CANADIAN IMMUNIZATION GUIDE

PART 2

PROTECTING CANADIANS FROM ILLNESS

Public Health Agency of Canada
Agence de la santé publique du Canada

Canada

TO PROMOTE AND PROTECT THE HEALTH OF CANADIANS THROUGH LEADERSHIP, PARTNERSHIP, INNOVATION AND ACTION IN PUBLIC HEALTH.

—Public Health Agency of Canada

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PART 2

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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 requirement	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 life cycle 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 life cycle 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.

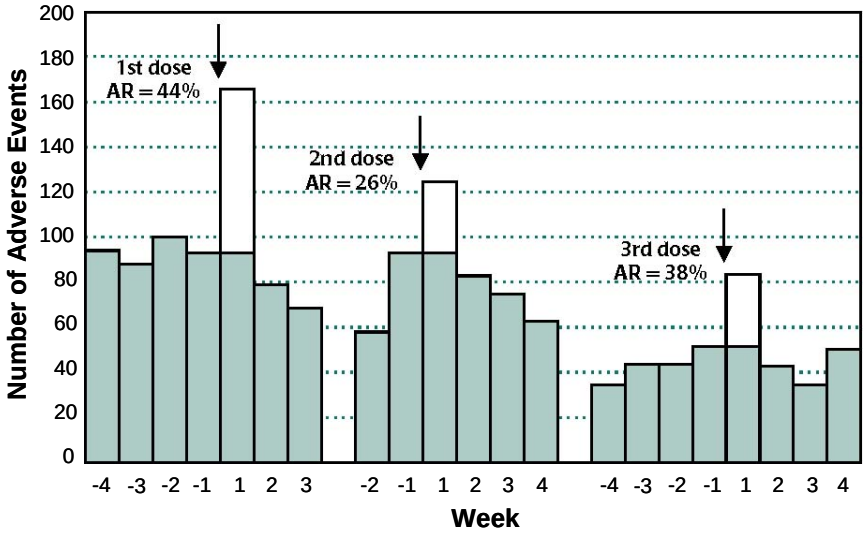
Table 3: Placebo-controlled randomized cross-over design to determine proportion of fever attributable to MMR vaccine*

	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)

SELECTED REFERENCES

Advisory Committee on Population Health and Health Security*. Final report: National Immunization Strategy*, 2003. Accessed November 2012.

Berkovic SF, Harkin L, McMahon JM et al. *De-novo mutations of the sodium channel gene SCN1A in alleged vaccine encephalopathy: a retrospective study*. Lancet Neurol 2006;5:488-92.

Council for International Organizations of Medical Sciences (CIOMS). *Report of CIOMS/WHO Working Group on Vaccine Pharmacovigilance: Definition and Application of Terms for Vaccine Pharmacovigilance.* 2012. Accessed December 2012.

Dellepiane N, Griffiths E, Milstien JB. *New challenges in assuring vaccine quality*. Bulletin WHO 2000;78(2):155-62.

De Serres G, Skowronski DM, Guay M et al. *Recurrence risk of oculorespiratory syndrome after influenza vaccination: randomized controlled trial of previously affected persons*. Arch Intern Med. 2004 Nov 8;164(20):2266-72. Erratum in: Arch Intern Med. 2005 Jan 24;165(2):145.

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.

Folb PI, Bernatowska E, Chen R. et al. *A global perspective on vaccine safety and public health: the Global Advisory Committee on Vaccine Safety*. Am J Public Health 2004;94(11):1926-31. Accessed November 2012.

Immunize Canada. *Fact sheet: Immunization Information on the Internet: Can you trust what you read?* Accessed November 2012. English version; French version.

Institute of Medicine. 2011. *Adverse Effects of Vaccines: Evidence and Causality*. Washington, DC: The National Academies Press.

Institute of Medicine. 2013. *The Childhood Immunization Schedule and Safety: Stakeholder Concerns, Scientific Evidence, and Future Studies.* Committee on the Assessment of Studies of Health Outcomes Related to the Recommended Childhood Immunization Schedule; board on Population Health and Public Health Practice. Washington, DC: The National Academies Press.

Offit PA. *The Cutter Incident – How America's First Polio Vaccine Led to the Growing Vaccine Crisis*. 2005. Yale University Press, New Haven and London.

Peltola H, Heinonen OP. *Frequency of true adverse reactions to measles-mumps-rubella vaccine.* Lancet 1986;1(8487):939-42.

Public Health Agency of Canada. F/P/T contact information for AEFI-related questions. Accessed April 28, 2013.

World Health Organization Global Advisory Committee on Vaccine Safety. *Bi-annual meeting reports, including summary lists of the topics discussed and full text details*. Accessed November 2012.

World Health Organization Vaccine Safety Net. Accessed November 2012 at:

World Health Organization. Guidelines for preparing core clinical safety information on drugs - report of the Council for International Organizations of Medical Sciences (CIOMS) Working Group III. Geneva: WHO, 1994. (Chapter 5, Good Safety Information Practice).

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)

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

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

Contraindications and selected 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

COMMON CONDITIONS AND CONCERNS

There are a number of conditions that may be raised as a concern about receiving a vaccine, that in fact should not delay or preclude immunization. For example, routine administration of vaccines should not be postponed in persons with minor illnesses, such as an upper respiratory tract infection, otitis media, mild gastrointestinal illness, or concurrent antibiotic therapy. Repeated infectious illnesses are common in early childhood and will not interfere with the efficacy of vaccines. Generally, if a person is well enough to present for immunization in the outpatient setting, he/she is well enough to be immunized.

Opportunities for immunization should not be lost because of unfounded concerns. Information and reassurance can generally allay reservations about receiving vaccines in these circumstances. The following identifies some of the common concerns and implications for immunization.

ACUTE ILLNESS (WITH OR WITHOUT FEVER)

In general, people with minor or moderate acute illness may receive vaccines. There is no increase in risk of adverse events following immunization and no interference with response to vaccine. There are three exceptions –

- If significant nasal congestion is present that might impede delivery of LAIV to the nasopharyngeal mucosa, TIV can be administered or LAIV could be deferred until resolution of the illness.
- In infants with moderate-to-severe gastroenteritis, rotavirus vaccine should be deferred until the condition improves unless deferral will result in scheduling of the first dose beyond the recommended age limit.
- Administration of oral cholera and travellers' diarrhea vaccine should be postponed in persons with acute gastrointestinal illness.

The risks and benefits of vaccinating a severely ill person need to be carefully assessed. The benefits of protection in a high risk exposure situation or when the window of opportunity is short (i.e., when travel or immunocompromise are imminent) need to be assessed against the risks that a vaccine-related adverse event (particularly fever) could complicate the management of the person. It is possible that systemic adverse events may complicate the medical management of an acute illness or that events associated with the acute illness may be misperceived as vaccine-related adverse events. Expert opinion is strongly recommended in this situation.

ADVERSE EVENT FOLLOWING PREVIOUS IMMUNIZATION

There are numerous adverse events following a previous immunization that may lead to concern regarding another immunization.

Extensive limb swelling following immunization

A severe injection site reaction to one vaccine is not associated with an increased risk of injection site reactions to other vaccines. Repeating a dose of a vaccine that was previously associated with a large injection site reaction may result in a similar reaction; however, there is no increased risk of systemic adverse events. A large injection site reaction may occur in a child after the fourth or fifth dose of a diphtheria toxoid-tetanus toxoid-acellular pertussis-containing vaccine. The presence of a large injection site reaction to a previous dose is not a contraindication to continuing the recommended schedule.

Severe injection site reactions occasionally occur in adults following receipt of diphtheria toxoid-tetanus toxoid-containing vaccine (Td). Further routine doses of Td vaccine should not be given for at least 10 years.

Hypotonic-hyporesponsive episode (HHE) following immunization

HHE may occur following immunization with pertussis-containing vaccine but occurs less frequently following receipt of current acellular pertussis-containing vaccines. There is evidence that there are no adverse consequences to these events.

Febrile seizure or syncope following immunization

Parents may hesitate to have their child have a vaccine if he/she had a history of a post-immunization febrile seizure. Likewise, people may hesitate to have a vaccine if they had an episode of syncope following a previous vaccine (such as may occur with HPV vaccine in a young girl).

Vaccines are safe to given when there is a history of a febrile seizure. For MMR vaccine for example, the risk of febrile seizures within 2 weeks following MMR vaccination was 1.56 per 1000 children overall, 3.97 per 1000 for siblings of children with a history of febrile seizures, and 19.47 per 1000 for children with a personal history of febrile seizures. This means when a child has a history of a febrile seizure 98% will *not* have a febrile seizure following an MMR vaccine. Children with a history of febrile seizures have no increased risk of developing a seizure disorder, such as epilepsy. Oral analgesics/antipyretics (such as acetaminophen or ibuprofen) can be used for treatment of minor adverse reactions such as fever or injection site discomfort that might occur following vaccination. There is no evidence that antipyretics prevent febrile seizures.

Vaccines are safe to give when there is a history of fainting after a vaccine. The likelihood of fainting can be reduced by measures that lower stress in those awaiting immunization, such as short waiting times, comfortable room temperature, preparation of vaccines out of view of recipients, and privacy during the procedure. People should be immunized while seated. Refer to Vaccine Administration Practices in Part 1 for additional information.

Inconsolable crying following immunization

Persistent or inconsolable crying and an unusual, high-pitched cry (most typically after pertussis vaccination) are not associated with any sequelae and are likely to be pain responses at the site of injection in young infants. Refer to Vaccine Administration Practices in Part 1 for comfort measures that can be taken.

Ocular-respiratory syndrome (ORS)

Oculo-respiratory syndrome is a usually transient condition characterized by bilateral conjunctivitis, facial edema, and upper respiratory symptoms that has been known to occur primarily after receiving influenza immunization. Symptoms typically appear 2 to 24 hours after vaccination and resolve within 48 hours of onset. If ORS occurred with lower respiratory symptoms, subsequent influenza vaccine is contraindicated. Refer to Influenza vaccine in Part 4 for additional information.

ALLERGIES

A history of allergies is one of the most common concerns that people have about vaccines. There are many types of allergic reactions and it is important to differentiate among them when considering implications for immunization.

Allergic reactions can be either immediate or delayed. An immediate hypersensitivity reaction usually occurs within moments or up to one hour after vaccine. It is IgE mediated (Type 3) and can be either mild (e.g. hives) or severe, such as anaphylaxis. Refer to Early Vaccine Reactions Including Anaphylaxis in Part 2 for additional information.

Delayed hypersensitivity reactions may appear several hours to days after immunization. These reactions include an Arthus or Type 3 reaction (a local vasculitis due to deposition of IgG-based immune complexes in dermal blood vessels) or more typically, a cell-mediated, delayed hypersensitivity or Type 4 reaction (typically a contact dermatitis). These are typically local reactions to a component of the vaccine.

Severe arthus-type injection site reactions are occasionally reported following receipt of diphtheria toxoid or tetanus toxoid-containing vaccines. There may be extensive painful swelling around the injection site, often involving the arm from shoulder to elbow and generally beginning 2 to 8 hours after injection. Persons experiencing severe injection site reactions should not receive further routine doses of Td vaccine for at least 10 years.

On close questioning, it may become evident that people think they have an allergy to a vaccine or vaccine component but it is not an allergy. Most adverse skin events associated with vaccines, for example, are simply a normal inflammatory response to a foreign substance. As these inflammatory reactions are not related to allergy, patients can receive subsequent vaccinations safely. People can be reassured if they have a mild hypersensitivity reaction, such as a contact dermatitis from either the vaccine or one of its components. People with a suspected moderate to severe hypersensitivity reaction, should be referred to an allergist for further testing. Suspected hypersensitivity should not be an ongoing reason to not administer vaccine. It should be investigated by an allergist to clarify whether the person may proceed with vaccination or not.

Egg allergy

Anaphylactic egg allergy is rare. People with egg allergy may be immunized with MMR or MMRV vaccines in the routine manner. The amount of egg/chicken protein in these vaccines have been found to be insufficient to cause an allergic reaction in egg-allergic individuals. Egg-allergic individuals may be vaccinated against influenza using TIV, without prior influenza vaccine skin test and with the full dose, irrespective of a past severe reaction to egg, with the following conditions. Those with mild reactions such as hives, or those who tolerate eggs in baked goods may be vaccinated in regular vaccination clinics. Those who have suffered from anaphylaxis with respiratory or cardiovascular symptoms should be vaccinated in a medical clinic, allergy office or hospital where appropriate expertise and equipment to manage respiratory or cardiovascular compromise is present. These individuals should always be kept under observation for 30 minutes. Referral to a specialist with expertise in allergies may be necessary in occasional circumstances where there is strong concern about proceeding with the recommendation above and the individual is at risk of complications from influenza. If the individual is not in a high-risk group, the need for vaccination may be reassessed. Data are not currently available to support these recommendations for LAIV.

OTHER ALLERGIES

People may report an allergy to a number of vaccine components, such as gelatin, latex, neomycin or thimerosol. Anaphylactic reactions to these components are extremely rare. When mild hypersensitivity reactions occur, vaccines that are administered subcutaneously or intramuscularly are generally safe. A thimerosol allergy is extremely rare. If there is a documented history of a delayed hypersensitivity reaction to thimerosal (such as a large local reaction or an eczematous rash), immunization with thimerosal-containing vaccines can proceed. In the rare instance of individuals with proven delayed hypersensitivity to thimerosol, they should be advised that long-lasting local or systemic cutaneous reactions can occur. They should report any reaction of concern following immunization so that it can be managed appropriately. Refer to Table 2 and Contents of Immunizing Agents Available for Use in Canada in Part 1 for additional information.

BLEEDING DISORDER

People with bleeding disorders should receive all recommended immunizations according to routine schedules when appropriate safety measures have been taken. Control of bleeding disorders should be optimized prior to immunization. Vaccine providers should ensure that there are no symptoms or signs compatible with an undiagnosed bleeding disorder (e.g. unexplained bruising). If such indicators are present before immunization, a diagnosis should be established before commencing immunization. When administering a parenteral vaccine, consider use of a small gauge needle and apply pressure for 5-10 minutes after the immunization. Refer to Immunization of Persons with Chronic Diseases in Part 3.

BREASTFEEDING

Following routine immunization of either a mother or her infant during breastfeeding there is no reduction in maternal or infant response to vaccines and no increase in the risk of adverse events for either mother or infant. There is some evidence that breastfeeding may have a beneficial effect in infants after vaccination and is associated with less fever and pain. BCG, smallpox and yellow fever vaccines are generally contraindicated in breastfeeding women but may be considered in high-risk situations.

CONCERNS ABOUT IMMUNIZATION

Concern about exposure to too many antigens

Parents often have a concern about exposing their young child to too many antigens when multiple vaccines are recommended at one time. It is useful to identify that the human immune system has an enormous capacity to respond to antigens; infants can respond to about 10,000 different antigens at any one time – and may do so when crawling on the floor. Immunization does not significantly add to the vaccinee's daily exposure to antigens. The vaccines given to young infants in Canada engage less than 0.01% of an infant's immune response capacity. Generally, vaccinees have similar immune responses whether vaccines are given at the same time or at different visits. Concomitant administration of most routine vaccines at the same visit does not result in increased rates of adverse reaction.

Concern about multiple injections

Routine administration of all age-appropriate doses of vaccines simultaneously is recommended for children without contraindications. There are no contraindications to giving multiple injections at the same visit and all opportunities to immunize should be utilized. Live viral vaccines given by injection may be either given concomitantly or a minimum interval of 4 weeks apart to address the hypothetical risk of interference from the vaccine given first on the vaccine given later. Generally if two live parenteral vaccines are indicated, it is preferable to them concomitantly to avoid the need for a follow up visit. Concomitant administration of vaccines may be critical when preparing for international travel. Refer to recently administered live viral vaccines.

People may need to be reassured that concomitant administration of most routine vaccines at the same visit does not result in decreased antibody responses or increased rates of adverse reaction. Giving multiple vaccines at one visit helps to ensure that people are up to date with the vaccines required for their age and risk factors.

Concern about thimerosol

It is not unusual for people to voice concerns about thimerosol and the effect it can have on brain tissue. Thimerosol is used as a preservative in some vaccines, but not in a dose that would cause safety concerns. If no allergic history is present, there is no legitimate safety reason to avoid the use of thimerosol-containing products, for children or adults, including pregnant women

CONCURRENT MEDICATION, INCLUDING BIOLOGICS

Antibiotic therapy

Antibiotic therapy, does not interfere with response to inactivated vaccines or most live vaccines with the following exceptions: Live, oral typhoid vaccine should be delayed until 48 to 72 hours after receipt of the last dose of antibiotics active against *Salmonella typhi*. BCG vaccine should not be administered to individuals receiving drugs with anti-tuberculous activity, including fluoroquinolones.

Anticoagulation

Individuals receiving long-term anticoagulation with either warfarin or heparin are not considered to be at higher risk of bleeding complications following immunization and may be safely immunized through either the intramuscular or subcutaneous route (as recommended for the vaccine product)without discontinuation of anticoagulation therapy. Give intramuscular administration with a small gauge

needle (23 gauge or smaller) and apply firm pressure to the injection site for 5 to 10 minutes. There is a paucity of evidence on whether there is an increased risk of bleeding complications following immunization with the newer types of anticoagulants, such as antiplatelet agents, but there is no reason to believe that they need to be treated any differently from those receiving other anticoagulants.

Antiviral therapy

Antiviral therapy does not interfere with response to inactivated vaccines or most live vaccines with the following exceptions:

- Varicella vaccine and herpes zoster vaccine may have reduced effectiveness if given concurrently with antivirals active against varicella zoster virus (such as acyclovir, valacyclovir, famciclovir). People taking long-term antiviral therapy should discontinue these drugs, if possible, from at least 24 hours before administration of varicella or herpes zoster vaccine and should not restart antiviral therapy until 14 days after vaccination.
- LAIV should not be administered until 48 hours after antiviral agents active against influenza (e.g., oseltamivir and zanamivir) are stopped, and antiviral agents should not be administered until at least 14 days after receipt of LAIV unless medically indicated. If antiviral agents are administered within this time frame (from 48 hours before to 14 days after LAIV), revaccination should take place at least 48 hours after the antivirals are stopped.

Recent administration of blood products containing antibodies

Passive immunization with human immune globulin or receipt of most blood products can interfere with the immune response to certain live vaccines. Measles-containing or varicella vaccines should be given at least 14 days prior to administration of an immune globulin preparation or blood product, or delayed until the antibodies in the immune globulin preparation or blood product have degraded. A risk-benefit assessment is needed for post-partum women who have received Rh immune globulin (RhIg) and require MMR or varicella vaccine (refer to Immunization in Pregnancy and Breastfeeding in Part 3 for additional information). Herpes zoster vaccine should be delayed until 3 months after a dose of intravenous immune globulin.

Salicylates

It is generally safe to be immunized when taking salicylates (acetylsalicylic acid, aspirin, or ASA) although some exceptions apply. LAIV is contraindicated in children and adolescents (2-17 years of age) currently receiving salicylates (e.g. ongoing treatment with aspirin-containing therapy) because of the association of Reye's syndrome with ASA and wild-type influenza infection. TIV is a good alternative. ASA-containing products should be delayed for 4 weeks after receipt of LAIV in children less than 18 years of age.

Another exception is varicella immunization. Varicella-containing vaccine manufacturers recommend avoidance of salicylate therapy for 6 weeks after varicella immunization because of an association between wild-type varicella, salicylate therapy and Reye's syndrome. Health care providers should weigh the theoretical risks associated with varicella vaccine against the known risks associated with wild-type varicella. Because adverse events have not been reported with the use of salicylates after varicella immunization, people with conditions requiring chronic salicylate therapy should be considered for immunization, with close subsequent monitoring. Refer to Immunization of Persons with Chronic Diseases in Part 3 for additional information.

NEUROLOGIC DISORDER

There is no evidence of increased risk of adverse events following immunization in persons with neurologic disorders. Such persons may be at increased risk of complications from vaccine preventable diseases such as influenza and should be immunized appropriately with the exception of people who experience an episode of GBS with onset within 6 weeks after immunization.

PREMATURE BIRTH

Premature infants respond adequately to vaccines used in infancy and are not at significantly increased risk of adverse events. In general, immunize premature infants per the routine immunization schedule, according to child's chronological age with the exception of hepatitis B vaccination of preterm infants with a birth weight of less than 2,000 grams. The response to hepatitis B vaccine may be diminished in such infants; refer to Hepatitis B Vaccine in Part 4 for additional information. Hospitalized premature infants should have continuous cardiac and respiratory monitoring for 48 hours after their first immunization.

SKIN DISORDERS

Vaccines are generally safe for people with skin disorders. For comfort, administer vaccine into non-affected area. There are two exceptions to this. Smallpox vaccine is contraindicated in those with eczema (atopic dermatitis) in non-outbreak situation; refer to Smallpox Vaccine in Part 4. BCG vaccine is contraindicated when there is extensive skin disease or burns; refer to Bacille Calmette-Guerin Vaccine in Part 4.

Table 2 provides a reader-friendly summary of common conditions and vaccine concerns that could be used as an educational tool when obtaining informed consent for immunization.

Table 2: Common conditions and vaccine concerns and implications for immunization

Condition or concern	Implications for immunization -
Acute illness, minor (including upper respiratory infection, diarrhea)	Safe[1] with the following exceptions: • **LAIV:** If significant nasal congestion is present that might impede delivery of LAIV to the nasopharyngeal mucosa, TIV can be administered or LAIV could be deferred until resolution of the illness. • **Rotavirus vaccine:** If moderate-to-severe gastroenteritis, defer until condition improves unless deferral will result in scheduling of the first dose beyond the recommended age limit.**Oral cholera** vaccine: defer until acute gastrointestinal illness resolved. • **Oral cholera and travellers' diarrhea vaccine** should be postponed in persons with acute gastrointestinal illness
Acute illness, severe	Need to consider risk-benefit. Refer to Acute Illness in text.
Adverse event following previous immunization	
Extensive limb swelling following immunization	Safe, even when it crosses a joint.
Febrile seizure or syncope after previous immunization	Safe; refer to Vaccine Administration Practices in Part 1 for general precautions.
Hypotonic-hyporesponsive episode (HHE)	Safe; no long term consequences from an HHE episode.
Inconsolable crying	Safe; refer to Vaccine Administration Practices in Part 1 for general comfort measures.

Condition or concern	Implications for immunization -
Oculo-respiratory syndrome (ORS)	Safe except: • **Influenza vaccine:** contraindicated if ORS is present with lower respiratory involvement. Refer to Influenza Vaccine in Part 4.
Allergies	
Allergies, known	Safe for most **non-anaphylactic allergies** with the following considerations: • **Vaccine components:** If suspected hypersensitivity or non-anaphylactic allergy to vaccine components, investigation is indicated which may involve immunization in a controlled setting. Consultation with an allergist is advised. **Diphtheria toxoid or tetanus toxoid-containing vaccines:** If there is a history of a severe Arthus-type reactions following diphtheria toxoid or tetanus toxoid-containing vaccines, recipients should not receive further routine doses of Td vaccine for at least 10 years. Refer to Part 4 Tetanus Toxoid for additional information.See specific allergies below.If a history of anaphylaxis to any component of a vaccine, refer to Contraindications Table 1. Refer to Contents of Immunizing Agents Available for Use in Canada in Part 1 for lists of immunizing agents available for use in Canada and their contents.
Egg allergy	Vaccines in those with a ***non-anaphylactic egg allergy*** is generally safe with the following considerations: • **Live attenuated Influenza vaccine (LAIV):** is not recommended due to a lack of data ***Anaphylactic egg allergy*** is rare. When present it is a contraindication to vaccines containing egg with the following exceptions: • **Trivalent Influenza Vaccine (TIV):** Egg allergic individuals may be vaccinated against influenza using TIV without prior influenza vaccine skin test and with the full dose, with consideration being given to the most appropriate setting for the vaccine administration (Refer to Egg Allergy in text for details). • **MMR and MMRV vaccines:** The amount of egg/chicken protein in these vaccines have been found to be insufficient to cause an allergic reaction in egg-allergic individuals.
Gelatin allergy	Generally safe. Most gelatin allergies are non-anaphylactic and gelatin-containing vaccines may be given. Anaphylactic allergy to gelatin is extremely rare. For an anaphylactic allergy see Contraindications Table 1.
Latex allergy	Generally safe. For non-anaphylactic latex allergies (e.g., history of contact dermatitis to latex gloves), vaccines supplied in vials or syringes that contain dry natural rubber or natural rubber latex may be given. Anaphylactic allergy to latex is very rare. For an anaphylactic allergy see Contraindications Table 1.

Condition or concern	Implications for immunization -
Neomycin allergy	Generally safe. Neomycin allergy is most often a contact dermatitis (i.e., a delayed hypersensitivity reaction) which is not a contraindication for administration of vaccines containing neomycin. For an anaphylactic allergy see Contraindications Table 1.
Thimerosal allergy	Generally safe. A local or delayed-type hypersensitivity reaction to thimerosal is not a contraindication to receipt of a vaccine that contains thimerosal. Thimerosol allergy is extremely rare. In the rare instance of individuals with proven delayed hypersensitivity to thimerosol, they should be advised that long-lasting local or systemic cutaneous reactions can occur with repeat injection. They should report any reaction of concern following immunization so that it can be managed appropriately For an anaphylactic allergy see Contraindications Table 1.
Bleeding disorder	Safe with the following measures: • Optimize control of bleeding disorder before immunization. • Give intramuscular administration with a small gauge needle (23 gauge or smaller) and apply firm pressure to the injection site for 5 to 10 minutes. Refer to Immunization of Persons with Chronic Diseases in Part 3
Breastfeeding	Generally safe with the following considerations: • **BCG vaccine:** Exercise caution because it is not known whether BCG is excreted in human milk. • **Japanese encephalitis vaccine**: should only be given if the risk of disease outweighs the unknown risk of vaccination to the woman and her breastfeeding infant. • **Yellow fever vaccine:** Generally, breastfeeding mothers should not receive yellow fever vaccine. • **Smallpox vaccine** is contraindicated for breastfeeding mothers in non-outbreak situations; special precautions required if needed for post-exposure prophylaxis. Refer to Smallpox Vaccine in Part 4. Refer to Immunization in Pregnancy and Breastfeeding in Part 3.
Concerns about immunization	
Exposure to too many antigens	Combination vaccines are safe. Most children are exposed to thousands of antigens a day.
Multiple injections	Multiple injections of vaccines are safe. • For live viral parenteral vaccines, it is *preferable* to give concomitantly (otherwise need to give at least 4 weeks apart). • Oral and intranasal live vaccines can be given at the same time as, or any time before or after, other live vaccines Refer to Vaccine Administration Practices in Part 1 for measures to address potential anxiety and discomfort.
Vaccine contains thimerosal	Vaccines that contain thimerosal are safe in children, adults and during pregnancy

Condition or concern	Implications for immunization -
Concurrent medication, including biologics	
Antibiotic therapy	Generally safe with the following exceptions: • **Live typhoid vaccine:** Delay immunization if on antibiotics active against *Salmonella typhi* until 48 to 72 hours after last dose, refer to Typhoid Vaccine in Part 4. • **BCG vaccine:** Delay immunization if receiving antibiotic therapy active against mycobacteria (including quinolones), delay BCG immunization until antibiotic therapy completed. Refer to Bacille Calmette-Guerin Vaccine in Part 4.
Anticoagulation	Generally safe with the following considerations: • Give intramuscular administration with a small gauge needle (23 gauge or smaller) and apply firm pressure to the injection site for 5 to 10 minutes. Less data for risk with newer anticoagulants such as antiplatelet agents. Refer to Immunization of Persons with Chronic Diseases in Part 3
Antiviral therapy	Generally safe with the following exceptions: • **LAIV, herpes zoster and varicella:** Consider timing of administration if antiviral drug active against virus in vaccine. Recommended interval between these vaccines and antiviral drugs are vaccine and antiviral specific. Refer to vaccine specific chapters in Part 4.
Blood products containing antibodies **(**immunoglobulins; transfusion of reconstituted red blood cells, platelets or plasma)	Generally safe to give vaccine with the following exceptions: • **MMR, varicella-containing vaccine or herpes zoster vaccine:** Consider timing of vaccines; recommended interval between blood product and these vaccines are vaccine and blood product specific. Refer to Recent Administration of Human Immune Globulin Products in Part 1 and vaccine specific chapters in Part 4. • Risk benefit assessment is needed for post-partum women who have received Rh immune globulin (RhIg) and require MMR or varicella vaccine. Refer to Immunization in Pregnancy and Breastfeeding in Part 3.
Salicylates	Generally safe with the following exceptions: • **LAIV:** *If on salicylate therapy:* LAIV is contraindicated.[2] Use TIV instead. *For intermittent salicylate use:* In children and adolescents, avoid salicylates for 4 weeks after receiving LAIV.[2] • **Varicella-containing vaccine:** *For chronic salicylate therapy:* Varicella-containing vaccine may be considered with close monitoring *For intermittent salicylate use:* Avoid salicylates for 6 weeks after receiving varicella-containing vaccine.[2] Refer to Immunization of Persons with Chronic Diseases in Part 3.

Condition or concern	Implications for immunization -
Inflammatory eye disease requiring steroid therapy	Generally safe with the following exception: • **Smallpox vaccine:** In a non-outbreak situation, defer svaccination until condition resolves or course of steroids completed. Refer to Smallpox Vaccine in Part 4.
Measles infection	Generally safe with the following exception: • **Varicella-containing vaccine:** Delay vaccination for 4-weeks. Refer to Varicella (Chickenpox) Vaccine in Part 4.
Neurologic disorders	
History or family history of febrile seizure	Safe; refer to Vaccine Administration Practices in Part 1 for general precautionary measures.
History of Guillain-Barre Syndrome (GBS)	Safe unless GBS occurred within 6 weeks of receiving previous dose of same vaccine. See Contraindications Table 1.
History of syncopal episodes	Vaccinate in a safe environment which could include being vaccinated lying down, remaining seated in immunization clinic setting, and being accompanied when leaving clinic. Refer to Early Vaccine Reactions Including Anaphylaxis in Part 2 and Vaccine Administration Practices in Part 1.
Multiple Sclerosis (MS)	Safe
Premature birth	Vaccines are safe when given to infants who weighed 1500 grams or more at birth.[3] Refer to Immunization of Infants Born Prematurely in Part 3.
Skin disorder	Vaccines are generally safe; for comfort, administer vaccine into non-affected area. **Smallpox vaccine** is contraindicated in those with eczema (atopic dermatitis) in non-outbreak situation; refer to Smallpox Vaccine in Part 4. If extensive skin disease or burns, **BCG vaccine** is contraindicated; refer to Bacille Calmette-Guerin Vaccine 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] Salicylates are avoided in these instances to decrease the risk of Reyes syndrome.

[3] Infants born prematurely (especially those weighing less than 1,500 grams at birth) are at higher risk of apnea and bradycardia following vaccination. Hospitalized premature infants should have continuous cardiac and respiratory monitoring for 48 hours after their first immunization.

BCG = Bacille Calmette-Guérin vaccine
LAIV = live attenuated influenza vaccine
MMR = measles-mumps-rubella vaccine
MMRV = measles-mumps-rubella-varicella vaccine

CONCERNS ABOUT CONDITIONS IN CLOSE CONTACTS OF VACCINEES

Vaccination provides protection at both an individual and population level. Some people may have conditions that preclude vaccination, but they can be protected by having the people around them vaccinated. Immunization of household contacts of immunosuppressed persons, pregnant women, and neonates provides important protection against transmission of disease in the household.

Up-to-date routine immunizations are recommended for household contacts of pregnant women, immunocompromised persons, and neonates with the following exceptions:

- TIV is preferred over LAIV for those in close contact with severely immunocompromised persons.
- If there are household contacts who have received live, oral polio vaccine in another country within the last 6 weeks, they should not have contact with immunocompromised persons.
- If a vaccine recipient develops a varicella-like rash, the rash should be covered and the vaccinee should avoid direct contact with the immunocompromised person for the duration of the rash
- Smallpox vaccine should not be administered to household contacts of an immunocompromised person in a non-emergency situation.
- Special precautions should be taken for unvaccinated pregnant household and other close contacts of persons receiving smallpox vaccine in order to eliminate viral transfer to these contacts.

Table 3 summarizes conditions in persons who may be in close contact with vaccinees and provides information for vaccine providers and vaccine recipients about the appropriateness and safety of vaccines in these circumstances.

Table 3: Conditions in close contacts of vaccinee

Condition in close contact	Safe[1] to be immunized with the following exceptions -
Close contact is immunocompromised	• **TIV** is preferred for household contacts of severely immunocompromised persons. • If **LAIV** received, vaccinee should avoid close association with severely immunocompromised person for at least 2 weeks. • Following **varicella vaccine**, if the vaccine recipient develops a varicella-like rash, the rash should be covered and the vaccinee should avoid direct contact with the immunocompromised person for the duration of the rash • Live, **oral polio vaccine**[2] contraindicated. • If a household contact (traveller or immigrant) has received live, **oral polio vaccine** within the last 6 weeks; they should avoid contact with immunocompromised persons. Refer to Poliomyelitis Vaccine in Part 4. • **Smallpox vaccine** should not be administered to household contacts of an immunocompromised person in a non-emergency situation • Refer to Immunization of Immunocompromised Persons in Part 3.
Close contact is a neonate/infant	• Defer **smallpox vaccine** (if non-outbreak situation). If smallpox vaccine is received, vaccine should avoid close contact with the neonate until the scab at the vaccination site falls off. • Refer to Immunization of Immunocompromised Persons in Part 3.

Condition in close contact	Safe[1] to be immunized with the following exceptions -
Close contact is a pregnant women	• Defer **smallpox vaccine** (if non-outbreak situation) • If **smallpox vaccine** needed in an outbreak situation, avoid contact with the pregnant woman until the scab at vaccination site falls off. • Refer to Immunization in Pregnancy and Breastfeeding in Part 3.

[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 sec 600.3.*

[2] Oral polio vaccine is not recommended or available in Canada

SELECTED REFERENCES

Centers for Disease Control and Prevention. *An ounce of prevention…what are the returns?* 1999;2nd ed. Accessed June 2012.

Centers for Disease Control and Prevention. *Chart of Contraindications and Precautions to Commonly Used Vaccines.* Accessed June 2012.

Centers for Disease Control and Prevention. *General recommendations on immunization Recommendations of the Advisory Committee on Immunization Practices (ACIP).* MMWR Morb Mortal Wkly Rep 2011;60(RR-2):1-61.

Centers for Disease Control and Prevention. *The Pink Book: Epidemiology and Prevention of Vaccine Preventable Diseases.* 12th ed.; May 2012.Accessed June 2012.

Centers for Disease Control and Prevention. *Recommendations and Guidelines: Conditions Commonly Misperceived as Contraindications to Vaccination.* Accessed June 2012.

Ess SM, Szucs TD. *Economic evaluation of immunization strategie*s. Clin Infect Dis 2002;35:294-97.

Halperin BA, Eastwood BJ, Halperin SA. *Comparison of parental and health care professional preferences for the acellular or whole cell pertussis vaccine*. Pediatr Infect Dis J 1998;17(2):103-9.

Tengs TO, Adams ME, Pliskin JS. *Five hundred live-saving interventions and their cost-effectiveness.* Risk Analysis 1995;15(3):369-90.

United States Food and Drug Administration. *Code of Federal Regulations. Title 21 – Food and Drugs. Chapter 1 – Food and Drug Administration*. Department of Health and Human Services. Sec 600.3. Revised April 1, 2012. Accessed February 2013.

Vestergaard M, Hviid A, Madsen KM, Wohlfahrt J, Thorsen P, Schendel D, Melbye M, Olsen J. MMR vaccination and febrile seizures: evaluation of susceptible subgroups and long-term prognosis. JAMA. 2004 Jul 21;292(3):351-7.

PART 2

EARLY VACCINE REACTIONS INCLUDING ANAPHYLAXIS

This chapter is intended as a guide for the initial management of vaccine recipients who develop vaccine reactions within a two hour period following immunization in a non-hospital setting (e.g., public health clinic, medical office). For a vaccine recipient with severe, life-threatening anaphylaxis, establishment of intravenous (IV) access for drug and fluid administration will be necessary, and endotracheal intubation and other manoeuvres may be required. These interventions are generally best performed by ambulance personnel or in a hospital's emergency department.

Since the publication of the *2006 Canadian Immunization Guide:*

- The intramuscular route has been preferentially recommended for injection of epinephrine for anaphylaxis management.
- The recommended steps for basic management of anaphylaxis in a non-hospital setting have been updated according to the *World Allergy Organization Guidelines for the assessment and management of anaphylaxis* published in 2011 and updated in 2012.
- Recommendations for adjunctive treatment of anaphylaxis have been revised.
- The dosing guidelines for epinephrine have been revised, and there is now more information regarding the use of auto-injectors.
- When a vaccine has been given subcutaneously an additional dose of epinephrine is no longer recommended at the injection site, as this is not part of the WAO guidelines and there is no evidence to support it.
- The recommended items in an anaphylaxis management kit have been revised.

FAINTING, ANXIETY OR BREATH-HOLDING

Fainting (vasovagal syncope), anxiety and breath-holding episodes are benign reactions to vaccination which occur more commonly than anaphylaxis.

FAINTING

During fainting, the individual suddenly becomes pale, loses consciousness and collapses to the ground. Fainting is sometimes accompanied by brief clonic seizure activity (i.e., rhythmic jerking of the limbs) which generally requires no specific treatment or investigation. Fainting is managed by placing the vaccinee in a recumbent position. Recovery of consciousness occurs within a minute or two, but the person may remain pale, diaphoretic and mildly hypotensive for several minutes.

The likelihood of fainting is reduced by measures that lower stress in those awaiting immunization, such as short waiting times, comfortable room temperature, preparation of vaccines out of view of recipients, and privacy during the procedure. To reduce injuries due to fainting, people should be immunized while seated. For those at risk of fainting, consider a recumbent position. Foster a safe environment and

educate vaccinees on avoiding unsafe activities, such as stair climbing or driving immediately after immunization. For example, school immunization programs may wish to institute a pairing policy (two students remain together) so vaccinees are not alone for the first 10 to 15 minutes after leaving the immediate clinic location, in case they faint and fall or begin to experience symptoms of anaphylaxis.

ANXIETY

People experiencing anxiety may appear fearful, pale and diaphoretic and complain of lightheadedness, dizziness and numbness, as well as tingling of the face and extremities. Hyperventilation is usually evident. Treatment consists of reassurance and rebreathing using a paper bag until symptoms subside.

BREATH-HOLDING

Breath-holding episodes occur in some young children when they are upset and crying hard. The child suddenly becomes silent but remains agitated. Facial flushing and perioral cyanosis deepens as breath-holding continues. Some episodes end with resumption of crying, but others end with a brief period of unconsciousness during which breathing resumes. No treatment is required beyond reassurance of the child and parents.

SWELLING AND URTICARIAL RASH AT THE INJECTION SITE

Swelling and urticarial rash (i.e., hives) at the injection site can occur but are not always caused by an allergic reaction. The swelling or hives should be observed for at least 30 minutes in order to ensure that the reaction remains localized, and if so, the vaccinee may leave after this observation period. Ice can be applied to the injection site for comfort. If the hives or swelling disappear and there is no evidence of any progression to other parts of the body and there are no other symptoms within the 30 minute observation period, further observation is not necessary. However, **if any other symptoms arise, even if considered mild (e.g., sneezing, nasal congestion, tearing, coughing, facial flushing), or if there is evidence of any progression of the hives or swelling to other parts of the body during the observation period, epinephrine should be given** (refer to the steps for basic management of anaphylaxis in a non-hospital setting).

A mild local reaction resolving by itself within a few minutes is not indicative of an allergic reaction and does not require special observation or specialized assessment prior to subsequent vaccination.

ANAPHYLAXIS

Anaphylaxis is a serious, potentially life-threatening allergic reaction to foreign antigens; it has been proven to be associated with vaccines. Anaphylaxis is rare with an estimated range of occurrence of 1-10 episodes per million doses of vaccine administered. Anaphylaxis is preventable in many cases and treatable in all. It should be anticipated in every vaccinee.

PRE-VACCINATION SCREENING

Prevention of anaphylaxis is critically important. Pre-vaccination screening includes screening for a history of anaphylaxis and identification of potential risk factors. It should include questions about possible allergy to any component of the vaccine(s) being considered in order to identify if there is a contraindication to administration.

POST-VACCINATION SCREENING

Most instances of anaphylaxis to a vaccine begin within 30 minutes after administration of vaccine. Therefore, vaccine recipients should be kept under observation for at least 15 minutes after immunization; 30 minutes is a safer interval when there is a specific concern about possible vaccine allergy. In low-risk situations, observation can include having vaccinees remain within a short distance of the vaccinator

(e.g., within the school when immunization is carried out in that setting) and return immediately for assessment if they feel unwell. As noted above, a pairing policy is recommended in school settings.

SIGNS AND SYMPTOMS OF ANAPHYLAXIS

In anaphylaxis, signs and symptoms develop over several minutes and by definition involve at least two body systems (e.g. the skin, respiratory, gastrointestinal or circulatory systems). The cardinal features of anaphylaxis are:

- itchy, urticarial rash
- progressive, painless swelling (angioedema) about the face and mouth, which may be preceded by itchiness, tearing, nasal congestion or facial flushing
- respiratory symptoms, including sneezing, coughing, wheezing, laboured breathing and upper airway swelling (indicated by hoarseness and/or difficulty swallowing) possibly causing airway obstruction
- gastrointestinal symptoms, including crampy abdominal pain and vomiting
- sudden reduced blood pressure or symptoms of end-organ dysfunction (e.g., hypotonia and incontinence). In infants, symptoms may also include fussiness, irritability, drowsiness or lethargy

Skin and mucosal symptoms are reported to occur in 80% to 90% of anaphylaxis cases and respiratory symptoms occur in up to 70%. Cardiovascular system symptoms such as chest pain, palpitations, or tachycardia occur in up to 45% and central nervous system symptoms of uneasiness, altered mental status, dizziness, or confusion occur in up to 15%. Gastrointestinal symptoms like nausea, vomiting and diarrhea may occur in up to 45% of anaphylaxis cases. Features of severe anaphylaxis include obstructive swelling of the upper airway, marked bronchospasm and hypotension. Hypotension can progress to cause shock and collapse. Unconsciousness is rarely the sole manifestation of anaphylaxis; it occurs only as a late event in severe cases.

The rate of progression or the severity of the anaphylactic episode can be difficult to predict at the start of anaphylaxis; however, rapid development of anaphylaxis following vaccination indicates that a more severe reaction is likely. Symptoms vary from one person to another and only a few symptoms may be present. Death can occur within minutes.

RISK FACTORS FOR SEVERE ANAPHYLAXIS

Anaphylaxis is a rare complication of immunization. Risk factors for increased severity of anaphylaxis include very young or old age; pregnancy; asthma; cardiovascular disease; and concurrent use of certain medications (i.e., angiotensin-converting enzyme [ACE] inhibitors, angiotensin receptor blockers [ARB] or beta-blockers). Even in these populations, however, anaphylaxis is rare.

ANAPHYLAXIS MANAGEMENT KITS

Appropriate preparation is important for a good outcome in anaphylaxis. **Anaphylaxis management kits should be readily available wherever vaccines are administered**. Epinephrine in an auto-injector or in a vial may be used to treat anaphylaxis; however, vials of epinephrine must be available for treatment of infants weighing less than 15 kg (refer to Epinephrine for additional information). Epinephrine solutions for injection (vials or auto-injectors) have a short shelf-life (generally 12 to 18 months) and past this time, will start to break down to inactive substances. Epinephrine and other emergency supplies should be checked on a regular basis and replaced when outdated. Refer to the list of essential items in an anaphylaxis management kit.

List of recommended items in an anaphylaxis management kit

Essential Items

- A clear, concise summary of the anaphylaxis emergency management protocol
- Laminated table of dosage recommendations for epinephrine and diphenhydramine hydrochloride (e.g. Benadryl) by weight and by age*
- Two vials of aqueous epinephrine 1:1000
- A range of autoinjectors of epinephrine labelled by age and weight (optional)
- One vial of injectable diphenhydramine hydrochloride
- Two – 1 cc syringes with attached needles (1 – 25 gauge,1 inch needle; 1 – 25 gauge, 5/8 inch needle)
- One – 25 gauge, 5/8 inch needle (extra)
- Two– 25 gauge, 1 inch and 1.5 inch needles (extra for larger adults)
- Scissors
- Alcohol swabs
- One nasopharyngeal airway and one oropharyngeal airway for each age range anticipated in the clinic
- Pocket mask
- Stethoscope and sphygmomanometer
- Tongue depressors
- Flashlight
- Wristwatch with second hand to measure pulse
- Cell phone if no easy access to onsite phone

Additional Items

(Depending on local circumstances, such as availability of ambulance personnel)-:

- IV lines and fluids, and related equipment (e.g., tourniquet)
- Oxygen and related equipment

*Refer to Table 1 and Table 2 for recommended dosing information.

MANAGEMENT OF ANAPHYLAXIS

Anaphylaxis is a medical emergency and rapid recognition and management can be life-saving. Every vaccine provider should be familiar with the signs and symptoms of anaphylaxis and be prepared to act quickly.

Protocols

Advance preparation for emergency management of anaphylaxis is essential. It is recommended that vaccine providers develop, post, and regularly rehearse a written anaphylaxis emergency management protocol. Protocols should specify the necessary emergency equipment, drugs and dosages, and medical personnel necessary to safely and effectively manage anaphylaxis. Refer to Steps for basic management of anaphylaxis for a summary of the basic management of anaphylaxis in a non-hospital setting.

Steps for basic management of anaphylaxis in a non-hospital setting
(Steps 1, 2, 3 should be done promptly and simultaneously)

1. **Assess** circulation, airway, breathing, mental status, skin, and body weight (mass). Secure an oral airway if necessary. **Direct someone to call 911**(where available) or emergency medical services.

2. **Position** the vaccine recipient on their back or in a position of comfort if there is respiratory distress; elevate the lower extremities. Place the vaccinee on their side if vomiting or unconscious. Pregnant anaphylactic vaccinees should be placed semi-recumbent on their left side with their legs elevated.

3. **Inject epinephrine intramuscularly in the mid-anterolateral aspect of the thigh:** 0.01 mg/kg body weight of 1:1000 (1 mg/mL) solution
   - ADOLESCENT or ADULT: maximum - 0.5 mg
   - CHILD: maximum - 0.3 mg

   Record the time of the dose.

   Repeat every 5 to 15 minutes as needed, for a maximum of three doses.

4. **Stabilize vaccinee;** perform cardiopulmonary resuscitation if necessary, give oxygen and establish intravenous access if available and give adjunctive treatment (i.e. diphenhydramine hydrochloride or Benadryl®) if indicated.

5. **Monitor** vaccinee's blood pressure, cardiac rate and function, and respiratory status.

6. **Transfer to hospital for observation.**

Adapted from Simons FE, Arudusso LR, Bilo MB et al. World Allergy Organization guidelines for the assessment and management of anaphylaxis. J Allergy Clin Immunol 2011;127(3):593e1-22.

Rapid assessment and positioning

Rapid intervention is of paramount importance. Assess airway, breathing and circulation; establish an airway if needed. When assessing the airway, look specifically at the lips, tongue and throat for signs of swelling. Position the person flat on the back, unless he/she is vomiting or unconscious (then place on the side) or in respiratory distress (may need to elevate head and chest for comfort). Legs should be elevated to help maintain blood pressure. Direct someone to call 911 or emergency medical services for transportation to hospital.

Epinephrine

Prompt administration of epinephrine is the priority and should not be delayed. Epinephrine is the treatment of choice for management of anaphylaxis in community and health care settings as it prevents and relieves upper airway swelling, hypotension and shock. In addition, it causes increased heart rate, increased force of cardiac contractions, increased bronchodilation, and decreased release of histamine and other mediators of inflammation. Epinephrine reaches peak plasma and tissue concentrations rapidly.

Failure to administer epinephrine promptly may result in greater risks to the anaphylactic vaccinee than using epinephrine improperly. If uncertain, err on the side of treatment; there are no contraindications to the use of epinephrine. If time is lost early in the treatment of an acute anaphylactic episode, subsequent management can become more difficult.

Epinephrine 0.01 mg/kg body weight of a 1:1000 (1 mg/mL) solution should be administered into the mid-anterolateral aspect of the thigh; the deltoid muscle of the arm is not as effective as the thigh in absorbing epinephrine. Scissors may be needed to cut clothing to establish access. If

scissors are not readily available, epinephrine may be administered through clothing. Although there is a slightly increased risk of infection, timely administration of epinephrine is the priority. The risk of infection can be addressed once the person has stabilized. Refer to Table 1 for epinephrine dosing guidelines. For infants less than 7 months of age, the dose of epinephrine should be determined by weight, if possible. For example, an infant weighing 4 kg (8.8 lb) should receive 0.04 mg of epinephrine in 0.04 mL of 1:1000 (1 mg/mL) solution.

Table 1: Dose of epinephrine (1:1000, 1 mg/mL solution), by age or weight

Age	Weight[1]	Dose by injection	Dose by autoinjector
0 – 6 months	Up to 9 kg (20 pounds)	0.01 mg/kg body weight	Not applicable
7 - 36 months	9 - 14.5 kg (20 - 32 lb)	0.1 - 0.2 mg	Not applicable
37 - 59 months	15 - 17.5 kg (33 – 39 lb)	0.15 - 0.3 mg [2]	Junior dose of 0.15 mg
5 - 7 years	18 - 25.5 kg (40 – 56 lb)	0.2 - 0.3 mg [2]	Junior dose of 0.15 mg
8 - 12 years	26 - 45 kg (57 – 99 lb)	0.3 mg [2]	If , less than 30 kg (66 lbs) give Junior dose If 30 kg or more: Give standard dose
13 years and older	46 + kg (100 + lb)	0.5 mg [3]	Give standard dose of 0.3mg

Adapted from Immunization Action Coalition. Medical Management of Vaccine Reactions in Children and Teens. Accessed June 2012. (http://www.immunize.org/catg.d/p3082a.pdf)
[1] Rounded weight at the 50th percentile for each age range
[2] Maximum dose for children 12 years of age and younger
[3] Maximum dose for adolescents

An epinephrine auto-injector (Allerject™, Anapen®, EpiPen® or Twinject®) may be used if the person who administers it is knowledgeable about proper use and the correct dose of epinephrine for age or body weight is available in the auto-injector. The junior dose is intended for children who weigh 15-30 kg. The “junior” or pediatric preparations contain 0.15 mg (0.3 mL) of epinephrine 1:2000 per dose (EpiPen® Jr.; Anapen Jr. 150) or 0.15 mg (0.15 mL) of epinephrine 1:1000 per dose (Twinject® 0.15 mg). The standard dose is intended for children and adults weighing 30 kg or more. The standard preparations contain 0.3 mg (0.3 mL) of epinephrine 1:1000 per dose.

Mild and transient effects such as pallor, tremor, anxiety, palpitations, headache and dizziness occur within minutes after injection of a recommended dose of epinephrine. These effects confirm that a therapeutic dose has been given.

Ensure the person lies down. Fatality can occur within seconds if the vaccinee stands or sits suddenly after epinephrine. People should remain in a recumbent position following receipt of an epinephrine injection and be monitored closely.

Adjunctive treatment

As an optional *adjunct* to epinephrine, a dose of diphenhydramine hydrochloride (e.g., Benadryl®) may be given to relieve itching, flushing, urticaria, and nasal and eye symptoms. Generally the injectable format is used although oral tablets or liquid elixir may also be used; in all formats the dosing is the same. Refer to Table 2 for diphenhydramine hydrochloride dosing guidelines. Diphenhydramine is generally not recommended for infants under 12 months of age, and should be used with caution between 12-23 months because it may cause drowsiness or paradoxical excitement. When given to children, dosage should be determined by weight (1mg/kg).

Table 2: Dose of diphenhydramine hydrochloride, by age

Age	**Weight** (pounds)	**Dose of diphenhydramine hydrochloride**
12-23 months[1]	7-12 kg (15-25 lbs)	6.25 - 12.5 mg
2 to 4 years	12-25 kg (25-55 lbs)	12.5 - 25 mg
5 to 11 years	25-45 kg (55-99 lbs)	25 - 50 mg
12 years and older	45 kg + (99 lbs or more)	50 mg

[1] Use with caution in children 12 – 23 months due to risk of sedation or paradoxical excitement.

When indicated, give high-flow supplemental oxygen (6 to 8 L/minute) by face mask or oropharyngeal airway (if available) to people with cyanosis, dyspnea or any other severe reaction requiring repeated doses of epinephrine.

People on beta-blockers may be more resistant to epinephrine.

Transfer to hospital

All vaccinees receiving emergency epinephrine must be transported to hospital immediately for evaluation and observation. Since the symptoms of an anaphylactic reaction can reoccur after the initial reaction (biphasic anaphylaxis) in up to 23% of adults and up to 11% of children, hospitalization is recommended for monitoring. Generally, patients are hospitalized overnight or monitored for at least 12 hours. A biphasic course of anaphylaxis is more likely to occur if the administration of epinephrine is delayed.

SELECTED REFERENCES

Campbell RL, Hagan JB, Manivannan V et al. *Evaluation of the National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network criteria for the diagnosis of anaphylaxis in emergency department patients.* J Allergy Clin Immunol 2012;129:748-52.

Centers for Disease Control and Prevention. *General Recommendations on Immunization Recommendations of the Advisory Committee on Immunization Practices (ACIP)*. MMWR Morb Mortal Wkly Rep 2011;60(2):1-61.

Dey Pharma L.P. *Product Monograph – EpiPen® and EpiPen® Jr.* March 2012.

Immunization Action Coalition. *Medical Management of Vaccine Reactions in Children and Teens*. Accessed June 2012.

Immunization Action Coalition. *Medical Management of Vaccine Reactions in Adult Patients*. Accessed June 2012.

Joint Task Force on Practice Parameters; American Academy of Allergy, Asthma and Immunology; American College of Allergy, Asthma and Immunology; Joint Council of Allergy, Asthma and Immunology. *The diagnosis and management of anaphylaxis: an updated practice parameter*. J Allergy Clin Immunol. 2005;115:S483-523.

Kim H, Fischer D. *Anaphylaxis.* Allergy Asthma Clin Immuno 2011;7(Suppl 1):S6.

Lincoln Medical Ltd. *Summary of Product Characteristics – Anapen 150*. 2006.

Lincoln Medical Ltd. *Summary of Product Characteristics – Anapen 300*. 2006.

Simons FE. *Anaphylaxis pathogenesis and treatment.* Allergy 2011;66(Suppl.96):31-34.

Simons FE, Arudusso LR, Bilo MB et al. *2012 Update: World Allergy Organization Guidelines for the assessment and management of anaphylaxis.* Curr Opin Allergy Clin Immunology 2012;12:389-99.

Simons FE, Arudusso LR, Bilo MB et al. *World Allergy Organization guidelines for the assessment and management of anaphylaxis.* J Allergy Clin Immunol 2011;127(3):593e1-22.

Simons KJ, Simons FE. *Epinephrine and its use in anaphylaxis: current issues.* Curr Opin Allergy Clin Immunol 2010;10:354-361.

Soar J, Pumphrey R, Cant A et al. *Emergency treatment of anaphylactic reactions – guidelines for healthcare providers.* Resuscitation 2008;77:157-169.

Verus Pharmaceuticals, Inc. *Prescribing Information - Twinject® 0.3 mg Auto-Injector and Twinject® 0.15 mg Auto-Injector*. August 2006.

Waserman S, Chad Z, Francoeur, MJ et al. *Management of anaphylaxis in primary care: Canadian expert consensus recommendations.* Allergy 2010;65:1082-92.

Winodradow J, Geppert G, Reinhard W et al. *Tako-tsubo cardiomyopathy after administration of intravenous epinephrine during an anaplylactic reaction*. Int J Cardiol 2011;147:309-11.

PART 2

ANAPHYLACTIC HYPERSENSITIVITY TO EGG AND EGG-RELATED ANTIGENS

This chapter summarizes the recommendations for vaccines with respect to anaphylactic hypersensitivity to egg and egg-related antigens. Since the publication of the *2006 Canadian Immunization Guide* recommendations regarding influenza vaccination of persons with egg allergy have been revised and recommendations for tick-borne encephalitis vaccine have been added.

GENERAL CONSIDERATIONS

Egg allergy is one of the most common food allergies of childhood, with a prevalence of 1% to 3% in children under 3 years of age. It is often associated with eczema in infants and asthma in young children. As most children outgrow their egg allergy, the prevalence in adulthood is much lower and is estimated at 0.1%. The most common egg allergy is to egg white. Cross-sensitivity with egg yolk and chicken protein has been described.

Vaccines that contain small quantities of egg protein can cause hypersensitivity reactions in some people with allergies to eggs. In Canada, there are several vaccines manufactured by processes involving hens' eggs or their derivatives, such as chick cell cultures. This manufacturing process may result in the following vaccines containing trace amounts of residual egg and chicken protein:

- measles-mumps-rubella (MMR) vaccines
- measles-mumps-rubella-varicella (MMRV) vaccine
- influenza vaccines
- tick-borne encephalitis (TBE) vaccine
- RabAvert®rabies vaccine
- yellow fever (YF) vaccine

Hypersensitivity reactions occurring following receipt of these vaccines varies considerably in relation to the amount of residual egg and chicken protein in the vaccine.

Anaphylaxis after vaccination is rare. It may occur in people with anaphylactic hypersensitivity to eggs and in those with no history of egg allergy, due to other components in the vaccine. Due to this lack of predictability, immunization should always be performed by personnel with the capability and facilities to manage anaphylaxis post-vaccination. Refer to Early Vaccine Reactions Including Anaphylaxis in Part 2 for additional information regarding management of anaphylaxis in non-hospital settings.

PRE-VACCINATION SCREENING

Individuals should be asked about allergies to egg or chicken prior to vaccination with influenza, TBE, YF, or RabAvert® rabies vaccines. Prior egg ingestion is not a prerequisite for immunization with egg protein-containing vaccine. It should be noted that any vaccine is contraindicated in people who have had an anaphylactic reaction to a previous dose of the vaccine. Referral to an allergy specialist is recommended.

Atopic diseases are not a contraindication to immunization with egg protein-containing vaccine.

MEASLES AND MUMPS-CONTAINING VACCINE

Anaphylaxis after vaccination with MMR vaccine is rare. Studies of egg-allergic subjects have shown that there is no increased risk of severe allergic reactions to MMR vaccine. For example, a 1994 study reported no anaphylactic reactions in 500 children with a history of egg allergy immunized with MMR vaccine. Numerous other studies had the same outcome. A literature review conducted in 2000 concluded that administration of MMR vaccine is safe in children with egg allergy and egg allergy should not delay measles vaccination.

The trace amount of egg protein in MMR and MMRV vaccines appears to be insufficient to cause an allergic reaction in egg-allergic individuals. Skin testing is *not* recommended prior to vaccination as it does not predict reaction to the vaccine. **MMR or MMRV vaccine can be administered in the routine manner to people who have a history of anaphylactic hypersensitivity to hens' eggs.** Hypersensitivity reactions that do occur following MMR and MMRV vaccine are usually due to other components of the vaccine, such as gelatin or neomycin.

INFLUENZA VACCINE

Anaphylaxis after vaccination with influenza vaccine is a rare consequence of hypersensitivity to a vaccine component. All influenza vaccines in Canada are currently manufactured by a process involving hens' eggs which may result in the vaccine containing trace amounts of residual egg protein. Although the ovalbumin (egg protein) content in influenza vaccines manufactured in eggs may vary from year to year, vaccines marketed in Canada are approved under a specification for ovalbumin content that is associated with low risks of adverse events.

Numerous studies have demonstrated that egg-allergic persons can safely receive trivalent inactivated influenza vaccine (TIV). People with egg allergy, especially those with chronic conditions such as asthma, benefit from receiving TIV. Because of the lack of data, the use of live attenuated influenza vaccine (LAIV) in egg-allergic persons is not recommended at this time.

Egg-allergic individuals may be vaccinated against influenza using TIV, without prior influenza vaccine skin test and with the full dose, irrespective of a past severe reaction to egg, with the following conditions. Those with mild reactions such as hives, or those who tolerate eggs in baked goods may be vaccinated in regular vaccination clinics. Those who have suffered from anaphylaxis with respiratory or cardiovascular symptoms should be vaccinated in a medical clinic, allergy office or hospital where appropriate expertise and equipment to manage respiratory or cardiovascular compromise is present. These individuals should always be kept under observation for 30 minutes.

REFERRAL

Referral to a specialist with expertise in allergies may be necessary in occasional circumstances where there is strong concern about proceeding with the recommendation above and the individual is at risk of complications from influenza. If the individual is not in a high-risk group, the need for vaccination may be reassessed.

SECOND DOSE IN YOUNG CHILDREN

Egg-allergic children who require a second dose of TIV during the same influenza season can, if the first dose is tolerated well, be given a second dose of the same product used for the initial administration, which need not be from the same vaccine lot.

COUNSELLING

The vaccine provider should discuss the risks of reactions, as should be done for any immunization, including the potential risk for an anaphylactic reaction after the observation period.

POST-VACCINATION OBSERVATION

All egg-allergic individuals receiving TIV should be observed post-vaccination for a 30 minute time period, which may be extended (e.g., to 60 minutes) as a precautionary measure for higher risk individuals. Appropriate emergency treatment and resuscitative equipment should be immediately available to manage potential severe reactions or anaphylaxis. Refer to Early Vaccine Reactions Including Anaphylaxis in Part 2 for additional information regarding management of anaphylaxis in non-hospital settings.

RABIES VACCINE

RabAvert® rabies vaccine is grown in chick embryo cell culture. Imovax® rabies vaccineis manufactured using human diploid cell cultures and therefore egg protein contamination is not an issue. **For pre-exposure vaccination, Imovax® rabies vaccine should be given to persons with a history of hypersensitivity reactions to egg or egg products** as a precautionary measure**.** For post-exposure prophylaxis, the use of Imovax® vaccine is preferred for persons with a history of hypersensitivity to egg. If Imovax® vaccine is not available, RabAvert® vaccine should be administered with strict medical monitoring and facilities for emergency treatment of anaphylactic reactions readily available.

TICK-BORNE ENCEPHALITIS VACCINE

Individuals with prior anaphylactic reactions to eggs or egg products should be vaccinated with TBE vaccine only under close clinical monitoring with readiness for emergency treatment.

YELLOW FEVER VACCINE

Yellow fever (YF) vaccine is prepared from virus grown in chick embryos and is the vaccine most likely to contain sufficient amounts of egg or chicken proteins to cause an allergic reaction in egg-allergic or chicken-allergic individuals. There have been several reports of anaphylactic reactions to YF vaccine in egg-allergic or chicken-allergic individuals; therefore, **YF vaccine should not be routinely administered to egg-allergic or chicken-allergic individuals.**

A 2010 case report documented a protocol for administration of YF vaccine in escalating doses to an egg-allergic individual with positive skin tests to YF vaccine. In a 2009 study of 7 egg-allergic subjects with strong local urticarial reaction to a 0.1 mL intradermal test dose of YF vaccine, the test dose was found to be sufficient to induce a protective antibody response. Referral of egg-allergic or chicken-allergic individuals to an allergy specialist is recommended as YF vaccination may be possible after careful evaluation, skin testing and graded challenge or desensitization.

SELECTED REFERENCES

Aickin R, Hill D, Kemp A*. Measles immunisation in children with allergy to egg*. Br Med J 1994;309:223-25.

Clark AT, Skypala I, Leech SC. *British Society for Allergy and Clinical Immunology guidelines for the management of egg allergy.* Clin Exp Immunol 2010;40:1116–29.

Des Roches A, Paradis L, Gagnon R, Lemire C, Bégin P, Carr S, Chan ES, Paradis J, Frenette L, Ouakki M, Benoît M, De Serres G; PCIRN (Public Health Agency of Canada/Canadian Institutes of Health Research Influenza Research Network). J Allergy Clin Immunol. 2012 Nov;130:1213-1216.

Erlewyn-Lajeunesse M, Lucas JS, Warner JO. *Influenza immunization in egg allergy: an update for the 2011–2012 season.* Clin Exp Immunol 2011;41:1367–70.

Fasano MB, Wood RA, Cooke SK et al. *Egg hypersensitivity and adverse reactions to measles, mumps and rubella vaccine*. J Pediatr 1992;120(6):878-81.

Forsdahl BA. *Reactions of Norwegian children with severe egg allergy to an egg-containing influenza A (H1N1) vaccine: a retrospective audit*. BMJ Open 2012:2:e000186.

Fox A, Lack G. *Case report. Egg allergy and MMR vaccination.* Br J Gen Pract 2003;53:801-02.

Freigang B, Jadavji TP, Freigang DW. *Lack of adverse reactions to measles, mumps and rubella vaccine in egg-allergic children*. Anna Allergy 1994;73:486-88.

Greenhawt, MJ, Spergel JM, Rank MA et al. *Safe administration of the seasonal trivalent influenza vaccine to children with severe egg allergy.* Ann All Asthma Imm 2012;09:426-30.

Gruenberg DA, Shaker MS. *An update on influenza vaccination in patients with egg allergy.* Curr Opin Pediatr 2011;23:566-572.

Herman JJ, Radin R, Schneiderman R. *Allergic reactions to measles (rubeola) vaccine in patients hypersensitive to egg protein.* J Pediatr 1983;102(2):196-99.

James JM, Burks AW, Roberson PK et al. *Safe administration of the measles vaccine to children allergic to eggs.* N Engl J Med 1995;332(19):1262-66.

Kelso JM, Yunginger JW. *Immunization of egg-allergic individuals with egg- or chicken-derived vaccines*. Immunol Allergy Clin North Am 2003;23(4):635-48.

Khakoo GA, Lack G. *Recommendations for using MMR vaccine in children allergic to eggs.* Br Med J 2000;320:929-32.

Munoz-Cano R, Sanchez-Lopez J, Bartra J et al. *Yellow fever vaccine and egg allergy: really a problem?* Allergy 2010;65:531-36.

National Advisory Committee on Immunization. *Egg allergy and MMR vaccine: New recommendations from the National Advisory Committee on Immunization.* Can Comm Dis Rep 1996;22-14:113-15.

National Advisory Committee on Immunization. *Statement on Seasonal Influenza Vaccine for 2013–2014.* Can Commun Dis Rep 2013;39-4

Roukens AH, Vossen AC, van Dissel JT et al. *Reduced intradermal test dose of yellow fever vaccine induces protective immunity in individuals with egg allergy.* Vaccine 2009;27:2408-09.

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