneumococcal conjugate, meningococcal conjugate, *Haemophilus influenzae* type b [Hib] vaccines) • Virus-like particle (e.g., human papillomavirus [HPV])

Adjuvants

An adjuvant is a substance that is added to a vaccine to enhance the immune response and to extend the duration of B and T cell activation. An adjuvant allows the reduction of the amount of antigen per dose or the total number of doses needed to achieve immunity and helps to improve the immune response in individuals with some degree of immune suppression (e.g., the elderly). The adjuvants used in vaccines currently marketed in Canada are:

- aluminum salts (aluminum hydroxide, aluminum phosphate, or aluminum hydroxyphosphate sulfate)
- AS04 (3-O-desacyl-4'-monophosphoryl lipid A adsorbed onto aluminum [as hydroxide salt])
- MF59C.1 (oil-in-water emulsion composed of squalene as the oil phase, stabilised with the surfactants polysorbate 80 and sorbitan trioleate, in citrate buffer).

Refer to Contents of immunizing agents available for use in Canada in Part 1 for a list of product specific adjuvants.

Preservatives
Chemicals (e.g., thimerosal, phenol, 2-phenoxyethanol) may be added to vaccines to prevent serious secondary infections as a result of bacterial or fungal contamination of the vaccine. Most vaccines available for use in Canada do not contain thimerosal.

Refer to Contents of Immunizing Agents Available for Use in Canada in Part 1 for a list of product specific preservatives.

Additives
Additives are substances that may be added to vaccines to:

- support the growth or purification of specific antigens or the inactivation of toxins, or both. They include: antibiotics added to prevent contamination during viral cell culture; substances needed for the growth of viruses, such as egg or yeast proteins, glycerol, serum, amino acids and enzymes; and formaldehyde, used to inactivate viruses and protein toxins. Most of these reagents are removed in subsequent manufacturing steps, but minute amounts may remain in the final product.
- support product quality or stability. Compounds may be added to vaccines for a variety of manufacture-related issues: controlling acidity (pH); stabilizing antigens through the manufacturing process, such as during freeze drying (lyophilizing); and preventing antigens from adhering to the sides of glass vials with a resultant loss in immunogenicity. Examples of such additives include potassium or sodium salts, lactose, polysorbate 20 or 80, and human serum albumin and animal proteins, such as gelatin and bovine serum albumin

Refer to Contents of Immunizing Agents Available for use in Canada in Part 1 for a list of product specific additives.

PASSIVE IMMUNIZING AGENTS – IMMUNE GLOBULINS

Passive immunization with immune globulins provides protection when vaccines for active immunization are unavailable or contraindicated, or in certain instances when unimmunized individuals have been exposed to the infectious agent and rapid protection is required (post-exposure immunoprophylaxis). Passive immunization also has a role in the management of immunocompromised people who may not be able to respond fully to vaccines or for whom live vaccines may be contraindicated. The duration of the beneficial effects provided by passive immunizing agents is relatively short and protection may be incomplete. Refer to Passive Immunizing Agents in Part 5 for additional information on passive immunizing agents.

VACCINE DEVELOPMENT

HOW VACCINE ARE DEVELOPPED

The first steps in the development of a vaccine include the identification of the microorganism or toxin that causes a significant burden of disease in the population and an understanding of the disease pathogenesis. Once the pathogen and pathogenesis are understood, research is initiated into the possibility of developing a vaccine to reduce the disease incidence, severity or both. New vaccines undergo a very rigorous development process, beginning with pre-clinical laboratory testing to ensure that the candidate vaccine produces the immune response needed to prevent disease and has no toxicities that would prevent its use in people. Clinical trials (human studies) then proceed through several phases involving progressively more study subjects. Vaccine Safety in Part 2 describes pre-clinical and clinical research throughout the vaccine life cycle and the accompanying regulatory requirements to ensure data and product quality.

HOW VACCINES WORK

Vaccines work at an individual level to protect the immunized person against the specific disease, as well as at a population level to reduce the incidence of the disease in the population, thereby reducing exposure of susceptible persons and consequent illness. Although the primary measure of effectiveness occurs at an individual level, there is also interest in decreasing or even eliminating disease at a population level.

HOW VACCINES WORK AT THE INDIVIDUAL LEVEL

The administration of a vaccine antigen triggers an inflammatory reaction that is initially mediated by the innate immune system and subsequently expands to involve the adaptive immune system through the activation of T and B cells. While the majority of vaccines provide protection through the induction of humoral immunity (primarily through B cells), some vaccines such as Bacille Calmette-Guerin (BCG) and herpes zoster act principally by inducing cell-mediated immunity (primarily though T cells).

Long-term immunity requires the persistence of antibodies, and/or the creation and maintenance of antigen-specific memory cells (*priming*), that can rapidly reactivate to produce an effective immune response upon subsequent exposure to the same or similar antigen.

MARKERS OF PROTECTION INDUCED BY VACCINATION

A *correlate* of protection is a specific immune response that is responsible for and statistically linked to protection against infection or disease. Following administration of most vaccines, prevention of infection has been shown to correlate predominantly with the production of antigen-specific antibodies. Serologic markers can be measured using enzyme-linked immunosorbent assays (ELISA), functional antibody activity such as the opsonophagocytic assay (OPA), or both. A *surrogate* of protection is a substitute immune marker, which may not be linked to protection against infection or disease. For example, serum antibodies may be produced for mucosal vaccines against rotavirus. Although serum antibodies against rotavirus serve as surrogates of protection, they are not necessarily directly protective against infection as this may require mucosal antibodies.

Immunogenicity means the vaccine's ability to induce an immune response. Vaccine-induced *seroconversion* is the development of detectable antigen-specific antibodies in the serum as a result of vaccination; *seroprotection* is a predetermined antibody level as a result of vaccination, above which the probability of infection is low. The seroprotective antibody level differs depending on the vaccine.

HOW VACINES WORK AT THE POPULATION-LEVEL

Vaccine efficacy refers to the vaccine's ability to prevent illness in people vaccinated in controlled studies. *Vaccine effectiveness* refers to the vaccine's ability to prevent illness in people vaccinated in broader settings (i.e., the "real world").

Herd Immunity refers to the immunity of a population against a specific infectious disease. The resistance of that population to the spread of an infectious disease is based on the percentage of people who are immune and the probability that those who are still susceptible will come into contact with an infected person. The proportion of the population required to be immune to reach herd immunity depends on a number of factors, the most important one being the transmissibility of the infectious agent either from a symptomatically infected person or from an asymptomatically colonized person.

The *reproduction number* (also called the basic reproductive rate) or R_0 is defined as the average number of transmissions expected from a single primary case introduced into a totally susceptible population. Diseases that are highly infectious have a high R_0 (e.g., measles) and require higher vaccine coverage to attain herd immunity than a disease with a lower R_0 (e.g., rubella, Hib).

Immunization (vaccine) coverage refers to the proportion of the population (either overall or for particular risk groups) that has been immunized against a disease. High immunization coverage is especially required for diseases that have a high reproduction number (R_0) to prevent further transmission. To stop

transmission of a given disease, there needs to be at least a specified percentage (1 minus $1/R_0$) of the population immune to the disease. For example, measles has an estimated R_0 of 15; therefore, at least 94% (1 minus 1/15 = 94%) of the population needs to be immune to prevent transmission of measles.

DETERMINANTS OF VACCINE RESPONSE IN INDIVIDUALS

The strength and duration of the immune system's response to a vaccine is determined by a number of factors as outlined in Table 2.

Table 2: Determinants of vaccine response in individuals

Vaccine type	The type of vaccine antigen and its immunogenicity directly influence the nature of the immune response that is induced to provide protection: • Live, attenuated vaccines generally induce a significantly stronger and more sustained antibody response. • Inactivated vaccines often require adjuvants to enhance antibody response, usually require multiple doses to generate high and sustained antibody responses, and induce vaccine antibodies that decline over time to below protective thresholds unless repeat exposure to the antigen reactivates immune memory. Pure polysaccharide vaccines induce limited immune response and do not induce immunologic memory.
Vaccine adjuvants and carrier proteins	• The addition of adjuvants to inactivated vaccines enhances immune response and extends the duration of B and T cell activation. • Conjugating (linking) a polysaccharide with a carrier protein (protein that is easily recognized by the immune system such as diphtheria or tetanus) leads to a significantly higher immune response.
Optimal dose of antigen	• Higher doses of inactivated antigens up to a certain threshold elicit higher antibody responses.
Interval between doses	• The recommended interval between doses allows development of successive waves of antigen-specific immune system responses without interference, as well as the maturation of memory cells
Age of vaccine recipient	• In early life, the immune system is immature, resulting in limited immune responses to vaccines. For example, children less than 2 years of age do not respond to polysaccharide vaccines. • In general, antibody responses to vaccines received early in life decline rapidly for most, but not all (e.g., hepatitis B) vaccines. • In older age, immune responses decline (*immunosenescence)* and can result in an increased incidence and severity of infectious diseases and a reduction in the strength and persistence of antibody responses to vaccines.
Pre-existent antibodies	• The immune response to vaccines received early in life may be influenced by the presence of maternal antibodies transferred across the placenta. • The immune response to live vaccines will be influenced by passively transferred antibodies, such as after blood product transfusion and immune globulins. Refer to Blood products, human immune globulin and timing of immunization in Part 1.
Status of the immune system	• Immune response to vaccines will be modified by the status of vaccine recipient's immune system. . Refer to Immunization of Immunocompromised Persons and Immunization of Persons with Chronic Diseases in Part 3.

EPIDEMIOLOGY AND IMMUNIZATION

Epidemiology provides data on the distribution and determinants of diseases. Epidemiology informs the first steps in vaccine development by describing the diseases caused by a particular pathogen in a particular population and indicating the need for vaccine development. As a vaccine is introduced into the population, epidemiology monitors the effect of the vaccine in the population by describing changes in the disease burden and the pathogens causing that disease. Epidemiology can also provide information regarding immunization coverage and vaccine safety.

Surveillance is the process of systematic collection, orderly analysis, evaluation and reporting of epidemiological data (particularly to public health officials who are in a position to take action), to inform disease control measures or policy decisions or both. Surveillance of vaccine preventable diseases, including immunization coverage and vaccine safety, is needed to:

- identify and quantify risk factors to enable appropriate control of communicable diseases.
- assist in the investigation, containment and management of vaccine preventable disease outbreaks or a signal of adverse events following immunization.
- monitor progress toward the achievement of set goals and targets in disease control programmes.
- provide up-to-date information to assist in the development of evidence-based guidelines.

Determining the *burden of disease* is important in setting immunization priorities. Burden of disease includes: the prevalence (total number of cases of a particular disease in a geographic area); the incidence (number of new cases of a particular disease in a geographic area over a specified period of time); the age or risk group that is most affected (e.g., infants, children, adults, the elderly, immunocompromised persons); the severity of the disease (e.g., as measured by time missed from work, hospitalization, complications or death); and the risk factors for disease that should be considered. These factors are particularly important when making vaccine recommendations regarding:

- groups who are susceptible to the disease and who require the direct protection of a vaccine; and
- groups who require indirect protection (herd immunity) because they may be susceptible to the disease but are not ideal target groups to receive the vaccine.

Evaluation of vaccine programs is the systematic investigation of the structure, activities, or outcomes of public health programs. It explores whether activities are implemented as planned and outcomes have occurred as intended, and why. Evaluation can help to support program implementation, and through its activities, builds on the program monitoring activities that immunization programs currently conduct in assessing whether program objectives have been met.

FUTURE OF VACCINOLOGY

Ongoing scientific advances in biotechnology, genetics and virology are providing new tools for vaccine development. This knowledge provides the basis for improving the effectiveness of existing vaccines, as well as the development of novel vaccines and vaccine delivery systems. These ongoing scientific advances in vaccine development need to be accompanied by scientific advances in epidemiological methods which can continue to inform the development and monitoring of new vaccines.

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PART 1

CONTENTS OF IMMUNIZING AGENTS AVAILABLE IN CANADA

The following tables provide a comprehensive list of contents of immunizing agents available in Canada. *Table 1* identifies all the active vaccines and *Table 2* identifies all passive immunizing agents. Vaccine providers should consult the product label, product leaflet, and/or product monograph for current product information. Manufacturers provide evidence of vaccine safety and efficacy and receive authorization for the immunizing agent only when it is used in accordance with the product monograph. Product monographs are available through Health Canada's Drug Product Database. (http://webprod5.hc-sc.gc.ca/dpd-bdpp/index-eng.jsp)

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Table 1: Types and contents of vaccines available for use in Canada

- For up-to-date, complete prescribing information consult the product leaflet or information contained within the product monographs available through Health Canada's Drug Product Database (http://webprod5.hc-sc.gc.ca/dpd-bdpp/index-eng.jsp)
- Any component in a vaccine may be a potential allergen. This table identifies most common allergens; adjuvants and preservatives may be potential allergens, but this is extremely rare.
- Information about the vaccine manufacturer/distributor is available in the Appendix of Vaccine Abbreviations

Brand name	Route	Vaccine type	Immunogen	Adjuvant	Preservative	Potential allergens	Other materials
Act-HIB®	IM	Subunit Conjugate	Hib			Tetanus toxoid carrier protein	Sodium chloride Sucrose Trometamol
ADACEL®	IM	Toxoid + Subunit	T d ap	Alum	PE		Formaldehyde Glutaraldehyde
ADACEL®-POLIO	IM	Toxoid + Subunit+ Inactivated	T d ap IPV	Alum	PE	Neomycin Polymyxin B Streptomycin	Bovine serum albumin Formaldehyde Glutaraldehyde Polysorbate 80 Water for injection
AGRIFLU®	IM	Inactivated - subunit	Inf			Egg protein Kanamycin Neomycin	Barium Calcium chloride Cetyltrimethylammonium bromide Citrates Disodium phosphate dihydrate Formaldehyde Magnesium chloride Polysorbate 80 Potassium chloride Potassium dihydrogen phosphate Sodium chloride Water for injection

Brand name	Route	Vaccine type	Immunogen	Adjuvant	Preservative	Potential allergens	Other materials
AVAXIM® **AVAXIM® Pediatric**	IM	Inactivated	HA	Alum	PE CH_2O	Neomycin	Medium 199 Hanks Polysorbate 80 Water for injection
BCG Vaccine	ID	Live attenuated	BCG			Latex in vial stopper	Disodium hydrogen phosphate Monosodium glutamate Polysorbate 80 Sodium chloride Sodium dihydrogen phosphate Water for injection
BOOSTRIX®	IM	Toxoid + Subunit	T d ap	Alum		Latex in plunger stopper of pre-filled syringe	Formaldehyde Glycine Polysorbate 80 Sodium chloride Water for injection
BOOSTRIX®-POLIO	IM	Toxoid + Subunit + Inactivated	T d ap IPV	Alum		Latex in plunger stopper of pre-filled syringe Neomycin Polymyxin B	Formaldehyde Medium 199 Sodium chloride Water for injection
CERVARIX™	IM	Recombinant	HPV	AS04		Latex in plunger stopper of pre-filled syringe	Hydrated sodium chloride Sodium dihydrogen phosphate dihydrate Water for injection
DUKORAL®	Oral	Subunit + Inactivated	Chol Ecol				Citric acid Disodium hydrogen phosphate Raspberry flavor Saccharin sodium Sodium carbonate Sodium citrate Sodium chloride Sodium dihydrogen phosphate Sodium hydrogen carbonate Water for injection

Brand name	Route	Vaccine type	Immunogen	Adjuvant	Preservative	Potential allergens	Other materials
ENGERIX®-B **ENGERIX®-B Pediatric dose**	IM	Recombinant	HB	Alum	Tm[1] PE[1]	Yeast protein Thimerosal	Disodium phosphate dihydrate Polysorbate 20 Sodium chloride Sodium dihydrogen phosphate dihydrate
FLUAD®	IM	Inactivated - subunit	Inf	MF59		Egg protein Kanamycin Neomycin	Barium Calcium chloride dihydrate Cetyltrimethylammonium bromide Disodium phosphate dihydrate Formaldehyde Magnesium chloride hexahydrate Polysorbate 80 Potassium chloride Potassium dihydrogen phosphate Sodium chloride Water for injection
FLUMIST®	IN	Live attenuated	Inf			Arginine Egg protein Gelatin Gentamicin	Dibasic potassium phosphate Monosodium glutamate Monobasic potassium phosphate Sucrose
FLUVIRAL® (2012-2013)	IM	Inactivated – split virus	Inf		Tm	Egg protein Thimerosal	Disodium hydrogen phosphate heptahydrate Formaldehyde Potassium chloride Potassium dihydrogen phosphate Sodium chloride Sodium deoxycholate Sucrose Water for injection
FLUZONE®	IM	Inactivated – split virus	Inf		Tm[1]	Egg protein Gelatin Neomycin Thimerosal[1]	Formaldehyde Gelatin Sucrose Triton® X-100

Brand name	Route	Vaccine type	Immunogen	Adjuvant	Preservative	Potential allergens	Other materials
FSME-IMMUN™	IM	Inactivated	TBE	Alum		Chick protein Egg protein Formaldehyde Gentamicin Latex in container of product Neomycin Protamine sulfate	Disodium hydrogen phosphate dihydrate Human albumin Potassium dihydrogen phosphate Sodium chloride Sucrose Water for injection
GARDASIL®	IM	Recombinant	HPV	Alum		Yeast protein	L-histidine Polysorbate 80 Sodium borate Sodium chloride Water for injection
HAVRIX® **HAVRIX® 720 JUNIOR**	IM	Inactivated	HA	Alum		Latex in plunger stopper of pre-filled syringe Neomycin	Amino acids Disodium phosphate Formaldehyde Monopotassium phosphate Polysorbate 20 Potassium chloride Sodium chloride Water for injection
IMOVAX® Polio	SC	Inactivated	IPV		PE	Neomycin Polymyxin B Streptomycin	Bovine serum Formaldehyde Medium 199 Hanks Polysorbate 80
IMOVAX® Rabies	IM	Inactivated	Rab			Neomycin Phenol red	Human albumin Water for injection
INFANRIX hexa™	IM	Toxoid + Subunit + Recombinant + Inactivated + Conjugate	D T aP HB IPV ++ (Hib)	Alum		Latex in plunger stopper of pre-filled syringe Neomycin Polymyxin B Tetanus toxoid carrier protein Yeast protein	Disodium phosphate Formaldehyde Glycine Lactose M199 Monopotassium phosphate Polysorbate 20 and 80

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Brand name	Route	Vaccine type	Immunity	Adjuvant	Preservative	Potential allergens	Other materials
							Potassium chloride Sodium chloride Water for injection
INFLUVAC®	IM	Inactivated - subunit	Inf			Chick protein Egg protein Gentamicin	Calcium chloride dihydrate Cetyltrimethylammonium bromide Disodium phosphate dihydrate Formaldehyde Magnesium chloride hexahydrate Polysorbate 80 Potassium chloride Potassium dihydrogen phosphate Sodium chloride Water for injection
INTANZA®	ID	Inactivated – split virus	Inf			Chick protein Egg protein Neomycin	Disodium phosphate dihydrate Formaldehyde Potassium chloride Potassium dihydrogen phosphate Sodium chloride Triton® X-100
IXIARO®	IM	Inactivated	JE	Alum			Disodium hydrogen phosphate Potassium dihydrogen phosphate Sodium chloride Water for injection
Menactra®	IM	Subunit -conjugate	Men			Diphtheria toxoid carrier protein	Sodium chloride Sodium phosphate dibasic (anhydrous) Sodium phosphate monobasic Water for injection
Meningitec®	IM	Conjugate	Men	Alum		Latex in vial stopper (vial presentation only) Diphtheria CRM_{197} toxoid carrier protein	Sodium chloride Water for injection

Brand name	Route	Vaccine type	Immunogen	Adjuvant	Preservative	Potential allergens	Other materials
Menjugate®	IM	Conjugate	Men	Alum		Latex in tip cap of syringe Diphtheria CRM_{197} toxoid carrier protein	Disodium phosphate heptahydrate Mannitol Sodium chloride Sodium dihydrogen phosphate monohydrate Water for injection
MENOMUNE® A/C/Y/W-135	SC	Subunit	Men		Tm[1]	Latex in stopper	Lactose Sodium chloride
Menveo™	IM	Conjugate	Men			Diphtheria CRM_{197} toxoid carrier protein	Disodium hydrogen phosphate bihydrate Potassium dihydrogen phosphate Sodium chloride Sodium dihydrogen phosphate monohydrate Sucrose Water for injection
M-M-R® II	SC	Live attenuated	Meas Mumps R			Neomycin Phenol red Porcine gelatin Residual components of chick embryo cell cultures	Fetal bovine serum Medium 199 with Hank's salts Minimum essential medium (Eagle) Monosodium L-glutamate monohydrate Potassium phosphate dibasic (anhydrous) Potassium phosphate monobasic Recombinant human albumin Sodium bicarbonate Sodium phosphate dibasic (anhydrous) Sodium phosphate monobasic Sorbitol Sucrose Water for injection
NeisVac-C®	IM	Subunit Conjugate	Men	Alum		Tetanus toxoid carrier protein	Sodium chloride

Brand name	Route	Vaccine type	Immunogen	Adjuvant	Preservative	Potential allergens	Other materials
NIMERIX™	IM	Conjugate	Men-P-ACYW-135				Sucrose Trometamol Sodium chlorideWater for injection
PEDIACEL®	IM	Toxoid + Subunit + Inactivated + Conjugate	D T aP IPV Hib	Alum	PE	Neomycin Polymyxin B Streptomycin Tetanus toxoid carrier protein	Bovine serum albumin Formaldehyde Glutaraldehyde Polysorbate 80
PNEUMO 23®	IM/ SC	Subunit	Pneu		P		Disodium phosphate Monosodium phosphate Sodium chloride Water for injection
PNEUMOVAX® 23	IM/ SC	Subunit	Pneu		P		Sodium chloride Water for injection
Prevnar® 13	IM	Conjugate	Pneu	Alum		Diphtheria CRM_{197} toxoid carrier protein	Polysorbate 80 Sodium chloride Succinic acid Water for injection
PRIORIX®	SC/ IM	Live attenuated	Meas Mumps R			Egg protein Neomycin	Amino acids Lactose Mannitol Sorbitol Water for injection
PRIORIX-TETRA®	SC/ IM	Live attenuated	Meas Mumps R Var			Egg protein Neomycin	Amino acids Lactose Mannitol Sorbitol Water for injection
QUADRACEL®	IM	Toxoid + Subunit + Inactivated	D T aP IPV	Alum	PE	Neomycin Polymyxin B	Bovine serum albumin Formaldehyde Glutaraldehyde Polysorbate 80

Brand name	Route	Vaccine type	Immunogen	Adjuvant	Preservative	Potential allergens	Other materials
RabAvert®	IM	Inactivated	Rab			Amphotericin B Chick protein Chlortetracycline Neomycin Polygeline (gelatin) Egg protein	Human serum albumin
RECOMBIVAX HB®	IM	Recombinant	HB	Alum		Latex in vial stopper Yeast protein	Formaldehyde Sodium borate Sodium chloride Water for injection
ROTARIX™	Oral	Live attenuated	Rot				Disodium adipate DNA fragments from porcine circovirus 1 Dulbecco's Modified Eagle Medium Sterile water Sucrose
RotaTeq®	Oral	Live	Rot				DNA fragments from porcine circoviruses 1 and 2 Fetal bovine serum Polysorbate 80 Residual protein from cell culture Sodium citrate dihydrate Sodium hydroxide Sodium phosphate monobasic monohydrate Sucrose
Smallpox (dried)[2]	ID	Live	Vaccinia			Latex in stopper of vaccine vial Neomycin Streptomycin	Bovine tissue (trace) Glycerol McIlvaine buffer Phenol
SYNFLORIX®	IM	Conjugate	Pneu	Alum		Latex in syringe components Diphtheria toxoid carrier protein	Sodium chloride Water for injection

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Brand name	Route	Vaccine type	Immunizing agent	Adjuvant	Presentation	Potential allergens	Other ingredients
						Tetanus toxoid carrier protein Non-typeable *Haemophilus influenzae* protein D carrier protein	
Td ADSORBED	IM	Toxoid	T d	Alum	PE		Formaldehyde Sodium chloride Water for injection
Td POLIO ADSORBED	IM	Toxoid + Inactivated	T d IPV	Alum	PE	Neomycin Polymyxin B	Bovine serum albumin Formaldehyde Polysorbate 80
TWINRIX® **TWINRIX® Junior**	IM	Inactivated + Recombinant	HA HB	Alum		Latex in plunger stopper of pre-filled syringe Neomycin Yeast protein	Amino acids Formaldehyde Polysorbate 20 Sodium chloride Water for injection
TYPHERIX®	IM	Subunit	Typh		P	Latex in plunger stopper of pre-filled syringe	Disodium phosphate dihydrate Sodium chloride Sodium phosphate dihydrate Water for injection
TYPHIM Vi®	IM	Subunit	Typh		P		Isotonic buffer solution
VAQTA®	IM	Inactivated	HA	Alum		Latex in vial stopper Neomycin	Bovine albumin DNA Formaldehyde Residual protein from cell culture Sodium borate Sodium chloride Water for injection
VARILRIX®	SC	Live attenuated	Var			Neomycin	Amino acids Human albumin Lactose Polyalcohols Water for injection

Brand name	Route	Vaccine type	Immunogen	Adjuvant	Preservative	Potential allergens	Other materials
VARIVAX® III	SC	Live attenuated	Var			Neomycin Porcine gelatin	Fetal bovine serum Monosodium L-glutamate Potassium chloride Potassium phosphate monobasic Residual protein from cell culture Sodium chloride Sodium phosphate dibasic Sucrose Urea Water for injection
VAXIGRIP®	IM	Inactivated – split unit	Inf		Tm[1]	Egg protein Neomycin Thimerosal[1]	Disodium phosphate dihydrate Formaldehyde Potassium chloride Potassium dihydrogen phosphate Sodium chloride Sucrose Triton® X-100
ViVAXIM®	IM	Subunit + Inactivated	Typh++ (HA)	Alum	PE CH_2O	Neomycin	Disodium phosphate dihydrate Medium 199 Hanks Polysorbate 80 Sodium chloride Sodium dihydrogen phosphate dihydrate Water for injection
Vivotif®	Oral	Live attenuated	Typh			Gelatin	Amino acid mixture Ascorbic acid Dibutyl phthalate Diethyl phthalate Erythrosine FD+C red 3 Ethylene glycol Hydroxypropylcellulose-phthalate Lactose Magnesium stearate

Brand name	Route	Vaccine type	Immunogen	Adjuvant	Preservative	Potential allergens	Other materials
							Red iron oxide Sucrose Titanium dioxide Yellow iron oxide
YF-VAX®	SC	Live attenuated	YF			Chick protein Egg protein Gelatin Latex in stopper of diluent vial	Sodium chloride Sorbitol
ZOSTAVAX®	SC	Live attenuated	Zos			Neomycin Porcine gelatin	Bovine calf serum Monosodium L-glutamate monohydrate Potassium chloride Potassium phosphate monobasic Residual protein from cell culture Sodium chloride Sucrose Sodium phosphate dibasic Water for injection

[1] multi-dose presentation only
[2] Smallpox vaccine (dried) is not available for general use. Smallpox vaccine (frozen liquid) is not a Health Canada authorized product but will be released under Health Canada's Special Access Program if required.

- The information in this table is based on the product information available as of January 2013.
- Empty boxes indicate that there are no materials of relevance in the product.

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ABBREVIATIONS (TABLE 1)

Route	
ID	intradermal
IM	intramuscular
IN	intranasal
SC	subcutaneous
Immunogen: ++ For products in which the immunogens of two different vials or chambers are combined, the contents of the second vial or chamber are noted as ++(immunogen)	
aP	acellular pertussis
ap	acellular pertussis (reduced)
BCG	Bacillus Calmette-Guérin
Chol	cholera
D	diphtheria
d	diphtheria (reduced)
Ecol	enterotoxigenic *Escherichia coli*
Hib	*Haemophilus influenzae* type b
HA	hepatitis A
HB	hepatitis B
HPV	human papillomavirus
Inf	influenza
IPV	inactivated poliomyelitis
JE	Japanese encephalitis
Men	meningococcus
Meas	measles
Mumps	mumps
Pneu	pneumococcus
Rab	rabies
Rot	rotavirus
R	rubella
TBE	tick-borne encephalitis
T	tetanus
Typh	typhoid
Var	varicella
YF	yellow fever
Zos	herpes zoster
Adjuvant	
Alum	aluminum-containing adjuvant
AS04	3-O-desacyl-4'-monophosphoryl lipid A adsorbed onto aluminum (as hydroxide salt)
MF59	squalene, polysorbate 80, sorbitan trioleate, sodium citrate, citric acid, water for inje
Preservative	
CH2O	formaldehyde
P	phenol
PE	2-phenoxyethanol
Tm	thimerosal

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Products with active drug identification numbers (DIN):
The following vaccines are authorized for marketing in Canada but are not generally available:

- Epaxal® (Berna Biotech Ltd.)
- Inactivated Poliomyelitis Vaccine – IPV (Sanofi Pasteur Ltd.)
- Infanrix™- IPV/Hib (GlaxoSmithKline)
- Infanrix™-IPV (GlaxoSmithKline)
- Liquid Pedvax HIB® (Merck Canada Inc.)
- Pentacel® (Sanofi Pasteur Ltd.)
- Prevnar® (Pfizer Canada Inc.)
- Tripacel® Hybrid (Sanofi Pasteur Ltd.)
- Vivotif® L (Berna Biotech Ltd.)
- Zostavax® II (Merck Canada Inc.)

Table 2: Types and contents of passive immunizing agents available for use in Canada

- For up-to-date, complete prescribing information consult the product leaflet or information contained within the authorized product monographs available through Health Canada's Drug Product Database (http://webprod5.hc-sc.gc.ca/dpd-bdpp/index-eng.jsp)
- Information about the passive immunizing agent manufacturer/distributor is available in the Appendix of Vaccine Abbreviations

Brand name	Route	Passive immunizing agent type	Protects against or treats	Preservative	Potential allergens	Other materials
Botulism Antitoxin-Behring	IV	Antitoxin	Bot	P	Equine protein	Sodium chloride Water for injection
ANTIDIPHTHERIA SERUM	IV	Antitoxin	D	P	Equine protein	Sodium chloride
GamaSTAN® S/D	IM	Immune globulin	HA Meas Var R			Glycine Human plasma protein Sodium chloride Water for injection
HepaGam B™	IM	Immune globulin	HB			Human plasma protein Maltose Polysorbate 80 Tri-n-butyl phosphate Triton® X-100
HyperHEP B® S/D	IM	Immune globulin	HB			Glycine Human plasma protein Sodium chloride Water for injection
HYPERRAB™ S/D	IM/ local	Immune globulin	Rab			Glycine Human plasma protein Sodium chloride Water for injection
HYPERTET™ S/D	IM	Immune globulin	Tet			Glycine Human plasma protein Sodium chloride Water for injection

Brand name	Route	Passive immunizing agent type	Protects against or treats	Preservative	Potential allergens	Other materials
IMOGAM® Rabies Pasteurized	IM/ local	Immune globulin	Rab		Latex in vial stopper	Glycine Human plasma protein Hydrochloric acid Sodium hydroxide Sodium chloride
SYNAGIS® (palivizumab)	IM	Humanized monoclonal antibody	RSV			Glycine Histidine Mannitol Water for injection
CNJ-016™	IV	Immune globulin	Vaccinia			Maltose Polysorbate 80 Water for injection
VariZIG™	IV/ IM	Immune globulin	Var			Glycine Human plasma protein Polysorbate 80 Sodium chloride Sodium phosphate Tri-n-butyl phosphate Triton® X-100

- The information in this table is based on the product information available as of January 2013.
- Empty boxes indicate that there are no materials of relevance in the product.

ABBREVIATIONS (TABLE 2)

Route	
IM	intramuscular
IV	intravenous
Protects against or treats	
Bot	botulism
D	diphtheria
HA	hepatitis A
HB	hepatitis B
Meas	measles
R	rubella
Rab	rabies
RSV	Respiratory Syncytial Virus
T	tetanus
Var	varicella
Preservative	
P	phenol

Products with active drug identification numbers (DIN):
The following passive immunizing agent is authorized in Canada but is not generally available:

- Immune Serum Globulin (Human) (Grifols Therapeutics Inc.)

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Offit PA, Jew RK. *Addressing parents' concerns: Do vaccines contain harmful preservatives, adjuvants, additives, or residuals?* Pediatrics 2003;112:1394-97.

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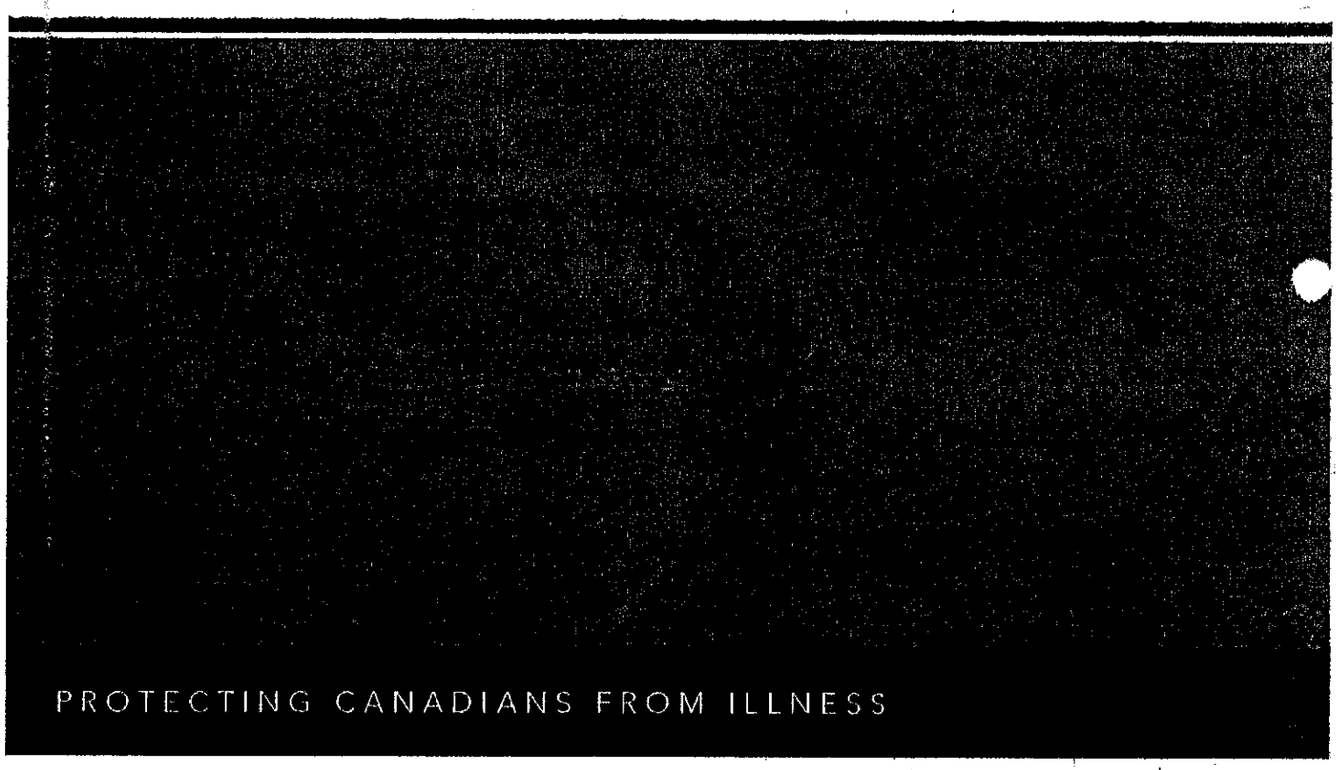
CANADIAN IMMUNIZATION GUIDE

PART 2



Public Health Agency of Canada
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PART 2

VACCINE SAFETY

As vaccine preventable infections have decreased, the spotlight of public and media concern has shifted to vaccine safety. Since vaccines are usually given to healthy people, especially children, tolerance for adverse events following immunization is low. Perceived vaccine safety risks receive as much media attention as real safety risks and can be difficult to dispel despite credible scientific evidence. Loss of confidence in the safety of vaccines threatens the continued success of immunization programs.

Vaccine pharmacovigilance has been defined as the science and activities related to the detection, assessment, understanding and communication of adverse events following immunization (AEFI) 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 vaccine pharmacovigilance, including gaining and maintaining public confidence in the safety of vaccines.

Health care providers can develop competency in pharmacovigilance by:

- Integrating into their practice knowledge about the main steps in vaccine development and evaluation (Public Health Agency of Canada [PHAC], Immunization Competencies for Health Professionals – Vaccine Development and Evaluation). (http://webqa.phac-aspc.gc.ca/im/ic-ci/index-eng.php - http://www.phac-aspc.gc.ca/im/ic-ci/5-eng.php#vaccinedevelopment)
- Anticipating, identifying, reporting and managing AEFI as appropriate to their practice setting (*Immunization Competencies for Health Professionals* – Adverse Events Following Immunization).(http://www.phac-aspc.gc.ca/im/ic-ci/5-eng.php#vaccinedevelopment)
- Providing evidence-based information on the benefits and risks of vaccines (*Immunization Competencies of Health Professionals* - Communication). (http://www.phac-aspc.gc.ca/im/ic-ci/6-eng.php#communication)

This chapter provides a general overview of pharmacovigilance concepts and activities in Canada as well as a summary of key information and resources related to the three immunization competencies listed above. Refer to the summary of key information related to vaccine pharmacovigilance in Canada.

The vaccine-specific chapters in Part 4 of this *Guide* contain key condensed pre-authorization and post-marketing evidence-based safety data. Detailed vaccine safety data are included in the relevant National Advisory Committee on Immunization (NACI) statements (http://www.phac-aspc.gc.ca/naci-ccni/) and in the vaccine's product monograph available through Health Canada's Drug Product Database. Refer to the Appendix for a definition of abbreviations used in this chapter. (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/databasdon/index-eng.php)

KEY INFORMATION RELATED TO VACCINE PHARMACOVIGILANCE IN CANADA

What: Vaccine pharmacovigilance is defined as the science and activities related to the detection, assessment, understanding and communication of AEFI and other vaccine-related or immunization-related issues, and to the prevention of untoward effects of the vaccine or immunization.

Why: To minimize the risk and maximize the benefit of vaccines and immunization.

Who: Government regulators, vaccine industry, public health officials, health care professionals, and consumers all have roles and responsibilities for pharmacovigilance (see Table 1)

How: Health Canada regulators have processes in place to maximize vaccine safety throughout the product life cycle – i.e., pre-marketing and post-marketing.

- It isn't possible to detect all vaccine side effects through pre-marketing studies, especially if the side effects are very rare (less than 1 in 10,000 subjects). Thus, continuous monitoring of the safety of marketed vaccines is essential for detection of and timely response to vaccine safety signals. A vaccine safety signal is any information that arises from one or multiple sources which suggests a new potentially causal association, or a new aspect of a known adverse reaction (increased severity and/or increased frequency), between immunization and an event or set of related events, that is judged to be of sufficient concern to justify verification and, as appropriate, remedial action.
- The Canadian Adverse Event Following Immunization Surveillance System (CAEFISS) is a joint effort of provincial/territorial (P/T) and federal public health authorities and their partners.
- Health care providers should report, without delay, all serious or unexpected AEFI to public health according to jurisdictional guidelines: (http://www.phac-aspc.gc.ca/im/ci-rp-eng.php)
  - **AEFI:** any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the usage of a vaccine. The adverse event may be any unfavourable or unintended sign, abnormal laboratory finding, symptom or disease.
  - **Serious adverse event (SAE):** one which is life-threatening and/or which results in any one or more of the following: hospitalization, prolongation of an existing hospitalization, permanent disability, congenital abnormality, fatal outcome.
  - **'unexpected' AEFI:** one which is not included in the official product label (as listed in the package leaflet and/or product monograph)
  - While prompt reporting of serious and/or unexpected AEFI is essential to detect emerging signals and monitor vaccine safety, one or even many AEFI reports do not constitute proof that a vaccine causes an AEFI. Causality assessment requires scientific or epidemiologic evidence to answer the question 'Can it?' and then accurate diagnosis and thorough investigation to try to answer the question 'Did it?'

VACCINE PHARMACOVIGILANCE ACTIVITIES IN CANADA

OVERVIEW

Vaccine safety assessment and monitoring is a continuum that spans all phases of the vaccine product 'life cycle' from discovery through market authorization and beyond. Many stakeholders (Refer to Table 1) and activities (Refer to Table 2) are involved. Some stakeholders such as vaccine manufacturers and regulatory authorities have roles and responsibilities throughout the product life cycle, whereas others such as public health authorities and vaccine providers are involved later in the process, from about the time the product is authorized for marketing in Canada.

A great deal is learned about vaccine safety during the testing period prior to market authorization. Testing proceeds in a step wise fashion from non-human to human studies. Clinical trials in humans start out small but increase in size and progressively assess immunogenicity, appropriate dose and schedule, safety and finally efficacy. Regulatory oversight is in place to ensure that all phases of testing and production are done in accordance with rigorous standards (Good Laboratory Practices, Good Clinical Practices, Good Manufacturing Processes).

With sufficient evidence that the product has a positive benefit to risk profile, regulators will authorize a new vaccine for marketing. About the same time national expert advisory groups such as NACI review the evidence to develop recommendations for use and public health authorities use a standard framework to determine whether or not publicly-funded immunization programs should be instituted.

Despite all the knowledge gained about a product by the time market authorization is given, there is still more to learn about the safety profile in terms of rare side effects or risk for increased frequency of adverse events. Thus ongoing monitoring of vaccine safety is standard throughout the life cycle and it may be necessary to do special studies to learn more about the safety profile or to investigate issues of concern that may emerge in the post-market period.

Regulatory activities also continue in the post-market period to ensure that all new lots of the product match the properties of those on which marketing approval was based and that product production is consistent and of high quality.

More detail on the specific processes and stakeholder activities in Canada that contribute to vaccine safety are provided below.

REGULATORY QUALITY OVERSIGHT AND PHARMACOVIGILANCE ACTIVITIES

Health Canada's Health Products and Food Branch (HPFB) has the mandate to take an integrated approach to managing the health-related risks and benefits of health products and food by:

- minimizing health risk factors to Canadians while maximizing the safety provided by the regulatory system for health products and food; and
- promoting conditions that enable Canadians to make healthy choices and providing information so that they can make informed decisions about their health.

The following provides a brief summary of how this is done.

AUTHORIZATION FOR MARKETING A VACCINE IN CANADA

Health Canada's Biologics and Genetic Therapies Directorate (BGTD) is the Canadian federal authority that regulates biological drugs, including vaccines. Before manufacturers or sponsors are eligible to market a product in Canada, they must submit a "New Drug Submission". This submission contains extensive information and data about the vaccine's safety, efficacy and quality, including the results of the preclinical and clinical studies, details regarding the production of the vaccine, packaging and labelling details, and information regarding therapeutic claims and side effects. The quality evaluation of the submission includes an onsite evaluation of the production facilities as well as laboratory testing of samples from three to five consecutive lots (or batches of vaccine production) to verify manufacturing consistency.

Upon careful review of the all the evidence, the BGTD determines whether the benefits of the vaccine outweigh its risks, and the risks can be mitigated. (i.e. risks decreased and their impact reduced), in accordance with Canada's Food and Drugs Act and Regulations. (http://laws-lois.justice.gc.ca/eng/regulations/C.R.C.%2C_c._870/index.html) If the submission meets all requirements, the BGTD will issue a Notice of Compliance (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/notices-avis/index-eng.php) and a Drug Identification Number (DIN) for market authorization.(http://www.hc-sc.gc.ca/dhp-mps/prodpharma/activit/fs-fi/dinfs_fd-eng.php)

Compliance with Good Manufacturing Practice (GMP) is an additional Health Canada requirement for selling vaccines in Canada. The Health Products and Food Branch Inspectorate (HPFBI) ensures this compliance through issuance of Establishment Licenses via its own GMP inspections or through Mutual Recognition Agreements with international regulatory bodies such as the European Medicines Agency.

QUALITY MONITORING ACTIVITIES

Vaccine lot release program

The purpose of the lot release program is to ensure to the extent possible that each newly manufactured batch of vaccine matches the lots used to generate the safety and efficacy data for market authorization. Each vaccine lot is subject to the lot release program before sale in Canada. Specifically, an official document containing results of key quality control tests performed throughout the manufacturing process of each individual lot must be submitted to and is reviewed by Health Canada before a release letter is issued to allow the sale of the lot on the Canadian market. Moreover, as part of its lot release program, Health Canada performs testing of most vaccine lots as per its Lot Release Guidelines. (http://www.hc-sc.gc.ca/dhp-mps/brgtherap/applic-demande/guides/lot/index-eng.php) In addition, vaccine manufacturers must submit a Yearly Biological Product Report, which summarizes the quality information for all the lots manufactured in their facility for each product. These strategies allow Health Canada to assess how well the manufacturing process is controlled and that the quality control tests remain suitable.

In addition, regular GMP inspections are conducted to ensure continued compliance to Good Manufacturing Practice and renewal of establishment licenses for vaccine manufacturing facilities.

SAFETY MONITORING ACTIVITIES

Canada Vigilance Program

Market authorization holders (i.e., the sponsors or manufacturers that have the legal authority to market their drug in Canada) are required to report serious adverse reactions to the Canada Vigilance Program, as mandated by the *Food and Drugs Act and Regulations*. This information is one of the tools that enable Health Canada to monitor the safety profile of vaccines to determine if their benefits continue to outweigh their risks. (http://www.hc-sc.gc.ca/dhp-mps/pubs/medeff/_fs-if/2011-cvp-pcv/index-eng.php)

Safety reports

The *Food and Drugs Act and Regulations* require market authorization holders to analyze adverse drug reaction data for safety concerns and prepare an annual summary report which represents a comprehensive assessment of the worldwide safety data of the vaccine. Market authorization holders must also notify Health Canada if they become aware of a significant change in the product benefit-risk profile.

Safety reports are assessed by Health Canada and, if specific safety issues are identified, additional safety information may be requested.

Risk management plans (RMP)

A risk management plan summarizes known important safety information about a health product; identifies gaps in knowledge; outlines how known and potential safety concerns will be monitored by the market authorization holder; and provides a proposal to minimize any identified or potential risk. Health Canada reviews the RMP when the market authorization holder is seeking authorization to market a new vaccine in Canada but can also request that a RMP be submitted at other times.

Product risk/benefit assessments

Health Canada can ask the market authorization holder to submit a benefit-risk assessment of a therapeutic health product when the benefit-risk profile of a product has changed. Health Canada evaluators reviewing benefit-risk assessments use science-based procedures to determine whether the benefits outweigh the risks or whether the product needs regulatory intervention.

Canadian Adverse Event Following Immunization Surveillance System (CAEFISS)

CAEFISS is a collaborative post-marketing federal/provincial/territorial (F/P/T) surveillance system with the following objectives:

- to continuously monitor the safety of marketed vaccines in Canada;
- to identify increases in the frequency or severity of previously identified vaccine-related reactions;
- to identify previously unknown AEFI that could possibly be related to a vaccine (unexpected AEFI);
- to identify areas that require further investigation and/or research; and
- to provide timely information on AEFI reporting profiles for vaccines marketed in Canada that can help inform immunization-related decisions.

CAEFISS includes spontaneous, enhanced and active AEFI reporting processes. Each province and territory has their own reporting system that includes activities at the local/regional as well as the provincial/territorial level. (Refer to the FPT contact information for AEFI-related questions) (http://www.phac-aspc.gc.ca/im/ci-rp-eng.php) All provincial and territorial systems are part of CAEFISS. Spontaneous AEFI reports may come from health care professionals, market authorization holders and the public. F/P/T immunization program authorities encourage vaccine providers and others to report AEFI of particular public health importance and sometimes conduct enhanced AEFI surveillance as part of new publicly-funded immunization programs or as a response to possible emerging vaccine safety signals. In some jurisdictions (Ontario, Quebec, Nova Scotia, Manitoba, New Brunswick, Saskatchewan and Northwest Territories) AEFI reporting is a legislated requirement.

There is also an active syndromic surveillance component to CAEFFIS. This is provided by the Immunization Monitoring Program – ACT-ive (IMPACT) which is described below.

Immunization Monitoring Program – ACT-ive (IMPACT)

IMPACT (http://www.cps.ca/en/impact) is a pediatric, hospital-based network funded by PHAC and administered by the Canadian Paediatric Society. IMPACT conducts a national surveillance network for adverse events following immunization, vaccine failures and selected vaccine preventable diseases in children. The 12 IMPACT hospitals encompass approximately 90% of tertiary care pediatric beds in Canada. Nurse monitors actively search for children admitted to IMPACT hospitals with neurologic and other high priority adverse events. The nurse monitors determine whether these events have followed immunization within a timeframe that could implicate vaccine as a possible cause. All such AEFI are reported to PHAC as well as to local public health officials.

How and when to report an AEFI

Vaccinees and/or their parents/caregivers should be advised to notify their vaccine provider or other healthcare provider about any concerns that arise following immunization. The provider can then assess these concerns and, if appropriate, complete an adverse event report. Providers submit reports to the appropriate jurisdictional authority (e.g. to local or provincial public health). In all cases, these are then reported to the federal authorities so each AEFI can be added into the national CAEFISS database. Refer to the FPT contact information for AEFI-related questions which also contains the AEFI Reporting Form and a user guide. (http://www.phac-aspc.gc.ca/im/ci-rp-eng.php)

The main purpose of post-marketing AEFI surveillance is to detect vaccine safety signals. The key criteria for reporting an AEFI are temporal association and a suspicion that the vaccine or immunization may have caused the event. One need not be sure that the AEFI was caused by either vaccine or immunization nor does an AEFI report prove causation. Unexpected events that are not listed in the product monograph should be reported. Expected common events such as vaccination site reactions or fever need not be reported unless they are more severe or frequent than usual. Part 4 of this *Guide* provides information on expected common adverse events for vaccines marketed in Canada.

Of greatest priority for timely reporting are serious AEFI (life-threatening and/or which result in any one or more of the following: hospitalization, prolongation of an existing hospitalization, permanent

disability, congenital abnormality, fatal outcome). Serious events should be investigated for other causes as appropriate, but reporting should be done without delay. Follow-ups can be sent using the same AEFI report form (specifying that it is a follow-up), and submitted by the same route, once the investigation is complete.

The national Adverse Events Following Immunization Report Form (http://www.phac-aspc.gc.ca/im/aefi-essi-form-eng.php) and User Guide to the Completion and Submission of the AEFI Reports provide detailed guidance for reporting an AEFI. (http://www.phac-aspc.gc.ca/im/aefi-essi_guide/index-eng.php)

AEFI report flow and associated activities

Local public health officials are usually the first to receive an AEFI report. Key activities include review by a public health professional for individual public health action related to the advisability of additional doses of implicated vaccine(s). Efforts may also be made to gather additional information, validate a report diagnosis, and follow up investigation results and/or final outcome of the AEFI. In some settings, the reports are entered into an electronic database. Vaccine safety issues such as unexpected events or increases in severity or frequency of expected AEFI, especially vaccination site reactions or allergic events, may first be recognized at the local level. Such concerns are communicated to appropriate regional and/or provincial/territorial personnel for further assessment and investigation if needed.

Provincial/territorial immunization programs receive and review all AEFI reports to carry out jurisdictional level analysis including estimation of rates of occurrence of specific AEFI and, in some cases, preparation of periodic jurisdictional summaries. With a larger volume of reports than is seen at local levels, this is another opportunity to identify possible safety signals and take action as appropriate. Actions may include: undertaking additional epidemiological investigation; consulting with experts, advising federal public health or regulatory authorities; or creating an AEFI alert to notify and seek input from all F/P/T vaccine safety leads (refer to Vaccine Vigilance Working Group). In addition to being the lead on jurisdictional pharmacovigilance activities, P/T vaccine safety coordinators remove personal identifiers in AEFI reports and send the reports to PHAC. Serious AEFI reports are forwarded to PHAC within 15 days or less.

The Vaccine Safety Section at PHAC receives AEFI reports from multiple sources (from provinces, federal jurisdictions, IMPACT, and manufacturers), identifies duplications and collates them into a national database. Serious events are given priority and are processed within 2 business days. The key activities at the national level include coding of AEFI using the International Medical Dictionary for Regulatory Activities (MedDRA) and medical case review to detect vaccine safety signals including any unexpected or unusual AEFI. Analyses are done regularly to search for vaccine safety signals and information is shared with Health Canada. Reports are produced for F/P/T and NACI review.

Vaccine Vigilance Working Group (VVWG)

This group includes members representing all federal (First Nations and Inuit Health Branch [FNIHB], National Defence and the Canadian Forces [DND], Royal Canadian Mounted Police [RCMP], Correctional Services of Canada [CSC]) and P/T immunization programs as well as Health Canada regulators and IMPACT. The working group reports to the Canadian Immunization Committee and its activities include:

- preparation of national guidelines and procedures for monitoring and management of AEFIs in Canada;
- providing a national forum to identify, share and promote best practices regarding vaccine pharamcovigilance; and
- providing a national vaccine safety sentinel network that can rapidly share and disseminate information to appropriate stakeholders regarding vaccine safety issues or signals

Table 1 provides an overview of the key stakeholder roles and responsibilities for pharmacovigilance in Canada. It is important to note that to be effective there needs to be good communication among

the key stakeholders. For example, scientists and regulators need to give information to health care providers, and health care providers need to give information to public health authorities who in turn collate and analyse information for regulators, healthcare providers, scientists and consumers.

Table 1: Key stakeholder roles and responsibilities for pharmacovigilance in Canada

Stakeholder	Specific group	Role/responsibility
Health Canada regulators (Health Products and Food Branch, HPFB)	Biologics and Genetic Therapies Directorate (BGTD)	• Requires sufficient evidence of safety, efficacy and quality to authorize vaccine for sale in Canada • Vaccine lot release program • Reviews/approves post-marketing product changes that could impact quality, safety or efficacy
	Marketed Health Products Directorate (MHPD)	• Collects suspected adverse reaction reports from market authorization holders • Conducts risk-benefit assessment • Reviews safety data submitted by market authorization holders (adverse reaction reports, safety reports, issue-specific safety reports, risk management plans, etc.) • Issues risk communications
	Health Products and Food Branch Inspectorate	• Provides establishment licensing and inspections • During inspections, monitors and enforces vaccine industry compliance with the *Food and Drugs Act and Regulations*, including Good Manufacturing Practice[1]
Vaccine industry	Vaccine market authorization holders	• Monitor the safety of their vaccines • Comply with the *Food and Drugs Act and Regulations*, including Good Laboratory Practice[2], Good Clinical Practice[3], and Good Manufacturing Practice
Public health authorities	Public Health Agency of Canada	• Collates, codes, reviews, analyzes and communicates national level AEFI report data from multiple sources
	Federal[4]/Provincial/Territorial (F/P/T) Health Jurisdictions (immunization programs)	• AEFI surveillance at the F/P/T jurisdictional level • F/P/T vaccine safety signal detection/investigation • Share de-identified AEFI report data with PHAC

Stakeholder	Specific group	Role/responsibility
	Local public health officials	• Report AEFIs to P/T public health officials • Individual public health action after an AEFI (e.g., AEFI validation and/or investigation; decisions on future re-immunization)
Health professionals	Scientists, expert clinicians and networks	• Conduct research and contribute to surveillance of vaccine and immunization safety
	Members of the National Advisory Committee on Immunization	• Review evidence on vaccine risk and benefit to provide expert recommendations for vaccine use
	Vaccine providers and other health care providers, as appropriate to their clinical and/or public health professional practice	• Administer vaccine • Identify, report and manage AEFI as part of their clinical and/or public health professional practice
Consumers	Vaccinees and their care providers	• Seek information needed to make decisions about vaccination • Notify their healthcare provider about AEFIs to enable prompt assessment, appropriate management, and timely reporting if indicated.

[1] Good Manufacturing Practice: guidelines to ensure that the vaccine production process:
- uses starting materials that are characterized with defined origin and acceptable quality;
- is validated by demonstration that all specifications of all steps are met at least 3 times in a row;
- is consistent with each new lot having the same characteristics of lots used in pre-authorization clinical trials that established safety and efficacy; and
- is done in a licensed establishment.

[2] Good Laboratory Practice: guidelines to ensure uniformity, consistency, reliability, reproducibility, quality and integrity of chemical pre-clinical safety testing

[3] Good Clinical Practice: standards for the conduct of clinical trials

[4] Federal jurisdictions include: First Nations and Inuit Health Branch (FNIHB), Department of National Defense (DND), Royal Canadian Mounted Police (RCMP) and Correctional Services of Canada (CSC).

EVALUATION OF VACCINE SAFETY AND QUALITY THROUGHOUT THE PRODUCT LIFE CYCLE

Prior to the 1960s, it was erroneously thought that everything that could be known about a product could be learned prior to product authorization. It is now known that while sufficient evidence of safety, efficacy and quality is an absolute requirement for regulators to grant authorization for marketing a product, sufficient evidence does not mean knowing everything that can be known about a product. It is impossible to learn everything about a product prior to authorization and efforts to do so delay proven product benefit from being realized in the population.

Pre-marketing studies are rigorously controlled to ensure that results are valid and reproducible. As a result, subjects in these studies are usually healthy with no underlying conditions. Post-marketing surveillance studies may be needed to determine whether the safety profile is the same in other target populations, such as the immunocompromised or those born prematurely or those with asthma, diabetes or other chronic diseases. In order to detect very rare adverse events (frequency of less than 1 in 10,000 subjects) it is necessary to have 30,000 to over 100,000 subjects in a controlled study. This is rarely

practical or possible and would delay the introduction of a proven effective vaccine into the population. The concept of a life cycle for vaccines and other marketed products underscores the fact that knowledge regarding product safety and efficacy must be sought after, as well as before, marketing authorization.

Table 2 describes what is learned about vaccine safety throughout the vaccine life cycle and the accompanying regulatory requirements to ensure data and product quality.

Table 2: Evaluation of safety and quality throughout the vaccine life cycle

Vaccine life cycle phase	Usual number of subjects	Regulatory requirements	Why it is done
Pre-marketing evaluation prior to issuance of the Notice of Compliance (NOC)			
Pre-clinical testing	None	Compliance with the *Food and Drugs Act and Regulations*, Good Laboratory Practice (GLP)[1]	• Provides information on possible efficacy and safety in laboratory and animal testing
Clinical trials	• Phase I: 10 – less than 100 • Phase II: 100-1,000 • Phase III: 1,000-30,000	Compliance with the *Food and Drugs Act and Regulations*, Good Clinical Practice (GCP)[2]	• Provides safety and efficacy data on humans • Phase I: very common adverse reactions (occurring in 10% or more of doses) • Phase II: common adverse reactions (occurring in 1% to less than 10% of doses) • Phase III: uncommon (occurring in 0.1% to less than 1% of subjects) and some rare (occurring in 0.01% to less than 0.1% of subjects) adverse reactions
Validation of manufacturing process, and control	Not applicable	Compliance with the *Food and Drugs Act and Regulations*, including Good Manufacturing Practice (GMP) [3] as well as with WHO, ICH and other international quality guidance documents	• Assesses quality of vaccine production process: o All steps in the manufacturing process from seed lot production to delivery as well as quality control tests must be validated • Documentation on production process, quality control and facilities must be submitted to the regulator for review prior to approval

Vaccine lifecycle phase	Usual number of subjects	Regulatory requirement	Why it is done
On-site evaluation of the manufacturing process	Not applicable	Compliance with the *Food and Drugs Act and Regulations*, including GMP as well as with WHO, ICH and other international quality guidance documents	• Monitors quality of vaccine production: o Health Canada product specialists are sent to the manufacturing site to assess the manufacturing process
Consistency testing	Not applicable	Compliance with the *Food and Drugs Act and Regulations*, including GMP	• Ensures quality of vaccine: o Samples from at least 3 consecutive lots are tested in Health Canada laboratories to ensure that the product is manufactured consistently
Establishment licensing	Not applicable	Compliance with the *Food and Drugs Act and Regulations*, GMP	• Ensures that the facilities in which the product (the active pharmaceutical ingredient) is manufactured are appropriate to the specifications that apply to that product.
Post-marketing regulatory oversight (post-NOC) and pharmacovigilance activities			
Lot release program	Not applicable	Compliance with the *Food and Drugs Act and Regulations*	• Ensures that each marketed lot of vaccine does not differ from vaccine lots shown to be safe and effective in clinical trials
Establishment inspections	Not applicable	Compliance with the *Food and Drugs Act and Regulations*, including GMP	• Ensures that the facilities in which the product (the active pharmaceutical ingredient) is manufactured are appropriate to the specifications that apply to that product[4] • Generally inspections occur every 2 to 3 years; however can be more or less frequent depending on the type of activity and product.

Vaccine lifecycle phase	Usual number of subjects	Regulatory requirement	Why it is done
Post-marketing studies to address gaps in the vaccine safety profile that could not be learned via pre-marketing testing	Phase IV: 100 to many thousands (depending on study objective)	There is no regulatory requirement, but it is suggested as part of guidance from Health Canada. May conduct large population-based epidemiologic studies to assess a signal and test hypotheses (accept or reject) related to a causal association between vaccine and adverse event.	• Expand data on vaccine safety profile in target population in case some rare adverse events not detected during pre-marketing phase • Assess safety profile in special populations not studied as part of pre-authorization trials (e.g., immunocompromised, diabetics etc.) • Study possible interactions with other vaccines
AEFI surveillance systems	Spontaneous, enhanced and/or active AEFI reporting systems	Compliance with the *Food and Drugs Act and Regulations* by market authorization holders CAEFISS activities are undertaken voluntarily, although some P/T require AEFI reporting as part of their public health legislation	• Detect new vaccine safety signals which could be: o increased severity or frequency of previously known adverse reactions o unexpected adverse reactions • Conduct special investigations to determine root cause of vaccine safety signals
Studies designed to test hypotheses related to vaccine-adverse event associations	Population-based epidemiologic studies and/or randomized controlled trials	May be requested by regulators in response to new safety signals	• Test hypothesis that a vaccine can cause an AEFI, including very rare events (less than 1 in 10,000 subjects)

[1] **Good Laboratory Practice:** guidelines to ensure uniformity, consistency, reliability, reproducibility, quality and integrity of chemical pre-clinical safety testing
[2] **Good Clinical Practice:** standards for the conduct of clinical trials
[3] **Good Manufacturing Practice:** guidelines to ensure that the vaccine production process:
- uses starting materials that are characterized with defined origin and acceptable quality;
- is validated by demonstration that all specifications of all steps are met at least 3 times in a row;
- is consistent with each new lot having the same characteristics of lots used in pre-authorization clinical trials that established safety and efficacy; and
- is done in a licensed establishment.

VACCINE – ADVERSE EVENT CASUALITY: CAN IT? DID IT? WILL IT?

Causality assessment can be used to answer three different questions related to vaccine causing an adverse event: Can it? Did it? Will it?

CAN IT? – VACCINE ATTRIBUTABLE RISK

"Can it?" uses scientific and epidemiologic methods, usually in large populations, to prove that there is a causal association between a vaccine and an adverse event. When the answer to "can it?" is yes, investigators also hope to identify the attributable risk related to the vaccine.

Ideally, the goal of safety studies is to determine vaccine attributable risk, defined as the difference between the frequency of an event in the vaccinated compared to unvaccinated population. Special study designs are needed to determine attributable risk such as those described below. While the first two studies were completed several years ago they remain relevant and are excellent examples of study designs that can inform vaccine safety.

The most rigorous study design is a *placebo-controlled randomized control trial*, especially those using a cross-over design. An elegant example of such a design is a Finnish study involving 581 twin pairs where one twin of each pair was first given measles-mumps-rubella (MMR) vaccine and 3 weeks later given a placebo whereas the other twin in the pair first received placebo and 3 weeks later the MMR vaccine. This was done in a double-blinded fashion (i.e., neither the researchers nor the subject caretakers knew whether a given injection was MMR vaccine or placebo). Adverse events were monitored for 21 days after immunization. The results of this classic study are shown in Table 3 and demonstrate two key points. First, fever is a common childhood event affecting 16% to 18% of the placebo group – i.e., a temporally associated coincidental event, related neither to vaccine nor to immunization. Secondly, the risk of fever attributable to MMR vaccine is 2% to 6% and occurs in the interval from 7 to 12 days after immunization.

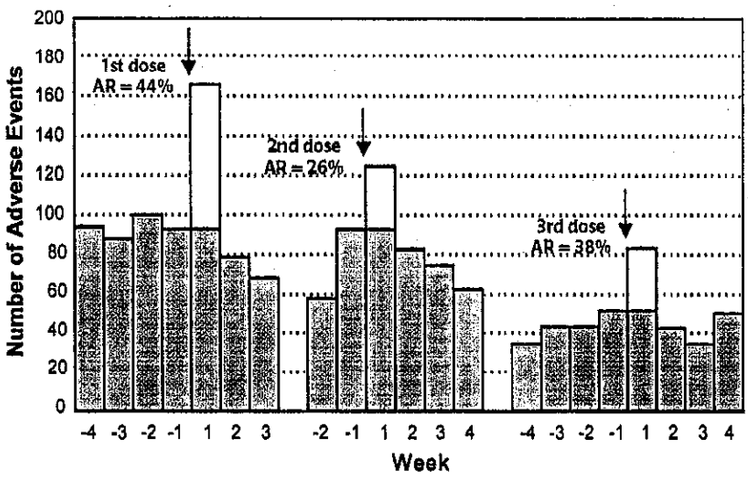
Table 3: Placebo-controlled randomized cross-over design to determine proportion of fever attributable to MMR vaccine*

	Days after injection				
	1 - 6	7 - 8	9 - 10	11 - 12	13 - 21
MMR vaccine	17.2%	20.3%	24.0%	19.9%	16.2%
Placebo	17.0%	18.0%	17.9%	17.5%	16.5%
Difference or attributable risk	0.2%	2.3%	6.1%	2.4%	– 0.3%

* Calculated from data presented in Table II in Peltola H, Heinonen OP. *Frequency of true adverse reactions to measles-mumps-rubella vaccine.* Reprinted with permission from Elsevier Science. Lancet 1986;1(8487):939-42.

An *epidemiologic cohort design* is another way to measure vaccine attributable risk. A Canadian example is shown in Figure 1. In this case, the study cohort was children immunized with 3 doses of hepatitis B vaccine and the measured outcomes were the number of illnesses or clinical symptoms compatible with any adverse event recorded during one week intervals from 4 weeks before to 3 weeks after each vaccine dose. Recorded adverse events increased in the week after hepatitis B immunization but returned to pre-vaccination levels thereafter. The attributable increase in adverse events due to hepatitis B vaccine was limited to the first week after immunization and was 44%, 26% and 38% after doses 1, 2 and 3 respectively. Therefore this means that there is a 44% increase risk of adverse events in the first week after the first dose of vaccine which is determined to be due to vaccine.

Figure 1: Cohort study design to determine proportion of adverse events attributable to hepatitis B vaccine*



Some bars represent relative attributable risk (AR=44%, AR=26%, AR=38%)
Arrows indicate vaccination.
*Reproduced with permission of the American Journal of Public Health from De Serres G. et al. *Importance of attributing risk in monitoring adverse events after immunization: hepatitis B vaccination in children*. Am J Public Health 2001;91(2):313-15.

Determining vaccine attributable risk for very rare adverse events (less than 1 in 10,000 subjects) is difficult. In controlled trials, study populations of 30,000 or more are needed. Once a vaccine with proven efficacy has been authorized and marketed in Canada, it is unethical to include placebo groups in studies among people for whom the vaccine is recommended. Thus, special epidemiologic methods are needed to try to control bias, especially related to non-random distribution of immunization in the population.

One powerful method for determining vaccine attributable risk for very rare adverse events is the *self-controlled case series design* which compares the risk of an event occurring during a defined risk period following vaccine exposure to other time intervals in the same individual's life where no vaccine exposure occurred. This technique has been successfully applied to address vaccine safety controversies (e.g., lack of causal link between MMR or thimerosal-containing vaccines and autism) as well as to quantify the attributable risk for some rare events that have been causally linked to vaccine (refer to Institute of Medicine).

DID IT? - AEFI CLUSTER AND INDIVIDUAL CASE CAUSALITY ASSESSMENT

In investigating AEFI clusters and individual cases, reviewers are trying to answer the question "Did it?" (i.e., did one or more administered vaccines cause the observed adverse event *or* would the event have happened anyway even if the vaccine hadn't been given).

An AEFI is reported based on a suspicion as opposed to a certainty that a given vaccine caused a given adverse event. The actual cause of the AEFI could be one or more of the following based on terms that have been defined by the Council for International Organizations of Medical Sciences (CIOMS) – World Health Organization (WHO) Working Group on Vaccine Pharmacovigilance:

- **Vaccine product-related reaction:** an AEFI that is caused or precipitated by a vaccine due to one or more of the inherent properties of the vaccine product. For example:
    - common to very common AEFI: vaccination site pain and swelling, fever

  - uncommon AEFI: hypotonic-hyporesponsive events (HHE) after infant vaccines;
  - rare AEFI: febrile seizure after MMR vaccine
  - very rare AEFI: anaphylaxis after any vaccine

- **Vaccine quality defect-related reaction:** an AEFI that is caused or precipitated by a vaccine that is due to one or more quality defects of the vaccine product including its administration device as provided by the manufacturer. Quality defect is defined as any deviation of the vaccine product as manufactured from its set quality specifications. An example of this occurred in 1955 when Cutter laboratories failed to completely inactivate polio virus in Salk vaccine lots leading to cases of polio infection. This event led to much stronger regulatory oversight of vaccine production and the implementation of Good Manufacturing Practices. With the current level of regulatory oversight to assess vaccine quality, a vaccine quality defect-related reaction is now rare. Nonetheless, the possibility must be considered and a high level of a vigilance maintained when new signals emerge.

- **Immunization error-related reaction:** an AEFI that is caused by inappropriate usage and, therefore, by its nature is preventable. Inappropriate usage is defined as vaccine handling, prescribing and/or administration other than what is authorized and recommended in a given jurisdiction based on scientific evidence or expert recommendation. An example of this is the development of a sterile nodule at the vaccination site because of using needles that are too short. When needles are too short, it results in subcutaneous deposition of alum-containing vaccine meant to be injected intramuscularly which can result in a sterile nodule.

- **Immunization anxiety-related reaction:** an AEFI arising from anxiety about the immunization (e.g., syncope or hyperventilation).

- **Coincidental event:** an AEFI that is caused by something other than the vaccine product, immunization error, or immunization anxiety (e.g., acute infection that may have been incubating but not clinically apparent at the time of immunization; emergence of a genetic disorder not yet diagnosed at the time of immunization.)

Each of the above types of adverse events must be considered as a possible 'root cause' whenever a vaccine safety signal is detected and verified. Sometimes it cannot be exactly determined what the root cause was. Depending on the seriousness of the signal it may be necessary to take immediate regulatory action (e.g., lot quarantine or recall) and/or public health action (e.g., suspend or modify immunization program) pending results of the investigation. A signal investigation requires a cooperative effort from multiple stakeholders including F/P/T public health officials, Health Canada regulators, vaccine market authorization holders and, often, vaccine researchers.

WILL IT? - APPLYING VACCINE SAFETY EVIDENCE TO RISK COMMUNICATION

Evidence regarding vaccine safety, as generated throughout the vaccine life cycle helps to inform the risk-benefit discussion between health care providers and potential vaccine recipients or their caregivers. Of greatest use is the determination of vaccine attributable risk. For example, to the question: Will MMR vaccine cause thrombocytopenia? Based on large epidemiologic studies, one can say that MMR vaccine will cause thrombocytopenia once for every 30,000 to 40,000 doses given. Evidence addressing other adverse events can be found in vaccine-specific chapters in Part 4 of this *Guide*.

GLOBAL PARTNERS

Vaccine pharmacovigilance is a global effort with many participants. Canada's global partners in vaccine pharmacovigilance are briefly described below with a link to more detailed information.

WORLD HEALTH ORGANIZATION (WHO)

The WHO has a mandate from member states to develop, establish and promote international standards with respect to a wide variety of products including biologics such as vaccines. Since 1965, the WHO has had a global program for International Drug Monitoring which is run out of the Uppsala Monitoring Centre in Sweden. (http://www.who-umc.org/) The main objective of the program is safety signal detection at a global level.

In 1999 the WHO established the Global Advisory Committee on Vaccine Safety (GACVS) (http://www.who.int/vaccine_safety/committee/en/index.html) to provide independent evidence-based responses to safety issues of global concern. The expert committee meets twice yearly (usually June and December) and publishes their conclusions and recommendations shortly thereafter in the WHO Weekly Epidemiological Record. The GACVS also maintains a subject-specific topic index at their website. As part of their work, GACVS established the Vaccine Safety Net which identifies and promotes websites on vaccine safety that adhere to good information practices. (http://www.who.int/vaccine_safety/initiative/communication/network/vaccine_safety_websites/en/)

COUNCIL FOR INTERNATIONAL ORGANIZATIONS OF MEDICAL SCIENCES (CIOMS)

The Council for International Organizations of Medical Sciences (http://www.cioms.ch/) is an international, non-governmental, non-profit organization established jointly by WHO and UNESCO in 1949 to facilitate and promote international activities in the field of biomedical sciences, including making recommendations on the assessment and monitoring of adverse reactions. The WHO and CIOMS jointly formed a Working Group to develop definitions relevant to vaccine pharmacovigilance which were published in 2012. (http://www.cioms.ch/index.php/publications/available-publications?task=view&id=40&catid=54)

BRIGHTON COLLABORATION

The Brighton Collaboration is a global expert network which seeks to create methodological standards for vaccine pharmacovigilance including standardized case definitions of AEFI. (https://brightoncollaboration.org/public/what-we-do/setting-standards/case-definitions.html) These case definitions have been adopted by the VVWG and are captured to some extent in the national Adverse Events Following Immunization Report Form. (http://www.phac-aspc.gc.ca/im/aefi-essi-form-eng.php)

INSTITUTE OF MEDICINE (IOM)

The IOM (www.iom.edu) was formed in 1970 by the United States National Academy of Sciences (NAS) and functions as an independent, expert professional body that examines issues of relevance to the health of the public. Since 2001, an absolute criterion for membership on IOM Immunization Safety Review Committees has been lack of any association with vaccine manufacturers or their parent organizations and no prior function as a legal expert witness.

For each issue studied, the IOM Immunization Safety Committee reviews all pertinent theoretical, experimental, clinical and epidemiologic evidence and hears presentations from the public and health professionals. The Committee starts from a neutral position, with no prior assumption regarding a positive or negative connection between the vaccine and the issue at hand. The scientific evidence is then reviewed, and biologic mechanisms for a possible causal association carefully considered. Prior to publication, each report is reviewed by an independent expert panel, chosen by the NAS and the IOM but anonymous to the Committee. Reviewer's comments are given due consideration, but ultimately the final published report represents the consensus of the IOM safety panel alone. The IOM website provides access to all committee reports, including the most recent reports published in 2011 and 2013. The 2011 Committee report (http://www.iom.edu/Reports/2011/Adverse-Effects-of-Vaccines-Evidence-and-Causality.aspx) considered the scientific evidence related to the safety of eight vaccines (MMR, varicella, influenza, human papillomavirus [HPV], hepatitis A, hepatitis B, meningococcal polysaccharide, meningococcal conjugate, and diphtheria toxoid-tetanus toxoid-acellular pertussis [DTaP]-containing vaccines). (http://www.iom.edu/Reports/2011/Adverse-Effects-of-Vaccines-Evidence-and-Causality.aspx) The 2013 Committee report focused on the safety of the United States immunization schedule for infants and children. (http://www.iom.edu/Reports/2013/The-Childhood-Immunization-Schedule-and-Safety.aspx)

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APPENDIX OF ABBREVIATIONS

Abbreviation	Definition
AEFI	Adverse event(s) following immunization
AR	Attributable risk
BGTD	Biologics and Genetic Therapies Directorate
CAEFISS	Canadian Adverse Event Following Immunization Surveillance System
CIOMS	Council for International Organizations of Medical Sciences
CNPHI	Canadian Network for Public Health Intelligence
CSC	Correctional Services of Canada
DIN	Drug identification number
DND	National Defence and the Canadian Forces
DTaP	Diphtheria toxoid-tetanus toxoid-reduced acellular pertussis
F/P/T	Federal/provincial/territorial
FNIHB	First Nations and Inuit Health Branch
GACVS	Global Advisory Committee on Vaccine Safety
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HHE	Hypotonic-hyporesponsive events
HPFB	Health Products and Food Branch
HPV	Human papillomavirus
IMPACT	Immunization Monitoring Program – ACT-ive
IOM	Institute of Medicine
MedDRA	Medical Dictionary for Regulatory Activities
MHPD	Marketed Health Products Directorate
MMR	Measles-mumps-rubella vaccine
NACI	National Advisory Committee on Immunization
NAS	United States National Academy of Sciences
NOC	Notice of Compliance
P/T	Provincial/territorial
PHAC	Public Health Agency of Canada
RCMP	Royal Canadian Mounted Police
RMP	Risk management plan
SAE	Serious adverse event
UNESCO	United Nations Educational, Scientific and Cultural Organization

Abbreviation	Definition
VVWG	Vaccine Vigilance Working Group
WHO	World Health Organization

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PART 2

CONTRAINDICATIONS, PRECAUTIONS AND CONCERNS

There are a number of reasons for not giving vaccines. Sometimes vaccines cannot be given or need to be delayed due to contraindications or precautions. Other times people have unfounded concerns that lead to hesitation to get vaccination when there is no increased risk for vaccination. It is critical for vaccine providers to distinguish among these different reasons.

This chapter defines contraindications and precautions and highlights contraindications and precautions contained in other chapters in the *Canadian Immunization Guide*. It also identifies common concerns and provides information to assist vaccine providers in responding to those concerns. In most cases, these concerns can be addressed with information and reassurance. This chapter is meant to be a user friendly guide to aid in determining whether a particular condition is a contraindication to vaccination, a precaution or a common concern that need not postpone or prevent vaccination.

A **contraindication** is a situation in which a drug, such as a vaccine, should **not** be used because the risk outweighs any potential therapeutic benefit.

A **precaution** is a condition that may increase the risk of an adverse reaction following immunization or that may compromise the ability of the vaccine to produce immunity. In general, vaccines are deferred when a precaution is present. However, there may be circumstances when the benefits of giving the vaccine outweigh the potential harm, or when reduced vaccine immunogenicity may still result in significant benefit to a susceptible, immunocompromised host.

Some precautions and contraindications depend on whether a vaccine is an attenuated live product or an inactivated product. See the list of inactivated vaccines and live, attenuated vaccines authorized and available for use in Canada. For complete vaccine-specific contraindications and precautions, consult the relevant chapter in the *Canadian Immunization Guide*, the product leaflet, or information contained within the vaccine's product monograph available through Health Canada's Drug Product Database. (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/databasdon/index-eng.php)

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Inactivated vaccines and live, attenuated vaccines authorized and available for use in Canada List

Inactivated vaccines	Live, attenuated vaccines
Acellular pertussis	Bacillus Calmette-Gérin (BCG)
Cholera and traveller's diarrhea	Herpes Zoster (shingles)
Diphtheria toxoid	Live attenuated influenza (LAIV)
Haemophilus influenzae type b (Hib)	Measles
Hepatitis A	Mumps
Hepatitis B	Rotavirus
Human papillomavirus (HPV)	Rubella
Inactivated poliomyelitis	Smallpox
Japanese encephalitis	Typhoid (oral formulation)
Meningococcal	Varicella (chickenpox)
Pneumococcal	Yellow fever
Rabies	
Tetanus toxoid-	
Tick-borne encephalitis	
Trivalent inactivated influenza (TIV)	
Typhoid (injectable formulation)	

CONTRAINDICATION AND PRECAUTIONS

Vaccine providers should question all clients about their current health and any chronic conditions to identify contraindications and precautions to the vaccine before each dose of vaccine is given. Checklists and routine screening questions are useful. Refer to Vaccine Administration Practices in Part 1 for additional information.

The following is a summary of some of the common contraindications and precautions.

ANAPHYLACTIC REACTION TO A VACCINE OR A COMPONENT OF A VACCINE

A vaccine is contraindicated in a person with a history of anaphylaxis after previous administration of the same vaccine and in a person with proven immediate or anaphylactic hypersensitivity to any component of the vaccine (with the exception of egg allergy in certain circumstances) or its container. In situations of *suspected* hypersensitivity or non-anaphylactic allergy to a vaccine or its components, investigation is indicated which may involve immunization in a controlled setting. Consultation with an allergist is advised.

ASTHMA, SEVERE

Asthma should be optimized before giving any vaccine. LAIV should not be administered to individuals with severe asthma (defined as currently on oral or high dose inhaled glucocorticosteriods or active wheezing) or those with medically attended wheezing in the seven days prior to vaccination. LAIV can be used in stable, non-severe asthmatics.

CONGENITAL MALFORMATION OF GASTROINTESTINAL TRACT OR HISTORY OF INTUSSUSCEPTION

Rotavirus vaccine is contraindicated in infants with a history of intussusception or uncorrected congenital malformation of the gastrointestinal tract that would predispose for intussusception.

GUILLAIN-BARRÉ SYNDROME (GBS) WITH ONSET WITHIN 6 WEEKS OF IMMUNIZATION

Cases of GBS or polyneuritis have been reported following administration of tetanus toxoid-containing vaccine and there has been one case report of relapsing GBS following each of three doses of vaccine. However, population studies have not supported a causal association. Cases of GBS or polyneuritis have also been reported following receipt of diphtheria toxoid-containing vaccine. While some evidence favours a causal relationship between tetanus toxoid and GBS, there is little evidence to support an independent association between receipt of diphtheria toxoid and GBS. Persons who develop GBS within 6 weeks of receipt of tetanus toxoid-containing vaccine should not receive a further dose. Those who develop GBS outside the 6-week interval may receive subsequent doses of the vaccine. If there is a history of both *Campylobacter* infection (which has been associated with GBS) and receipt of a tetanus and diphtheria toxoid-containing vaccine within the 6 weeks before the onset of GBS, consultation with an infectious disease specialist is advised.

In a review of studies between 1976 and 2005, the United States Institute of Medicine concluded that the 1976 swine flu vaccine was associated with an elevated risk of Guillain-Barré Syndrome (GBS). However, evidence was inadequate to accept or reject a causal relation between GBS in adults and seasonal influenza vaccination. More recent studies suggest that the absolute risk of GBS in the period following seasonal and A(H1N1)pdm09 influenza vaccination is about one excess case per 1 million vaccines. The risk of GBS associated with influenza vaccination must be balanced against the risk of GBS associated with influenza infection itself. In general, it is recommended to avoid subsequent influenza vaccination of persons known to have had GBS within six weeks of a previous influenza vaccination.

IMMUNOCOMPROMISED PERSONS

In general, **immunocompromised people should not receive live vaccines because of the risk of disease caused by the vaccine strains.** People who are severely immunocompromised or in whom immune status is uncertain should not be given live vaccines. In less severely immunocompromised people, the benefits of vaccination with routinely recommended live vaccines may outweigh risks. When considering immunization of an immunocompromised person with a live vaccine, **approval from the individual's attending physician should be obtained before vaccination.** In complex cases, referral to a physician with expertise in immunization and/or immunodeficiency is advised.

Suspicious family or medical history for immunodeficiency disorders

People who have a suspicious history for immunodeficiency disorders (e.g., known or suspected family history of congenital immunodeficiency disorder or HIV infection, or history of failure to thrive and recurrent infection), should not be immunized with a live vaccine until they have been fully investigated and T cell dysfunction ruled out. Immunodeficiency states may be undiagnosed in young children presenting for routine immunizations, which include live vaccines. This is particularly important to consider in infants receiving live vaccines (e.g. BCG or travel vaccines) before 12 months of age since underlying conditions are less likely to be diagnosed in younger children. Refer to Immunization of Immunocompromised Persons in Part 3 for further information.

Immunosuppressive therapy

Vaccination status should be reviewed for prior to commencing immunosuppressive therapy. If vaccines cannot be given prior to initiation of therapy, it is advisable to delay vaccines until after immunosuppressive therapy has stopped. Inactivated vaccines should be delayed 3 months (to ensure immunogenicity) and live vaccines should be delayed 1-3 months (to reduce the risk of disease caused by the vaccine strain) The interval between discontinuation of immunosuppressive drugs and vaccine administration may vary with the intensity of the immunosuppressive therapy, underlying disease and other factors (e.g., inactivated vaccines can be administered if required for post-exposure

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or outbreak management).

If immunosuppressive therapy cannot be stopped, live vaccines are generally contraindicated, although the risk to benefit ratio may favour immunization if only low doses of immunosuppressive drugs are required and there is significant risk of development of disease. The use of live vaccines in persons on low dose immunosuppression is under review by the National Advisory Committee on Immunization (NACI).

In general, the above advice is the same for people taking immunusuppressive monoclonal antibodies such as rituximab or TNF-inhibitors (such as infliximab and adalimumab). An additional consideration is that monoclonal antibodies taken during pregnancy can be transferred to the fetus and their effects may persist after birth. Consultation with an immunologist is strongly advised prior to giving live vaccines to an infant who may have been exposed to monoclonal antibodies during pregnancy or breastfeeding. Refer to Immunization of Immunocompromised Persons, Immunization in Pregnancy and Breastfeeding, Immunization of Persons with Chronic Diseases in Part 3 for additional information.

PREGNANCY

In general, live vaccines are contraindicated in pregnancy, as there is a theoretical risk to the fetus; however, there are circumstances in which vaccination with a live vaccine may be considered.

In general, routine inactivated vaccines may be administered to pregnant women, if indicated. HPV vaccine is not recommended for use in pregnancy although no adverse outcomes of pregnancy or adverse events to the developing fetus have been reported.

TUBERCULOSIS, ACTIVE, UNTREATED

MMR, MMRV, varicella, and herpes zoster vaccines are contraindicated in individuals with active, untreated tuberculosis as a precautionary measure. Although tuberculosis may be exacerbated by natural measles infection, there is no evidence that measles or varicella-containing vaccines have such an effect. BCG vaccine is contraindicated for individuals with a positive tuberculin skin test, although immunization of tuberculin reactors has occurred frequently without complications.

Table 1 summarizes common contraindications and selected precautions for inactivated and live vaccines. Vaccine-specific contraindications and precautions are contained in the relevant chapters in Part 4. Refer to Contents of Immunizing Agents Available for Use in Canada in Part 1 for a detailed list of inactivated and live vaccines and their contents.

Table 1: Contraindications and selected precautions for vaccine administration for inactivated and live vaccines

Contraindications and selected precautions	Type of vaccine		Comments
	Inactivated	Live	
Anaphylaxis			
Anaphylaxis after *previous dose of a vaccine*	*Contraindicated* if receiving the same vaccine	*Contraindicated* if receiving the same vaccine	Refer to Early Vaccine Reactions Including Anaphylaxis in Part 2.
Proven[2] immediate or anaphylactic hypersensitivity to *any component of the vaccine or its container* (e.g., latex)	*Contraindicated* if receiving vaccine containing the same component[3]	*Contraindicated* if receiving vaccine containing the same component[3]	

Contraindications and selected precautions	Type of vaccine		Comments
	Inactivated	Live	
Asthma, severe[4]	*No contraindication* Subjects anchored within this page[1]	**LAIV** *contraindicated* for individuals with severe asthma[4] or those with medically attended wheezing in the 7 days prior to vaccination.	Asthma control should be optimized prior to any vaccine. Refer to Influenza Vaccine in Part 4.
Congenital malformation of gastrointestinal tract, uncorrected	*No contraindication* or precaution[1]	**Rotavirus vaccine** *contraindicated* due to increased risk of intussusception.	
Guillain-Barre Syndrome within 6 weeks of receiving a vaccine	Generally *contraindicated* if receiving the same vaccine. For influenza vaccine, the risk of GBS associated with influenza vaccination must be balanced against the risk of GBS associated with influenza infection itself.[5]	Generally *contraindicated* if receiving the same vaccine. For influenza vaccine, the risk of GBS associated with influenza vaccination must be balanced against the risk of GBS associated with influenza infection itself.[5]	Refer to vaccine-specific chapters in Part 4
Immunocompromised persons due to underlying condition	*No contraindication* For complex cases, referral to a physician with expertise in immunization and/or immunodeficiency is advised.[1]	*Contraindicated* if severely immunocompromised May be able to give vaccine in milder cases of immunosuppression or when potential benefit outweighs potential risk.	Refer to Immunization of Immunocompromised Persons in Part 3
Immunosuppressive therapy (e.g., cancer treatment, monoclonal antibodies)	*No contraindication*; may need to delay inactivated vaccines 1 to 3 months after finishing immunosuppressive therapy[1]	*Contraindicated* in most cases. Consultation with an immunologist is strongly advised prior to vaccinating an infant who has been exposed to monoclonal antibodies (MABs). MABs taken during pregnancy can be transferred to the fetus and their effects may persist during infancy. Likewise MABs may be transferred through breast milk.	Decision to delay or defer vaccination dependent on type and dose of immunosuppressive agent and risk benefit assessment. Refer to Immunization of Immunocompromised Persons in Part 3

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Contraindications and related precautions	Type of vaccine		Comments
	Inactivated	Live	
Intussusception, past history	*No contraindication or precaution*[1]	Rotavirus vaccine *contraindicated*	
Pregnancy	Generally *no contraindications* for routine vaccines[1]	Generally *contraindicated*	Refer to Immunization in Pregnancy and Breastfeeding in Part 3.
	Precaution - HPV vaccine (due to lack of data)		
Tuberculosis, active, untreated	*No contraindications* for routine vaccines[1]	MMR, MMRV, univalent varicella, herpes zoster, and BCG vaccines *contraindicated*	Refer to vaccine-specific chapters in Part 4.

[1] Safe: defined in the context of therapeutic products, such as vaccines, as "...the relative freedom from harmful effect to persons affected, directly or indirectly, by a product when prudently administered, taking into consideration the character of the product in relation to the condition of the recipient at the time." From: US Food and Drug Administration, *Code of Federal Regulations Title 21*.

[2] If *suspected* hypersensitivity or non-anaphylactic allergy to vaccine or vaccine components (e.g., yeast, gelatin), investigation is indicated if receiving same vaccine or vaccine containing the same component. May involve immunization in a controlled setting. Consultation with an allergist is advised.

[3] Except for administration of trivalent inactivated influenza (TIV), measles-mumps-rubella, or measles-mumps-rubella-varicella vaccines to egg-allergic persons.

[4] Severe asthma: defined as currently on oral or high dose inhaled glucocorticosteroids or active wheezing.

[5] Those who develop GBS outside the 6 week interval may receive subsequent doses of the vaccine..

BCG = Bacille Calmette-Guérin vaccine
HPV = human papillomavirus vaccine
LAIV = live attenuated influenza vaccine
MMR = measles-mumps-rubella vaccine
MMRV = measles-mumps-rubella-varicella vaccine
Tdap = tetanus toxoid, diphtheria toxoid (reduced), acellular pertussis (reduced) vaccine