– Part I –
General Considerations

Vaccines are good! There is no reason to suffer from a disease if there is a safe, effective way to prevent it, and vaccines have proven their utility and effectiveness time and time again. Readers are invited to consult the table on the back of this *Guide,* which highlights the incredible victories against disease won by vaccines.

The range of immunizing agents available in Canada continues to expand as new vaccines and immune globulins are licensed, and improvements in or modifications to currently available preparations are made. The use of these agents for both active and passive immunization must, therefore, be evaluated continually as the incidence and significance of the diseases against which they confer protection change spontaneously or as a result of vaccine use. However, when the incidence of a particular communicable disease falls because of the success of a vaccine, the public or health policy makers may question the need to continue the immunization program concerned. This attitude may very well result in lower vaccine coverage and, inevitably, resurgence of the disease, unless it can be totally eradicated. Although the ultimate aim of those concerned with immunization is the elimination of vaccine-preventable diseases, eradication is rarely a practical possibility. Only in infections such as smallpox, poliomyelitis and measles, which are restricted to humans and involve no other host, is eradication possible today. Immunization programs may need continuous evaluation to adjust to new improvements, but policy makers and the public must keep advocating their continuation in order to avoid resurgence.

An ideal vaccine should confer long-lasting, preferably lifelong, protection against the disease with a single or a small number of doses. It should be inexpensive enough for wide-scale use, stable enough to remain potent during shipping and storage, and should have no adverse effect on the recipient. Some vaccines come close to meeting these criteria; others do not. Each vaccine has its own characteristics, and generalizations are difficult to make; consequently, each is considered separately in this *Guide*.

Some vaccines consist of inactivated organisms or purified components. Others, particularly vaccines against viral diseases, contain live microorganisms. These have the advantages that the dose is small (minimizing production costs) because the virus replicates within the recipient, and that the stimulus (or process) more closely resembles that associated with natural infection. However, live vaccines demand particular care in many ways: in storage, when they may inadvertently be inactivated; in the choice of the individual immunized, since live agents are usually not appropriate for immunodeficient people or, in some cases, for pregnant women; and with regard to changes in virulence and possible spread to contacts of vaccinees and to the environment. Also, because live vaccines produce infection, they can on occasion produce some of the symptoms and complications of the disease they are

meant to prevent, though at much lower frequency than that associated with the disease.

In this *Guide*, information is presented on the immunizing agents available in Canada and their use in the prevention of communicable diseases. Recommendations on routine immunization of infants and children are discussed in some detail, and an attempt is made to answer most of the day-to-day queries from providers regarding immunization.

Because of variation in manufacturers' products, precise details of the dosage and route of administration of individual products are not usually given. Readers are referred to manufacturers' labelling and package inserts for this information. As well, the manufacturer has sought approval of the vaccine and provided evidence as to its safety and efficacy only when it is used in accordance with the product monograph. Updates of the information in the product monographs are made infrequently. Recommendations for use and other information set out in the *Guide* may differ from those set out in the product monograph(s) of the Canadian licensed manufacturer(s) of the vaccine. The advice and recommendations set out in this *Guide* are based upon the best and most current publicly available scientific knowledge.

Cost Benefit

The World Bank has stated that immunization should be first among the public health initiatives in which governments around the world invest. ***Vaccination programs are considered to be the most cost-beneficial health intervention and one of the few that systematically demonstrate far more benefits than costs.***

Tengs and colleagues reviewed 587 life-saving interventions and their cost-effectiveness, and concluded that routine immunization programs for children were among the most cost-effective and among the very few that save more money than they cost (i.e., it costs more not to undertake these programs in terms of lives or life years saved). The cost of the 587 interventions reviewed ranged from less than zero (i.e., those that save more resources than they cost) to more than $99 billion per year of life saved (Table 1). The median cost was US$42,000 per year of life saved.

Many cost-benefit studies of routine immunization programs have been conducted, and they almost always demonstrate a very positive cost-benefit ratio, commonly ranging from 7:1 to 80:1. Very few studies of immunization programs, however, have been or are being conducted in Canada. Recent cost-benefit studies of the introduction of a routine two-dose measles vaccination schedule and replacement of the pertussis whole-cell vaccine with the new acellular products have indicated that these two strategies were highly cost-beneficial and in the long term would result in savings of several hundred millions of dollars.

The new vaccines being introduced may seem very expensive, at least initially, when compared with vaccines currently in general use. However, in most cases, the cost-

– Table 1 –

Cost per Life Year Saved for Selected Life-saving Interventions (from Tengs et al)

Measles, mumps and rubella immunization for children	≤0
Smoking cessation advice for pregnant women who smoke	≤0
Mandatory seat belt law	$69
Mammography for women aged 50	$810
Chlorination of drinking water	$3,100
Smoking cessation advice for people who smoke more than one pack per day	$9,800
Driver and passenger airbags/manual lap belts (vs. airbag for driver only and belts)	$61,000
Smoke detectors in homes	$210,000
Ban on products containing asbestos (vs. 0.2 fibres/cc standard)	$220,000
Low cholesterol diet for men over age 20 and over 180 mg/dL	$360,000
Crossing control arm for school buses	$410,000
Radiation emission standard for nuclear power plants	$100,000,000
Chloroform private well emission standard at 48 pulp mills	$99,000,000,000

effectiveness (cost to prevent one undesired incident e.g., death, hospitalization, infection and complications) is relatively low and compares very favourably with the other commonly used treatments or preventive measures. These vaccines should be promoted on the basis of the benefits they provide at an acceptable cost. Research should also be encouraged in order to find the best effective delivery schedule at the least cost. As an example, the number of doses needed can be evaluated to determine the most effective combination. Policy makers should promote the inclusion of money in immunization programs for post-marketing studies, which will lead to further improvements to and benefits from those programs.

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General Cautions and Contraindications

A guide to true contraindications to immunization as well as to conditions considered to be precautions rather than contraindications is provided in Table 2. The Table also lists other conditions commonly but inappropriately classified as contraindications, such as mild acute illness with or without fever, mild to moderate local reactions to a previous dose of vaccine, current antimicrobial therapy, and the convalescent phase of an acute illness. For complete information regarding a particular vaccine, the reader is invited to consult the specific vaccine chapter of the *Guide*.

Minor illnesses such as the common cold, with or without fever, frequently occur in young children and are not contraindications to immunization. Such infections do not increase the risk of adverse effects from immunization and do not interfere with immune responses to vaccines. Deferring immunization because of acute mild illnesses often results in incomplete immunization of children who will either need later catch-up vaccinations or develop vaccine-preventable disease. Moderate to severe illness with or without fever is a reason to defer *routine* immunization with most vaccines. This precaution avoids superimposing adverse effects from the vaccine on the underlying illness or mistakenly identifying a manifestation of the underlying illness as a complication of vaccine use. However, if the vaccine is required because of likely exposure to disease or if the child is unlikely to return to continue immunization in a timely fashion, the vaccine may be given despite the intercurrent illness.

Allergic conditions *per se* (e.g., eczema and asthma) are not contraindications to immunization unless there is a specific allergy to a vaccine component. Special precautions may be required for some vaccines prepared in eggs or avian tissue. The section on egg allergy (page 12) and the sections on individual vaccines should be consulted when dealing with an egg allergic individual. Recently, concern has been expressed regarding exposure to thimerosal, a mercurial, contained in vaccines. In Canada, the only thimerosal-containing vaccine included in the regular childhood immunization schedule is hepatitis B vaccine, and thimerosal-free hepatitis B vaccines are now available in Canada. Other routine childhood vaccines such as those for measles, mumps, and rubella (MMR) and Pentacel™ (for diphtheria, tetanus, acellular pertussis, *Haemophilus influenzae* type b, and inactivated polio) do not contain thimerosal as a preservative. Therefore, NACI does not recommend any alteration to the current infant immunization policies. Some vaccines contain trace amounts of antibiotics (e.g., neomycin) or other compounds associated with the vaccine's production or packaging to which patients may be hypersensitive. No currently recommended vaccine contains penicillin or its derivatives. Yeast allergy is not a contraindication to immunization unless there has been documented anaphylactic sensitivity to yeast.

Bovine-derived materials are essential components in the production process of vaccines. The risk of transmitting variant Creutzfeld Jakob Disease (vCJD) from vaccines containing bovine-derived material is theoretical. Studies in the U.K. did not

– Table 2 –

Contraindications to and Precautions for Commonly Used Vaccines*

Vaccine**	True contraindications	Precautions†	Not a contraindication
All vaccines	• Anaphylactic reaction to a previous dose of vaccine • Anaphylactic reaction to a constituent of a vaccine	• Moderate to severe illness with or without fever	• Mild to moderate local reactions to previous injection of vaccine • Mild, acute illness with or without fever • Current antimicrobial therapy ***with the exception of live bacterial vaccines*** • Convalescent phase of an acute illness • Prematurity • Breastfeeding • Recent exposure to infectious disease • Personal or family history of allergy
DPT	• Anaphylactic reaction to a previous dose of vaccine	• Hypotonic-hyporesponsive state within 48 hr after prior dose of DPT	• Fever ≥ 40.5°C after prior dose of DPT • Family history of sudden infant death syndrome • Convulsion within 48 hr of prior dose of DPT • Family history of convulsions • Persistent inconsolable crying lasting ≥ 3 hr within 48 hr after prior dose • Pre-existing neurologic conditions • Prior history of pertussis
IPV	• Anaphylactic reaction to neomycin		
MMR	• Anaphylactic reaction to previous dose or to neomycin • Pregnancy • Severe immunodeficiency (See section on Immunization in Immunocompromised Hosts)	• Recent administration of IG (see Table 7)	• Tuberculosis or positive TB skin test • Simultaneous TB skin testing • Current antimicrobial therapy • Infection with HIV (1994 Pediatric HIV Classification categories E, N1, A1) • Egg allergy
Hib			• History of Hib disease

– Table 2 *con't* –

Contraindications to and Precautions for Commonly Used Vaccines*

Vaccine**	True contraindications	Precautions†	Not a contraindication
Hepatitis A and B			• Pregnancy
Influenza	• Anaphylactic reaction to a previous dose; known anaphylactic hypersensitivity to eggs manifested as hives, swelling of the mouth and throat, difficulty in breathing, hypotension and shock		• Pregnancy
Meningococcal vaccines	• Hypersensitivity to any component of the vaccine; history of signs of hypersensitivity after previous administration of the vaccine		• Pregnancy
Pneumococcal vaccines	• Hypersensitivity to any component of the vaccine including diphtheria toxoid	• Possible history of latex sensitivity	• Pregnancy
Varicella	• Immunocompromised people (see Varicella chapter) • Pregnancy	• Recent administration of blood, plasma, IG or VZIG (see Table 7)	• History of contact dermatitis to neomycin • Patients with nephrotic syndrome or those undergoing hemodialysis and peritoneal dialysis • Patients taking low doses of inhaled steroids

* For complete information regarding a particular vaccine, the reader is invited to consult the specific vaccine chapter of the *Guide.*

** DPT = diphtheria, pertussis and tetanus vaccine, IPV = inactivated poliovirus vaccine, MMR = measles, mumps and rubella vaccine, Hib = *Haemophilus influenzae* type b conjugate vaccine

† The events or conditions listed as precautions are not contraindications but should be carefully considered in determining the benefits and risks of administering a specific vaccine. If the benefits are believed to outweigh the risks (e.g., during an outbreak or foreign travel) the vaccine should be given.

show a relation between vaccines and any of the 52 vCJD cases. At a Food and Drug Administration meeting in the United States, in July 2000, the theoretical risk of vaccine-related vCJD was estimated at one in 40 billion and may be even less. For more details see http://www.fda.gov/cber/BSE/risk.htm. In Canada, commonly used vaccines included in the routine schedule are made from bovine-derived material coming from countries proven to be free of bovine spongiform encephalopathy (BSE). By the end of this year (2001), all vaccines using bovine-derived material will come from BSE-free countries and, despite the fact that the risk is theoretical, manufacturers are moving towards finding alternative components to these materials.

At the current time, there is no conclusive evidence to support a link between MMR immunization and inflammatory bowel disease (IBD). Neither wild type nor vaccine strain measles virus has been isolated from the tissues of patients with IBD, and immunohistochemical- and nucleic acid-based investigations have yielded conflicting results. An Institute of Medicine review recently concluded that there was no evidence to support a causal association between MMR vaccination and autism.

There is no evidence to support withholding immunization with MMR from anyone for whom it is indicated because of a diagnosis of multiple sclerosis or other conditions considered to involve autoimmunity, muscular dystrophy or other evolving neurologic conditions.

It is prudent to keep vaccinees under observation for immediate reactions or syncope for a period of at least 15 minutes after inoculation or for a longer period if hypersensitivity is a possibility. Epinephrine should be available for immediate use when immunizing agents are injected in order to treat the extremely rare but serious complication of anaphylaxis (see page 14).

Should a significant untoward reaction follow an injection of any vaccine, the provider should postpone further doses, report the reaction to the local public health authority and seek expert advice. **The use of partial doses for continuation of a course of vaccine is not recommended in any circumstances except for desensitization purposes.**

Adverse Events

Safety has always been an important issue in the use of vaccines, both because they are often universally recommended and because they are generally administered to otherwise healthy people to prevent disease. As a result, the level of tolerance for adverse events associated with vaccines is lower than that for therapeutic drugs.

Both local and systemic adverse reactions may follow the use of immunizing agents, most of them occurring shortly after immunization and others appearing only later. Mild vaccine-associated adverse events (e.g., fever and swelling) are relatively common, predictable and self-limited; serious or unexpected adverse reactions can, rarely, develop.

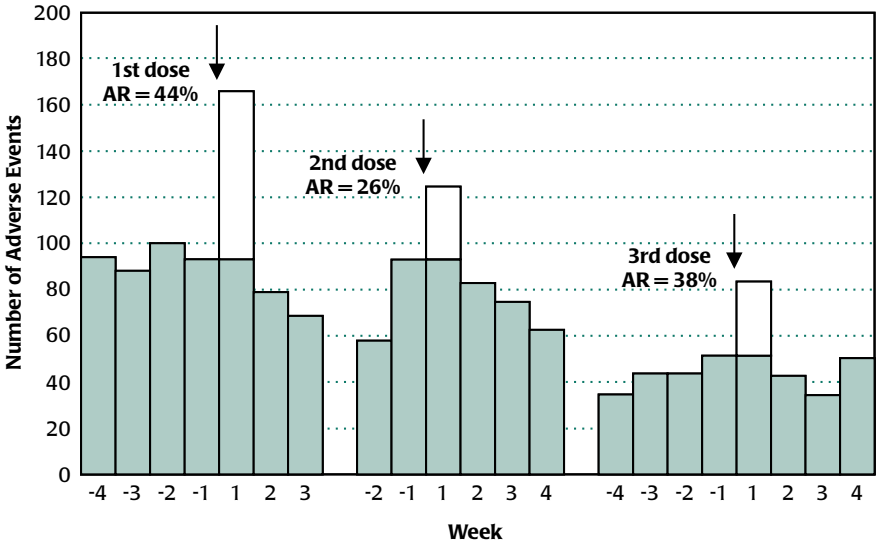
Assessing attributable risk

When an adverse event occurs after immunization, it is possible that it was caused by the vaccine, but it is also possible that it would have happened if no vaccine had been administered, because on any given day there is some illness in the population even in the absence of immunization. It is therefore necessary to take into account this "background" level of health problems when assessing the frequency of adverse events associated with particular vaccines.

The Figure below illustrates that not all health problems noted after immunization are truly caused by it. In a population of immunized children, the number of illnesses or clinical symptoms compatible with an adverse event increased in the week after hepatitis B immunization but returned to pre-vaccination levels thereafter. The vaccine can be implicated only for this "excess" of illness (or attributable risk).

In line with this demonstration, clinical trials have repeatedly shown that placebo recipients occasionally experience adverse events, and these are clearly not attributable to the vaccine. Adverse events with other etiologies are common and simply occur by chance shortly after the administration of a vaccine.

Total Number of Adverse Events in the Weeks Preceding and Following Each of the 3 Doses of Hepatitis B Vaccine and the Proportion of These Events Attributable to the Vaccine (compared with the incidence during the week preceding vaccination)*



Note. White bars represent relative attributable risk (AR). Arrows indicate vaccination.

* Reproduced with the kind 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.

– Table 3 –

Percentage of Children with Fever After MMR Immunization or Placebo Injection in 581 Twin Pairs*

	Days after injection				
	1-6	7-8	9-10	11-12	13-21
MMR	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;April 26:939-42.

In a Finnish study of cross-over design, each twin of 581 pairs of twins was given MMR vaccine or placebo in a blinded fashion, and 3 weeks later was administered the other substance. Each child was followed up over 21 days for adverse reactions. As can be seen in Table 3, which illustrates one condition (fever) monitored, some children in the placebo group experienced fever throughout the follow-up period, and the only significant difference (called excess or attributable risk) between placebo and MMR groups occurred between day 7 and day 12.

What happened with fever can happen with other illnesses. Immunized patients suffering from symptoms that became evident after immunization but were not caused by it understandably suspect the vaccine. This chance association illustrates the greatest vulnerability of universal immunization programs, even those involving a vaccine that is 100% safe. It also explains why health care providers are confronted so often with reports of unusual and severe adverse events that are temporally related to but generally not caused by vaccines. Only very large and well-controlled studies are adequate to assess the causality of these fairly rare events. In such studies, the frequency of the adverse events in otherwise comparable vaccinated and unvaccinated individuals is used to estimate the risk that is truly attributable to the vaccine.

Types of reactions

Local reactions after immunization usually consist of swelling or induration, tenderness, and redness or erythema at the injection site. More severe local reactions occasionally occur, such as inflammatory cellulitis without bacterial infection (e.g., after DT or DPT-containing vaccines). Although post-vaccination inflammatory cellulitis can usually be differentiated from bacterial cellulitis by the absence of fever and the general condition of the patient, this distinction can sometimes be difficult to make.

Systemic reactions may include fever, rash, joint or muscle pain, fainting, seizures or other central nervous system symptoms. Fainting immediately after immunization is usually due to apprehension and should not be confused with anaphylaxis.

Allergic reactions, such as urticaria, rhinitis, brochospasm and anaphylaxis, are rare. They may be due to a specific allergy to any component of the vaccine (which may include antibiotics, egg protein, stabilizers such as gelatin, or a preservative). If the specific cause of a serious allergic reaction following immunization can be identified, that particular component must **never** be given again. If the specific cause is not identified, no component of the vaccine should be given again except on the advice and under direct supervision of an experienced physician.

Severe reactions, local or systemic, may indicate that additional doses of the same agent should be avoided. The physician should seek expert advice in such instances, as continuing the immunization series may still be possible (or even necessary, as for post-exposure rabies immunization) under controlled conditions.

Vaccine providers should be aware of the incidence and nature of adverse reactions to immunizing agents. Although signed consent is not required, parents and patients must always be informed about both the benefits and risks of the vaccines. They should be reminded of the risks of the targeted diseases and given the opportunity to ask questions. It should be recorded in patients' charts that such discussion took place. In addition, it may be helpful to provide information brochures written in lay language (see Communication issues in immunization, page 43).

Pregnant women

Immunization of pregnant women with killed or recombinant vaccine is safe; however, the use of live, attenuated vaccines is contraindicated. Should such immunization take place inadvertently, it should be reported. In almost every instance, termination of pregnancy is not warranted (see chapters on the specific vaccines), but in such cases the woman should be followed to term by public health authorities.

Vaccine safety monitoring in Canada

Large-scale trials — however ideal — to detect all possible rare, adverse events cannot usually be carried out before licensure because the number of subjects included in such trials can be quite limited (5,000 to 15,000). Therefore, the reporting of adverse events is vital to monitor the safety of vaccines and generate hypotheses that can be tested by controlled study.

It is important that such reporting include not only well-established adverse events but also any severe or unusual events not previously associated with the vaccine, so as to trigger investigation of possible new associations. This is particularly true for the newer vaccines, of which there is limited use or experience. As a result, truly rare adverse events caused by the vaccine can be detected only with post-marketing surveillance, when large numbers of individuals are immunized. In addition, surveillance of adverse events is important to detect any change in the frequency of

known events and to monitor vaccine lots that have been released, should they not perform as expected.

In Canada, there are two main surveillance systems: a passive surveillance system that collects data on any adverse event reported by all health care providers, and an active surveillance system operating through pediatric hospitals, known as IMPACT.

For the passive system, all adverse events should be reported using a standardized form available through public health units. This form permits the reporting of common adverse events but also has a section to describe any severe or unusual occurrences after immunization. Parents and patients should therefore be advised to notify their health care provider about any significant adverse event. To facilitate detailed monitoring and follow-up of adverse reactions, the lot number and manufacturer of the vaccine should be recorded in the vaccine recipient's medical record.

Physicians and other health care personnel should report serious adverse events associated with immunization to their local health unit or medical officer of health. Appendix I provides a list of defined events that should be reported. An example of a reporting form can be found in Appendix II and is available, with instructions, in the *Compendium of Pharmaceuticals and Specialties*. The local public health offices forward completed reports to the provincial health department, which then sends them to the Centre for Infectious Disease Prevention and Control, at Health Canada. This federal office is responsible for post-marketing surveillance of adverse events temporally associated with immunizing agents. Only non-nominal information is sent, and thus confidentiality is maintained. Updated reports on adverse events are published periodically and are available at the Health Canada website (http://www.hc-sc.gc.ca/hpb/lcdc/bid/di/nation_e.html).

To enhance surveillance of rare but severe adverse events, Canada has implemented an active surveillance network: the Immunization Monitoring Program Active (IMPACT), a pediatric, hospital-based network funded by Health Canada. This network collects information on potentially vaccine-related, severe adverse events and serious illness for which new or improved vaccines are being used or may be introduced in the near future. The 13 IMPACT hospitals make up approximately 85% of tertiary care pediatric beds in Canada. This program reports results regularly through the *Canada Communicable Disease Report* (CCDR).

Special review of serious and unusual events is conducted by the Advisory Committee on Causality Assessment (ACCA), which comprises pediatricians, immunologists, epidemiologists and other experts. The mandate of ACCA is to evaluate the degree to which such events are linked to the implicated vaccine in order to detect potential signals of concern (for more information see http://www.hc-sc.gc.ca/hpb/lcdc/bid/di/acca_e.html).

Canadian health authorities are very sensitive to vaccine safety. A national meeting on vaccine safety was convened in November 2000 in order to emphasize the importance of vaccine safety and to issue recommendations to further improve the vaccine

safety program in Canada. These recommendations were published in the *CCDR* in October 2001.

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Anaphylactic Hypersensitivity to Egg and Egg-Related Antigens

Vaccines that contain small quantities of egg protein can cause hypersensitivity reactions in some people with allergies to eggs. The likelihood of such reactions occurring varies considerably among vaccines. Adverse reactions are more likely to occur to vaccines against yellow fever and influenza, which are prepared from viruses grown in embryonated eggs. In contrast, the measles and mumps vaccine viruses most widely used in Canada are grown in chick embryo cell culture; after these viruses have undergone extensive purification steps, the final vaccine products *may* contain trace quantities of avian proteins, resembling proteins present in hens' eggs. A measles-rubella combination vaccine, MoRu-Viraten Berna®, contains no avian proteins and can be used without regard to egg allergy.

Anaphylaxis after measles vaccination is rare. It has been reported both in people with anaphylactic hypersensitivity to eggs and in those with no history of egg allergy. In some of these instances **it is hypersensitivity to gelatin that is responsible for the anaphylactic reaction.** As well, allergy to other components of the vaccine, such as neomycin, has been hypothesized but not proven.

Several studies have reported uneventful routine MMR immunization in egg-allergic people and in those with positive MMR skin tests, whereas others have reported occasional adverse reactions despite the use of MMR skin testing and graded challenge vaccination. In the largest summary of the literature, none of the 284 children with egg allergy confirmed by blinded food challenge showed any serious adverse

events with routine measles immunization (95% confidence interval [CI] 99.0%-100%). Routine immunization was tolerated by all 1,209 children with a positive skin test to egg (95% CI 99.75%-100%) and by 1,225 (99.84%) of 1,227 children with a history of allergy to egg (95% CI 99.41%-99.98%).

In view of the cumulative data indicating the safety of measles immunization in people with a history of anaphylactic hypersensitivity to hens' eggs and the lack of evidence of the predictive value of MMR skin testing, NACI does not recommend routine MMR skin testing in these individuals. As with all immunization, NACI recommends immunization by personnel with the capability and facilities to manage vaccine-associated adverse reactions such as anaphylaxis.

No special precautions are necessary for children with minor egg hypersensitivity if they can uneventfully ingest small quantities of egg as a food ingredient or if they are immunized with the measles-rubella vaccine that is free of avian proteins. No special measures are necessary for children who have never been fed egg before their MMR immunization, and prior egg ingestion should not be a prerequisite for MMR immunization. The following guidelines should be used for people with anaphylactic hypersensitivity to hens' eggs (urticaria, swelling of the mouth and throat, difficulty breathing or hypotension):

- Yellow fever vaccine and influenza vaccines that are prepared from viruses grown in embryonated eggs should not be given unless the risk of the disease outweighs the small risk of a systemic hypersensitivity reaction. Re-immunization with yellow fever or influenza vaccine is contraindicated in an individual with a previous anaphylactic reaction to the vaccine.
- Egg allergy is not a contraindication to immunization with MMR. People with this allergy may be immunized in the routine manner without prior testing. As an additional precaution, however, it may be prudent to observe them for 30 minutes after immunization for any signs of an allergic reaction.
- MMR vaccine (or measles or measles-rubella vaccine) is contraindicated in people with a previous anaphylactic reaction to a vaccine containing one of these components. See Measles chapter for other considerations about allergy and MMR.
- If there is a compelling reason to re-immunize an individual who has had a prior anaphylactic reaction to the same vaccine, or to administer yellow fever or influenza vaccines prepared in embryonated chicken eggs to an individual with anaphylactic hypersensitivity to hens' eggs, skin testing and graded challenge can be considered. For instance, in one study involving 83 egg-allergic people, all tolerated the influenza vaccine when it was administered in two intramuscular doses at a single visit (one-tenth of the dose given initially followed by nine-tenths 30 minutes later) without significant allergic reaction. However, because of the possibility of a hypersensitivity reaction during the skin test or the graded challenge, testing should be performed in an appropriately equipped facility by skilled personnel familiar with the procedures and with the treatment of anaphylaxis.

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Anaphylaxis: Initial Management in Non-Hospital Settings

This section is intended as a guide for the initial management of patients in a public health clinic or similar non-hospital setting. In a patient with severe, life-threatening anaphylaxis, establishment of intravenous access for drug and fluid administration will be necessary, and endotracheal intubation and other manoeuvres may be required. These interventions are ordinarily best performed in a hospital's emergency department.

Anaphylaxis is a potentially life-threatening allergic reaction to foreign protein antigens such as food and bee stings. It is a rare complication of immunization but, even so, it should be anticipated in every vaccinee. Prevention is the best approach. Pre-vaccination screening should include questions about possible allergy to any component of the product(s) being considered in order to identify this contraindication. As avoidance is not always possible, every vaccine provider should be familiar with the symptoms of anaphylaxis and be ready to initiate management and administer appropriate medications. Most instances begin within 30 minutes after an injection of vaccine; shorter intervals to onset foretell more severe reactions. Thus vaccine recipients should be kept under supervision 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, supervision can include having vaccinees remain within a short distance of the vaccinator (e.g., within a school being used for immunization) and return immediately for assessment if they feel unwell.

Anaphylaxis is one of the rarer events reported in the post-marketing surveillance system for vaccine adverse events. Based on the latest analysis of complete national data, the annual rate of anaphylaxis ranges from 0.11 to 0.31 reports per 100,000 doses of vaccines distributed.

Anaphylaxis must be distinguished from fainting (vasovagal syncope), anxiety and breath-holding spells, which are more common and benign reactions. 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), but this generally requires no specific treatment or investigation. Fainting is managed simply by placing the patient in a recumbent position. Recovery of consciousness occurs within a minute or two,

but patients may remain pale, diaphoretic and mildly hypotensive for several more 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 during fainting spells those at risk are best immunized while seated.

People experiencing an anxiety spell 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 spells occur in some young children when they are upset and crying hard. The child is suddenly silent but obviously agitated. Facial flushing and perioral cyanosis deepens as breath-holding continues. Some spells end with resumption of crying, but others end with a brief period of unconsciousness during which breathing resumes. Similar spells may have been evident in other circumstances. No treatment is required beyond reassurance of the child and parents.

In the case of anaphylaxis, changes develop over several minutes and usually involve at least two body systems (affecting the skin, respiration, circulation). Unconsciousness is rarely the sole manifestation of anaphylaxis. It occurs only as a late event in severe cases.

The cardinal features of anaphylaxis are

- itchy, urticarial rash (in over 90% of cases);
- 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;
- hypotension, which generally develops later in the illness and can progress to cause shock and collapse.

An inconstant early feature is swelling and urticarial rash at the injection site. This is more likely to be evident with vaccines injected subcutaneously rather than intramuscularly.

Anaphylaxis is described as mild or early when signs are limited to urticarial rash and injection site swelling. At this stage symptoms may arise from other systems (e.g., sneezing, nasal congestion, tearing, coughing, facial flushing) but are associated with minimal dysfunction. Features of severe disease include obstructive swelling of the upper airway, marked bronchospasm and hypotension.

Management of anaphylaxis

The following steps describe the management of anaphylaxis. Steps 1 to 4 are meant to be done rapidly or simultaneously. **The priority is prompt administration of epinephrine (step 4)**, which should not be delayed if earlier steps cannot quickly be completed.

1. Call for assistance, including an ambulance.
2. Place the patient in a recumbent position (elevating the feet if possible).
3. Establish an oral airway if necessary.
4. **Promptly administer 0.01 mL/kg (maximum 0.5 mL) of aqueous epinephrine 1:1,000 by subcutaneous or intramuscular injection in the opposite limb to that in which the vaccination was given.** Speedy intervention is of paramount importance; failure to use epinephrine promptly is more dangerous than using it improperly.

   The subcutaneous route of epinephrine injection is appropriate for mild or early cases, and a single injection is usually sufficient. Severe cases should receive intramuscular injections because they lead more quickly to generalized distribution of the drug.

   Dosing can be repeated twice at 20-minute intervals if necessary, again avoiding the limb in which the vaccination was given. A different limb is preferred for each dose to maximize drug absorption. Severe reactions could require these repeat doses to be given at shorter intervals (10 to 15 minutes).

   The epinephrine dose should be carefully determined. Calculations based on body weight are preferred when weight is known. Recording the weight of children before routine immunization is recommended when feasible. Excessive doses of epinephrine can add to patients' distress by causing palpitations, tachycardia, flushing and headache. Although unpleasant, such side effects pose little danger. Cardiac dysrhythmias may occur in older adults but are rare in otherwise healthy children.

   When body weight is not known the dose of aqueous epinephrine 1:1,000 can be approximated from the subject's age (Table 4).

   The anaphylactic state in patients receiving beta-adrenergic antagonist therapy (for elevated blood pressure) will be more resistant to epinephrine therapy.

   Since anaphylaxis is rare, epinephrine vials and other emergency supplies should be checked on a regular basis and replaced if outdated.

Adrenaline kit contents:

Copy of the anaphylaxis procedures/doses
2 – 1 cc syringes with attached needles (1 – 25 gauge, 5/8" needle/1 – 25 gauge, 1" needle)
2 vials of adrenaline 1:1,000 (within expiration time frame)
1 vial of diphenhydramine
1 – 25 gauge, 5/8" needle (extra)
1 – 25 gauge, 1" needle (extra)
2 alcohol swabs (optional)

– Table 4 –

Appropriate Dose of Epinephrine According to Age

Age	Dose	
2 to 6 months*	0.07 mL	(0.07 mg)
12 months*	0.10 mL	(0.10mg)
18 months* to 4 years	0.15 mL	(0.15 mg)
5 years	0.20 mL	(0.20 mg)
6-9 years	0.30 mL	(0.30 mg)
10-13 years	0.40 mL†	(0.40 mg)
≥ 14	0.50 mL†	(0.50 mg)

* Dose for children between the ages shown should be approximated, the volume being intermediate between the values shown or increased to the next larger dose, depending on practicability.

† For a mild reaction a dose of 0.3 mL can be considered.

5. If the vaccine was injected subcutaneously, an additional dose of 0.005 mL/kg (maximum 0.3 mL) of aqueous epinephrine 1:1,000 can be injected into the vaccination site to slow absorption. This should be given shortly after the initial dose of epinephrine (Table 4) in moderate to severe cases. It is generally not repeated. Local injection of epinephrine into an intramuscular vaccination site is contraindicated because it dilates vessels and speeds absorption of the vaccine.

6. As an adjunct to epinephrine, a dose of diphenhydramine hydrochloride (Benadryl®) can be given. It should be reserved for patients not responding well to epinephrine or to maintain symptom control in those who have responded to epinephrine (epinephrine being a short-acting agent), especially if transfer to an acute care facility cannot be effected within 30 minutes. Oral treatment (oral dose: 1-2 mg/kg to a maximum single dose of 100 mg) is preferred for conscious patients who are not seriously ill because Benadryl® is painful when given intramuscularly. This drug has a high safety margin, making precise dosing less important. The approximate doses for injection (50 mg/mL solution) are shown in Table 5.

– Table 5 –

Appropriate Dose by Injection of Diphenhydramine Hydrochloride (50 mg/mL Solution)

Age	Dose	
< 2 years	0.25 mL	(12.5 mg)
2-4 years	0.50 mL	(25.0 mg)
5-11 years	1.00 mL	(50.0 mg)
≥12 years	1.00-2.00 mL	(50-100 mg)

7. Monitor vital signs and reassess the situation frequently, to guide medication use.
8. Arrange for rapid transport to an emergency department. Since 20% of anaphylaxis episodes follow a biphasic course with recurrence of the reaction after a 2-9 hour asymptomatic period, hospitalization or a long period of observation is recommended for monitoring. For all but the mildest cases of anaphylaxis, patients should be hospitalized overnight or monitored for at least 12 hours.

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Immunization During Pregnancy

Immunization during pregnancy may be indicated if the risk of infection is high, the illness would cause significant risk to the mother or fetus, and the risk of adverse effects from the vaccine is acceptably low. When these conditions do not prevail, any vaccination should be deferred until after delivery. There is a theoretical risk to the fetus from live-virus vaccines, but specific fetal damage from administration of currently licensed vaccines during pregnancy has not been reported. Should a congenital defect occur following a pregnancy during which the mother was immunized, blame may be attributed, perhaps wrongly, to the vaccine. When a vaccine is indicated during pregnancy, consider delaying administration until the second or third trimester, if possible, to reduce the risk of inappropriate attribution of cause.

There is no evidence to suggest that pregnant women are at increased risk of allergic reactions after immunization. However, a severe anaphylactic reaction and its treatment can have dramatic adverse consequences for the fetus. As well, fever is a possible reaction to many vaccines; epidemiologic and animal studies indicate that maternal hyperthermia during the first trimester of pregnancy may be teratogenic. The magnitude of this risk is not known precisely.

Inactivated vaccines and toxoids are generally considered safe for the fetus, whereas live vaccines are contraindicated. Tetanus immunization for women who have never received a primary series or who suffer a tetanus-prone wound, and influenza immunization for those at high risk of complications (see chapter on Influenza Vaccine) are particularly important to consider. Live attenuated yellow fever vaccine may be administered to pregnant women only if they will be exposed to an ongoing epidemic. There is no known risk from passive immunization of pregnant women with immune globulins.

Should a pregnant woman receive a contraindicated vaccine inadvertently, the incident should be signaled to the local public health department and the outcome of the pregnancy monitored for possible adverse events. Since there is no or extremely low risk of congenital defects from mumps, measles, and rubella vaccine, pregnancy termination should never be proposed. The effect of varicella vaccine on the fetus is not known, but data collected to date do not suggest that it poses a particular fetal risk.

Immunization with live, attenuated virus for children from families with pregnant women is not contraindicated and should never be postponed for this reason.

Vaccinators are advised to consult with an expert in pregnancy and immunization before deciding on the necessity for immunization during pregnancy.

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Immunization and Breast-Feeding

Breast-feeding does not adversely affect immunization of the infant with either live or killed vaccines and may, in fact, improve the immune response to some vaccines. Infants who are breast-fed should receive all recommended vaccinations at the usual times.

Lactating mothers who have not received the recommended immunizations may safely be given vaccine against rubella, measles, mumps, tetanus, diphtheria, influenza, *Streptococcus pneumoniae*, hepatitis A, hepatitis B, polio and varicella. Inactivated polio vaccine may safely be given to lactating mothers who have not previously been immunized or who are travelling to a highly endemic area.

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Immunization of Children with Neurologic Disorders

Children with neurologic disorders can undergo routine vaccinations. For those with seizure disorders that might be exacerbated by fever, prophylactic doses of acetaminophen (15 mg/kg) can be used.

Immunization in Immunocompromised Hosts

The number of immunocompromised people in Canadian society is steadily increasing for a variety of reasons. These include our increasingly sophisticated understanding of "normal" and altered immunity (e.g., IgG subclass deficiencies, mannose binding protein deficiency, cytokine receptor deficiencies); recognition of the subtle immunodeficiencies associated with chronic illnesses (e.g., diabetes, cirrhosis, alcoholism, renal disease) and the extremes of age; accumulation of individuals with absent or dysfunctional spleens; the expanding range of illnesses treated with immunomodulatory agents (e.g., autoimmune diseases, inflammatory conditions); the HIV pandemic; accumulation of long-term survivors after organ transplantation; and the increased use of ablative therapy for cancer and other conditions.

The number of immunizations to which immunocompromised people are likely to be exposed is also increasing. There is an ever-enlarging spectrum of vaccines available and an increasing number of vaccines included in universal programs; as well, efforts are under way to fully immunize adolescents, adults and the elderly. Individuals with significant illness can now travel with relative ease (e.g., people infected with HIV, see CATMAT statement on travel and HIV as well as a recent review by Mileno and Bia). Furthermore, both basic and clinical investigations have recently contributed to the discovery of novel strategies (for instance, increased dose, route of delivery, novel adjuvant systems) for eliciting successful immune responses in immunocompromised individuals.

Therefore, the frequency and complexity of questions dealing with immunization in immunocompromised hosts will only increase with time. Still further complexity is

added by the fact that the relative degree of immunodeficiency varies over time in many people. The decision to recommend for or against any particular vaccine will depend upon a careful, case-by-case analysis of the risks and benefits.

There is potential for serious illness and death in both the underimmunization and overimmunization of these people. Immunization of those with significant immunodeficiency should be performed only in consultation with experts.

General principles

Several general principles apply to the immunization of immunocompromised individuals:

- maximize benefit while minimizing harm;
- make no assumptions about susceptibility or protection
  - a history of childhood infection or previous immunization may be irrelevant;
- immunize at the time when maximum immune response can be anticipated
  - immunize early, when immunologic decline is predictable
  - delay immunization if the immunodeficiency is transient (if this can be done safely)
  - stop or reduce immunosuppression to permit better vaccine response;
- consider the immunization environment broadly
  - spread of vaccine strain varicella to family members of the vaccinee
  - immunization status of both donor and/or recipient in the setting of bone marrow (BMT) or stem cell transplantation;
- avoid live vaccines, unless
  - data are available to support their use
  - the risk of natural infection is greater than the risk of immunization;
- monitor vaccinees carefully and boost aggressively
  - the magnitude and duration of vaccine-induced immunity are often reduced
  - some vaccine strain organisms can persist for years in compromised hosts.

Approach to vaccination of immunodeficient individuals

The approach to immunizing people with immunodeficiency varies with the precise nature of the defect. Additional considerations include the age of the individual (affecting the types of vaccine and the relative urgency of immunization) and factors that influence the risk of exposure to the different pathogens (e.g., endemic, epidemic, professional, travel related). The most common situations are discussed below in broad categories of immunodeficiency. Excellent reviews of this subject are available (Loutan 1997, Pirofski & Casadevall 1998, McFarland 1999, Mileno & Bia 1998, Burroughs & Moscona 2000, Molrine & Hibberd 2001).

Otherwise "normal" individuals with chronic illness or advanced age

These individuals are not necessarily more susceptible to vaccine-preventable diseases but are more likely to suffer significant illness and death from these infections. With the possible exception of yellow fever immunization in those > 65 years of age (see Yellow Fever Vaccine), there are no absolute contraindications to the use of any vaccine in these people.

Particular attention should be paid to annual influenza immunization and at least one dose of pneumococcal vaccine and Td every 10 years (see appropriate vaccine specific chapters). Hepatitis A and/or B immunization may be appropriate in people with chronic liver disease, since they are at risk of fulminant hepatitis. Consider early immunization for individuals who are likely to need solid organ transplantation (e.g., immunization against hepatitis B in those with deteriorating renal disease).

The immune response to vaccines will be suboptimal in many of these people, but there is now good evidence that such limited responses may be improved in some cases with readily accessible strategies, such as increasing the antigen dose (e.g., 40 µg hepatitis B surface antigen dose for patients undergoing hemodialysis). Active verification of immune status (e.g., annual verification of hepatitis B serostatus in hemodialysis patients) and immunization or re-immunization (e.g., against *Haemophilus influenzae* in children < 10 years of age) may be important for some individuals who are at continued high risk.

Splenic disorders

Asplenia or hyposplenism may be congenital, surgical or functional. A number of conditions not typically thought of as immunocompromising can lead to functional hyposplenism. These include sickle cell anemia, thalassemia major, essential thrombocytopenia, celiac disease and inflammatory bowel disease. There are no contraindications to the use of any vaccine in these patients. Particular attention should be paid to ensuring optimal protection against ubiquitous encapsulated bacteria (*Streptococcus pneumoniae*, *Haemophilus influenzae*), to which these individuals are highly susceptible. They should also receive annual influenza immunization. Meningococcal immunization (quadrivalent) is essential for hyposplenic and asplenic individuals who reside in or travel to areas where meningococcal disease is endemic.

There are no data dealing specifically with the periodicity of booster doses in hyposplenic and asplenic patients, although antibody titres are known to decrease with time. Certainly, the 23-valent pneumococcal vaccine should be recommended for everyone who received the original 14-valent product. The current vaccine can be used to safely boost antibody titres at least once after 5 years. Meningococcal immunization can be boosted every 2 to 3 years. (In young patients < 10 years it may be prudent to verify the presence of antibodies directed against *H. influenzae* and re-immunize as needed.)

Careful attention should be paid to immunization status when "elective" surgical splenectomy is planned so that all of the necessary vaccines can be delivered at least 2 weeks before removal of the spleen. It is likely that the protein-conjugated meningococcal and pneumococcal vaccines will significantly improve responses in these individuals. At the current time, however, the number of meningococcal and pneumococcal serotypes for which conjugated formulations are available is quite limited (e.g., 7 or 9 pneumococcal capsular polysaccharides versus 23 in the unconjugated formulation). As a result, conjugated polysaccharide vaccines should be added to immunization schedules as they become available rather than replacing the currently available polysaccharide products. (Note: when available, the conjugated products should be given first.)

Congenital immunodeficiency states

This is a varied group of conditions that includes defects in antibody production (e.g., agammaglobulinemia, isotype and IgG subclass deficiencies and hyper-IgM syndromes), complement deficiencies, defects in one or more aspects of cell-mediated immunity (CMI) and mixed deficits. Individuals with defects in antibody and complement have unusual susceptibility to the encapsulated bacteria and members of the enteroviridae family (e.g., polio, coxsackie and echoviruses), and individuals with mixed and T cell defects are particularly susceptible to intracellular pathogens (virtually all viruses and some bacteria, fungi and parasites). Although the defects and susceptibility patterns are very different, the approach to immunization is quite similar for these individuals. Component and inactivated vaccines can and should be administered in all of these conditions, despite the fact that many vaccinees will respond poorly, if at all. Live vaccines are generally not recommended for these patients, although limited clinical data suggest that MMR can be administered without undue risk in many of those with pure antibody defects.

Antibody defects: Particular attention should be given to ensuring that individuals with this condition are immunized against pneumococcal and meningococcal disease and *Haemophilus influenzae*. Although oral poliovirus vaccine (OPV) is no longer routinely used in Canada, it remains a licensed product and is used in many other countries. OPV should not be used in the affected individual or any of his or her family members. Other live vaccines may be considered on a case-by-case basis after a thorough review of the risks and benefits.

As a general rule, people with antibody defects can be protected from many of the vaccine-preventable infections with the use of intravenous immunoglobulin (IVIG) or pathogen-specific IG preparations. Inactivated vaccines should be given when IVIG-supported immunoglobulin levels are as low as possible. Again, improved responses with the conjugated polysaccharide products can be anticipated in many individuals, but careful attention will need to be given to coverage of pneumococcal and meningococcal serotypes and appropriate boosting.

T cell, natural killer and mixed CMI-antibody defects: Live vaccines are contraindicated. Inadvertent live vaccine administration and exposure to natural infections

must be dealt with by rapid administration of serum IG or pathogen-specific IG with or without appropriate antiviral or antibacterial treatment.

Granulocyte defects: There are no contraindications to the use of any vaccine.

Long-term steroids/azathioprine/cyclosporine/cyclophosphamide/ Remicade

Long-term immunosuppressive therapy is used for organ transplantation and an increasing range of chronic infectious and inflammatory conditions (e.g., inflammatory bowel disease, psoriasis, systemic lupus erythematosis). These therapies have their greatest impact on cell-mediated immunity, although T cell-dependent antibody production can also be adversely affected. Ideally, all appropriate vaccines or boosters should be administered to these individuals at least 10-14 days before the initiation of therapy. If this cannot be done safely, immunization should be delayed until at least 3 months after immunosuppressive drugs have been stopped or until such therapy is at the lowest possible level.

There is no contraindication to the use of any inactivated vaccine in these people, and particular attention should be paid to the completion of childhood immunizations, annual influenza immunization and pneumococcal immunization (with a booster after 5 years). Active verification of immune status and immunization or re-immunization may be important for some individuals (e.g., against *H. influenzae* in children < 10 years of age or hepatitis B for renal transplant recipients). Live vaccines are generally contraindicated, although the risk to benefit ratio for several of these vaccines can favour immunization if only low doses of immunosuppressive drugs are required and there is significant risk of wild-type infection (e.g., varicella vaccine in seronegative individuals). On the theoretical grounds that vaccine-induced immunostimulation might trigger an anti-transplant response, some centres choose to rely on IG preparations (e.g., in a measles outbreak) with or without appropriate antimicrobial drugs, to avoid vaccines.

High dose steroids: Only high dose, systemic steroids (e.g., 2mg/kg of prednisone or a maximum daily dose of 20 mg for more than 2 weeks) interfere with vaccine-induced immune responses. Of course, reasonable clinical judgement must be exercised in the risk to benefit review of each case. Topical and inhaled steroids have no known impact on oral or injected vaccines. A period of at least 3 months should elapse between high dose steroid use and administration of both inactivated or component vaccines (to ensure immunogenicity) and live vaccines (to reduce the risk of dissemination). Children with adrenogenital syndrome and those receiving physiologic replacement doses of glucocorticoids can follow the routine immunization schedule without restriction.

Immunoablative therapy (e.g., cancer therapy, total body irradiation, marrow/stem cell transplantation)

If time permits, careful consideration must be given to the pre-ablation immunization status of the patient and, in the case of allogenic BMT, the donor. It is well

established that disease and immunization histories in both the host and the donor (i.e., in adoptive transfer) can influence immunity after ablation or transplantation. Although the logic underlying programmatic immunization of these patients is compelling, there are relatively few data that address important immunization-related questions after ablative therapies (e.g., optimal timing, requirement for boosters, overall efficacy, cost-benefit). A recent U.S. national survey demonstrated striking inconsistencies in pre- and post-ablative immunization policies and what the authors felt to be "under-utilization" of vaccines in this setting.

General principles in this setting include the following:

- Live vaccines are contraindicated before ablation when significant marrow infiltration is present (varicella immunization in patients with leukemia may be an exception to this rule when given under protocol).
- Administer all appropriate vaccines or boosters at least 10-14 days before ablative therapy if this can be accomplished without delaying the initiation of chemotherapy.
- In allogenic BMT, consider the administration of all appropriate vaccines or boosters to the donor at least 10-14 days before the marrow harvest.
- Wait at least 12 months after ablative therapy before administering live vaccines and then only if there is no ongoing immune suppressive treatment or graft-versus-host disease.
- Inactivated or component vaccines can be given as soon as the total lymphocyte count exceeds 500, but responses are likely to be very poor soon after transplantation. A primary immunization schedule should be re-initiated at 12 months after transplantation in children whose original schedule was disrupted. Immunization or re-immunization should also be offered to adults with either a full primary series or verification of response after at least two booster doses of each vaccine.
- Consider documentation of responses to the most important pathogens (e.g., *H influenzae*, measles, varicella).

Illnesses that progressively weaken the immune system (e.g., HIV, myelodysplasias)

With the exception of BCG (Bacille Calmette-Guérin), there are no contraindications to the use of any vaccine (including MMR) early in the course of these illnesses. As these conditions progress, the use of live vaccines becomes increasingly dangerous, and the risks and benefits of a particular vaccine (and the alternative therapies available) need to be carefully considered.

Early immunization is not only safer but is also more effective in these conditions. There is no contraindication to the use of inactivated or component vaccines at any time. Particular attention should be paid to the completion of childhood immunizations, pneumococcal immunization (boosted once after 5 years), annual influenza immunization and possibly booster doses against *H. influenzae*. Exposure to wild-type infections must be addressed promptly with general serum or specific IG preparations

with or without antimicrobial therapy, since the rates of death in people with these illnesses can be very high (e.g., 50% to 70% mortality from measles in patients with AIDS).

In the case of HIV, consensus "cut-offs" have been determined for the use of some vaccines (Table 6). Although concerns have been raised about increases in HIV viral load, which can occur after a number of routine immunizations, these changes are transient and should not prevent the administration of any appropriate vaccine. The only situation in which deferral of an otherwise appropriate immunization might be recommended would be that of an HIV-positive woman who has decided (against medical advice) to breast-feed.

Immunocompromised travellers

Although the degree and range of infectious disease risks can increase dramatically when an immunocompromised individual boards an airplane or boat, the basic principles already outlined still apply. Evidence is accumulating to suggest that several live vaccines (including yellow fever vaccine) can be considered for people with asymptomatic HIV infection whose $CD4^+$ T cell count is > 200. However, the risks and benefits of each live vaccine must be carefully evaluated for every traveller. When a certificate of yellow fever vaccination is required but this vaccine is contraindicated, a letter of deferral should be supplied to the patient.

– Table 6 –

Vaccination of Individuals with Immunodeficiency

Vaccine	HIV/AIDS	Severe immuno-deficiency	Solid organ transplantation	BMT	Chronic disease age/alcoholism	Hypo- or asplenia
Inactivated/Component Vaccines						
DPT (Td)	Routine use*	Routine use	Recommended†	Recommended	Routine use	Routine use
IPV	Routine use	Routine use	Recommended	Recommended	Routine use	Routine use
Hib	Routine use	Routine use	Recommended	Recommended	Routine use	Recommended (confirm response in children <10)
Influenza	Recommended	Recommended	Recommended	Recommended	Recommended	Recommended
Pneumococcal	Recommended	Recommended	Recommended	Recommended	Recommended	Recommended
Meningococcal	Use if indicated	Use if indicated	Use if indicated	Use if indicated	Use if indicated	Use if indicated
Hepatitis A	Recommended (gay men, IVDU)	Use if indicated	Use if indicated	Use if indicated	Recommended (chronic liver disease)	Use if indicated
Hepatitis B	Recommended (gay men, IVDU)	Routine use	Routine use	Routine use	Recommended (chronic liver or renal disease)	Routine use

– Table 6 *con't* –

Vaccination of Individuals with Immunodeficiency

Vaccine	HIV/AIDS	Severe immuno-deficiency	Solid organ transplantation	BMT	Chronic disease age/alcoholism	Hypo- or asplenia
Live Vaccines						
MMR	Routine use‡ (if no significant compromise)	Contraindicated	Consider at 24 mo (min. suppressive Rx)	Consider at 24 mo (no suppressive Rx, no GVHD)	Use if indicated	Use if indicated
OPV	Contraindicated (use IPV instead)	Contraindicated (use IPV instead)	Contraindicated (use IPV instead)	Contraindicated (use IPV instead)	If indicated use IPV	If indicated use IPV
Varicella	Use if indicated (asymptomatic disease)	Contraindicated	Consider at 24 mo (min. suppressive Rx)	Consider at 24 mo (no suppressive Rx, no GVHD)	Use if indicated	Use if indicated
Oral typhoid	Contraindicated (use IM vaccine instead)	Contraindicated (use IM vaccine instead)	Contraindicated (use IM vaccine instead)	Contraindicated (use IM vaccine instead)	If indicated use IM	If indicated use IM
BCG	Contraindicated	Contraindicated	Contraindicated	Contraindicated	Use if indicated	Use if indicated
Yellow fever	Contraindicated	Contraindicated	Consider at 24 mo (no suppressive Rx, no GVHD)	Consider at 24 mo (no suppressive Rx, no GVHD)	Use if indicated	Use if indicated
Oral cholera	Contraindicated	Contraindicated	Contraindicated	Contraindicated	Use if indicated	Use if indicated

* Routine vaccination schedules should be followed with age-appropriate booster doses.

† Vaccination and/or re-vaccination recommended with or without verification of serologic response.

‡ Most HIV positive children can receive the first MMR vaccine without significant risk. Administration of the second MMR dose (particularly in adults) must be evaluated on a case-by-case basis.

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Immunization of People with Hemophilia and Other Bleeding Disorders

For individuals with bleeding disorders, immunization should be carried out using a fine gauge needle of appropriate length. After the injection, firm pressure should be applied, without rubbing, to the injection site for at least 5 minutes. Administration can be subcutaneous or intramuscular depending on the product. If there is concern that an injection may stimulate bleeding, it can be scheduled shortly after administration of anti-hemophilia therapy.

Any patient with a bleeding disorder who needs plasma-derived products is at higher risk of contracting hepatitis A or B and should be offered the vaccine. Please refer to the appropriate chapter in the Guide for information on dosage.

Immunization of Infants Born Prematurely

Premature infants whose clinical condition is satisfactory should be immunized with full doses of vaccine at the same chronological age and according to the same schedule as full-term infants, regardless of birth weight. In premature infants, maternally derived antibody is present at lower titres and for a shorter duration than in mature infants. As well, the severity of vaccine-preventable illnesses may be greater in this population. Therefore, immunization of premature infants should not be delayed.

Antibody response to immunization is generally a function of post-natal age and not of maturity. Although studies demonstrate conflicting results, premature infants may have weaker antibody responses to several vaccinations than full-term controls. Despite this, vaccine efficacy remains high.

Healthy premature infants generally tolerate immunizations well, as compared with full-term infants. However, premature infants who are sick and have been hospitalized and those who have had significant apnea as a result of prematurity or chronic lung disease may experience a transient increase or recurrence of apnea after immunization.

The response to hepatitis B vaccine may be diminished in infants with birth weights below 2000 g. Routine immunization of infants of mothers negative for hepatitis B surface antigen (HBsAg) should be delayed until the infant reaches 2000 g or 2 months of age. Infants born to women who are HBsAg positive should receive hepatitis B immune globulin (HBIG) within 12 hours of birth and the appropriate dose of vaccine (see chapter on Hepatitis B Vaccine).

If the mother's status is unknown, the vaccine should be given in accordance with the recommendations for the infant of an HBsAg positive mother. The maternal status should be determined within 12 hours, and if the mother is HBsAg positive the infant should receive HBIG.

Pre-term infants with chronic respiratory disease should be immunized against influenza annually, beginning in the fall when they have reached 6 months of age. Delay of immunization has resulted in unnecessary deaths. Certain premature infants should also receive respiratory syncytial virus (RSV) immune globulin to decrease the likelihood of serious RSV infection requiring hospitalization and supplemental oxygen therapy (see chapter on Passive Immunizing Agents).

Timing of Vaccine Administration

For most products that require more than one dose or booster doses for full immunization, intervals longer than those recommended between doses do not lead to a reduction in final antibody concentrations. Therefore, as a general rule, *interruption of a series of vaccinations for any reason does not require starting the series over again, regardless of the interval elapsed.* However, there are exceptions, such as immunization against rabies. By contrast, doses given at less than the recommended interval may result in less than optimal antibody response and should not be counted as part of a primary series.

There are obvious practical advantages to giving more than one vaccine at the same time, especially in preparation for foreign travel or when there is doubt that the patient will return for further doses of vaccine. Most of the commonly used antigens can safely be given simultaneously. No increase in the frequency or severity of clinically significant side effects has been observed. The immune response to each antigen is generally adequate and comparable to that found in patients receiving these vaccines at separate times. Commercially prepared combinations of vaccines are convenient to use.

Unless specified by the manufacturer, inactivated vaccines should never be mixed in the same syringe. They can be given simultaneously, but at separate anatomic sites, consideration being given to the precautions that apply to each individual vaccine. No inactivated vaccine has been shown to interfere with the immune response to another inactivated vaccine; thus, no particular interval between inactivated vaccines need be respected, except when it is the second dose of the same vaccine, e.g., inactivated polio virus vaccine.

Live parenteral vaccines should never be mixed in the same syringe, but may be administered simultaneously at different sites. One live parenteral vaccine may interfere with the effectiveness of another, and to minimize this possibility two or more live vaccines should preferably be administered either on the same day or be separated by an interval of at least 4 weeks. The administration of oral typhoid vaccine (Ty21a) and oral cholera vaccine should be separated by at least 8 hours.

Recent Administration of Human Immune Globulin Products

Passive immunization with products of human origin can interfere with the immune response to live viral vaccines. For measles vaccine, the recommended interval between immune globulin (IG) administration and subsequent immunization varies from 3 to 10 months, depending on the specific product given, as shown in Table 7.

For an optimum response to rubella or mumps vaccine given as individual components, there should be an interval of at least 3 months between administration of IG or blood products and immunization. If given as combined MMR, then the longer intervals, as recommended in Table 7, should be followed to ensure that there is an adequate response to the measles component. For women susceptible to rubella who are given Rh immune globulins in the peripartum period, consult the chapter on Rubella Vaccine for specific recommendations regarding the timing of rubella immunization.

If administration of an IG preparation becomes necessary **after** MMR vaccine or its individual component vaccines have been given, interference can also occur. If the interval between administration of any of these vaccines and subsequent administration of an IG preparation is < 14 days, immunization should be repeated at the interval indicated in the Table, unless serologic test results indicate that antibodies were produced. If the IG product is given more than 14 days after the vaccine, immunization does not have to be repeated.

Because there is little interaction between IG preparations and inactivated vaccines, the latter can be given concurrently or after an IG preparation has been used. The vaccine and IG preparation should be given at different sites. There are no data to indicate that IG administration interferes with the response to inactivated vaccines, toxoids or the live vaccines for yellow fever, typhoid, cholera and polio.

Storage and Handling of Immunizing Agents

Immunizing agents are biological materials that are subject to gradual loss of potency from deterioration and denaturation. Loss of potency can be accelerated under certain conditions of transport, storage and handling, and may result in failure to stimulate an adequate immunologic response, leading to lower levels of protection against disease. Conditions that result in loss of potency vary among products. Manufacturer and NACI recommendations generally specify that most products should be stored at temperatures from +2° to +8° C. Exceptions exist (e.g., yellow fever and varicella vaccines) for which the recommended storage conditions are outlined in the manufacturer's product leaflets.

The term "cold chain" as used in this statement refers to all equipment and procedures used to ensure that vaccines are protected from inappropriate temperatures and light, from the time of transport from the manufacturer to the time of administration.

– Table 7 –

Guidelines for the Interval Between Administration of Immune Globulin Preparation or Blood, and Vaccines Containing Live Measles Virus

Product	Indication	Dose	Interval (Months)
Immune globulin (IG)	Hepatitis A		
	• Contact prophylaxis	0.02 mL/kg	3
	• International travel	0.06 mL/kg	3
	Measles prophylaxis		
	• Normal contact	0.25 mL/kg	5
	• Immunocompromised host	0.5 mL/kg	6
Intravenous immune globulin (IVIG)	Treatment of antibody deficiency	160 mg/kg 320 mg/kg 640 mg/kg	7 8 9
	Treatment of idiopathic thrombocytopenic purpura or Kawasaki disease	> 1280 mg/kg to ≤ 2000 mg/kg	11
Hepatitis B immune globulin (HBIG)	Hepatitis B prophylaxis	0.06 mL/kg	3
Rabies immune globulin (RIG)	Rabies prophylaxis	20 IU/kg	4
Tetanus immune globulin (TIG)	Tetanus prophylaxis	250 units	3
Varicella immune globulin (VIG)	Varicella prophylaxis	125 units/ 10 kg	5
Washed red blood cells		10 mL/kg IV	0
Reconstituted red blood cells		10 mL/kg IV	3
Whole blood (Hct 36%)		10 mL/kg IV	6
Packed red blood cells		10 mL/kg IV	6
Plasma/platelet products		10 mL/kg IV	7
Intramuscular respiratory syncytial virus immune globulin		15 mg/kg	0
Intravenous respiratory syncytial virus immune globulin		750 mg/kg/ month	9

The effects of exposure to adverse environmental conditions, such as freezing, heat, and light, are cumulative. Data are available to indicate that certain products remain stable at temperatures outside of +2° to +8° C for specified periods of time, but mechanisms rarely exist for monitoring cumulative exposures. Additionally, different products are often transported and stored in the same container. Therefore, it is recommended that all biologicals for immunization be maintained at +2° +8°C at all times, unless otherwise specified in the product leaflet. Management of products that have been exposed to adverse conditions should be guided by specific instructions pertaining to the event from the vaccine supplier.

Monitoring of the vaccine cold chain is required to ensure that biologicals are being stored and transported at recommended temperatures. Testing of product potency or seroconversion rates as indicators of cold chain integrity are rarely feasible.

Refer to the product leaflet of each immunizing agent for specific instructions related to storage and handling. The following general principles apply.

Multi-dose vials: Multi-dose vials should be removed from the refrigerator only to draw up the dose required and should be replaced immediately.

Lyophilized (freeze dried) vaccines: For optimal potency, freeze dried vaccines (e.g., MMR, varicella, BCG, conjugate *Haemophilus* b) should be reconstituted immediately before use with the diluent provided for that purpose. Reconstituted vaccines, including yellow fever vaccine, should be used within 1 hour of reconstitution; if unused, they should be discarded. There are slight variations in the time intervals recommended by specific manufacturers, and users should refer to the product leaflet to guide timing of reconstitution.

Light exposure: Measles, mumps, rubella, varicella and BCG vaccines should be protected from light at all times by storage of the vials in the cartons provided. After reconstitution, if vaccines are not used immediately, they **must** be kept at +2° to +8° C and protected from light.

Freezing: The liquid inactivated and adsorbed vaccines should not be used if they have been frozen. These include DTaP, DT, DTaP-Polio, DT-Polio, Td, Td-Polio, hepatitis A and B vaccines, influenza and pneumococcal vaccines. Prior to use, liquid vaccines should be inspected and should not be used if visible indications of freezing are apparent or if a temperature recording device shows that the vaccine was exposed to temperatures below -2° C.

A positive "shake test" is the finding that liquid vaccine that was frozen and then thawed contains granular particles that can be seen immediately upon shaking. One half-hour after shaking, the supernatant is almost clear but granular particles form on the bottom of the vial. The "shake test" may be positive after freezing of adsorbed vaccines (e.g., DPT Polio, DPT, DT, Td and Td Polio); however, a positive shake test result does not consistently occur after freezing. Therefore, when other signs indicate that the vaccine may have been frozen, the vaccine should not be used, even if the "shake test" is negative.

Unreconstituted live virus vaccines, such as MMR and rubella vaccines, may be used after they have been frozen, but repeated freezing and thawing should be avoided.

Expiry: Vaccines should not be used beyond their expiry date. For expiry dates specified as month/year, products are deemed to expire on the last day of the specified month.

All vaccines that cannot be used because of expiry or adverse environmental exposure should be returned to the source for appropriate recording of returns and disposal, or should be appropriately disposed of locally and the quantities involved reported to the officials in charge of vaccine management in the jurisdiction. The vaccine supplier will be able to provide specific instructions.

Refrigerators: The temperature in frost-free refrigerators may cycle widely and should be monitored to ensure that cycling is within the acceptable range. Special "maximum-minimum" thermometers are commercially available for purchase and are useful for most office storage. More expensive, constant chart-recording thermometers with alarms are appropriate for larger vaccine storage depots. Non-frost-free refrigerators should be defrosted regularly and immunizing agents stored in a functioning fridge during the defrosting process. Fridges older than 10 years are more likely to malfunction and to have breaks in the seal around the door, leading to temperature instability. Half-size "under the counter" fridges are less reliable than full size "kitchen" fridges. Placement of full plastic water bottles in the lower compartment and door shelves of the fridge and ice packs in the freezer compartment will help stabilize temperatures, especially in the event of a power failure.

Recommended office procedures

The following office procedures should be implemented to ensure that storage of vaccines is optimized:

- Designate and train a specific staff person to be responsible for managing vaccines.
- Post storage and handling guidelines on the refrigerator.
- Use insulated storage containers with ice packs for transport of vaccines; to avoid freezing, do not place vaccine packages in direct contact with ice packs.
- Place newly delivered vaccines into the refrigerator immediately upon delivery to the office.
- Store vaccines in the middle of the refrigerator to avoid the coldest and warmest parts of the refrigerator; do not store vaccines on the door shelves.
- Place a maximum-minimum thermometer on the middle shelf of the fridge.
- Read, record and re-set the thermometer at least once daily.
- Secure the electrical cord from the fridge to the wall outlet to prevent accidental power interruptions.

- Ensure that the fridge door does not swing open by installing a fail-safe (e.g., Velcro™) closing mechanism.
- Do not store food or biological specimens in the same fridge as vaccines.
- Rotate stock so that vaccines with the earliest expiry date are at the front of the shelf.
- Only remove vaccine from fridge immediately before administration.
- If refrigerator malfunction is suspected on the basis of temperature readings, obtain servicing immediately and store the vaccine in an alternative fridge in the meantime.
- In the event of an identified cold chain break, seek advice from your local public health authority about whether the vaccine(s) may continue to be used; while awaiting advice, keep the vaccines stored in appropriate conditions.
- When a cold chain break is identified after vaccine has been administered, consult with your local health department about management of the situation. Information required to assess the circumstances will include the name of the vaccine(s), and the duration and temperatures of exposure. People immunized with vaccines whose potency is likely to have been jeopardized may need to be tested for serologic evidence of immunity or be re-vaccinated.

Periodic cold chain surveys are worthwhile to evaluate awareness, equipment and practices as well as the frequency of breaks in the cold chain during transport from depots and storage in peripheral offices. These should be undertaken by provincial/territorial and local immunization programs.

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Immunization Technique

Injection site

The injection site should be carefully chosen to avoid major nerves and blood vessels. The best sites for subcutaneous or intramuscular immunizations are the deltoid area or the anterolateral surface of the thigh. The latter is the site of choice for infants < 1 year of age because it provides the largest muscle. In children > 1 year of age, the deltoid is the preferred site since use of the anterolateral thigh results in frequent complaints of limping due to muscle pain. Children should be well restrained before injection.

The chosen site should be cleansed with a suitable antiseptic, such as isopropyl alcohol, which is allowed to dry on the skin before the injection is given. A separate, sterile needle and syringe should be used for each injection, and after use should be carefully disposed of in a container designed for this purpose.

Because of decreased immunogenicity reported with several vaccines, the buttock is not recommended as an immunization site, except when large volumes must be given, e.g., of immunoglobulin. If the buttock is used, care must be exercised to avoid injury to the sciatic nerve by selecting a site in the upper, outer quadrant of the gluteus maximus and avoiding the central area.

Route of administration

Immunization should be given by the route of administration recommended by the manufacturer of each vaccine (see Table 8). An appropriate size and length of needle

– Table 8 –

Routes of Administration

Vaccine	Preferred route of administration
BCG	Intradermal
Cholera	Oral
Diphtheria toxoid (fluid)	Subcutaneous (SC)*
Diphtheria toxoid (adsorbed)†	Intramuscular (IM)
Hepatitis A	IM
Hepatitis B	IM
Haemophilus influenzae type b conjugate vaccine	IM
Influenza	IM
Japanese encephalitis	SC
Meningococcal polysaccharide	SC
Meningococcal conjugate	IM
Measles	SC
MMR (measles, mumps and rubella)	SC
MR (measles and rubella)	SC
Penta and Pentacel†	IM
Pertussis (monovalent acellular)	IM
Pneumococcal polysaccharide	SC
Pneumococcal conjugate	IM
Polio (IPV)	SC
Polio (OPV)	Oral
Rabies	IM
Rubella	SC
Tetanus toxoid (adsorbed)†	IM
Typhoid – oral – Vi capsular	Oral IM
Varicella	SC
Yellow fever	SC

* The vaccines that are listed as SC only should not be given intramuscularly because of the lack of efficacy data for this route.

† Any vaccine combination containing adsorbed antigen must be administered intramuscularly because of the risk of subcutaneous nodule or sterile abscess if it is administered subcutaneously. Examples are Td (tetanus and diphtheria), DTaP.

should be chosen to ensure that the vaccine is deposited within the proper tissue layer.

For subcutaneous injections, a 25 gauge, 1.6 cm (5/8 inch) needle is normally recommended. Insert it at a 45° angle into the tissues below the dermal layer of the skin.

For intramuscular injections, a longer needle is needed:

- at least 2.2 cm (7/8 inch) for those with little muscle mass, such as infants
- at least 2.5 cm (1 inch) for others

Needles of these lengths are recommended to avoid sterile abscess in subcutaneous tissue. There is no risk if the injection is too deep.

After inserting the needle into the site, pull back on the plunger to determine whether the needle has entered a blood vessel. If so, withdraw the needle, select a new site, and use new materials.

For intradermal injections, choose a fine gauge needle (e.g., 26 or 27 gauge). With the bevel facing upwards, insert the needle under the outer layer of skin at an angle almost parallel to the skin. Insert the needle so that the bevel penetrates the skin. Inject the solution slowly for greater patient comfort and to avoid spraying and leaking. If this is done correctly, a bleb should appear in the skin at the injection site.

Immunization Records

Each person who is immunized should be given a permanent personal immunization record. Individuals should be instructed to retain the record, produce it for updating whenever they receive a vaccination and keep it in a safe place. Parents should maintain these records on behalf of their children. In the future, improvements in information technology may allow retrieval of the immunization record from the personal health card or from health data registries. However, these changes will not replace the need for personal, written records.

Record-keeping procedures should facilitate the retrieval of immunization records. It is essential that the health care provider maintain a separate, permanent record of the immunization history of each individual on the medical chart, in a readily accessible section that is not to be archived. Headings on this record should include the following:

- trade name of the product
- disease(s) against which it protects
- date given
- dose
- site and route of administration

- manufacturer
- lot number.

Manufacturers should be encouraged to produce peel-off labels for use on the chart when the product is administered, to assist with completeness of the record. The record should also include relevant serologic data (e.g., rubella serologic results) and documented episodes of adverse vaccine events.

Refer to the *National Guidelines for Childhood and Adult Immunization Practices* (page 58) for additional information about the use and maintenance of immunization records.

Immunization of Children and Adults with Inadequate Immunization Records

Many people present to health care providers and public health officials with inadequate immunization records. In the absence of a standardized approach to their management, they may be under- or over-immunized. The greatest concern with over-immunization relates to vaccine against diphtheria, pertussis or tetanus because of the potential for a higher incidence of local adverse reactions.

In every instance, an attempt should be made to obtain the person's immunization records from his or her previous health care provider. Written documentation of immunization is preferred; in some instances, information obtained by telephone from the health care provider with the exact dates of immunization may be accepted. For children, parental reports of prior immunization correlate poorly with actual immunity and should not be accepted as evidence of immunization.

Although the potency of vaccines administered in other countries can be generally assumed to be adequate, immunization schedules vary, and the age at immunization (e.g., against measles), the number of doses and the intervals between doses should be reviewed in determining the need for additional doses of vaccines. In many countries outside of Canada, mumps and rubella vaccines are in limited use, and measles vaccine alone is generally given. *Haemophilus influenzae* type b conjugate, hepatitis B and varicella vaccines are also in limited use.

Routine serologic testing of children and adults without records to determine immunity is not practical. Instead, the following approach is recommended:

- All children and adults lacking written documentation of immunization should be started on a primary immunization schedule as appropriate for their age (see pages 61 and 62).
- MMR, polio, *Haemophilus influenzae* type b conjugate, pneumococcal conjugate, meningococcal conjugate, hepatitis B, varicella and influenza vaccines can be given without concern about prior receipt of these vaccines because adverse effects of repeated immunization have not been demonstrated.

- Children who develop a serious adverse local reaction after administration of DPT, DTaP, DT or Td should be individually assessed before they receive additional doses of these vaccines. Serologic testing for specific IgG antibodies against diphtheria and tetanus may demonstrate immune status and guide the need for continued immunization. There are no established serologic correlates for protection against pertussis.
- Pneumococcal polysaccharide or conjugate vaccine should be given if the individual is in a high-risk group (see Pneumococcal Vaccine) and a record cannot be found, since in most studies local reaction rates after revaccination have been similar to rates following initial vaccination.

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Talking with Patients About Immunization

This section is a departure from the usual style of the Guide. While the chapters on specific vaccines and general recommendations provide scientific guidance, the following two sections contain material to assist in counselling individuals and parents about questions they may have regarding the safety and effectiveness of immunizations. Suggestions for communicating with news media are also included.

There is a real concern in Canada's public health community that misconceptions about vaccine safety threaten to reduce immunization coverage to levels that would open the door to epidemics of disease rarely seen in developed countries today. Indeed, this has already happened in several countries in recent decades.

As well, the success of vaccines in preventing disease means that many health care providers practising today, and certainly most parents of young children, may never have seen a life-threatening case of diphtheria, polio or even measles. Because immunization requires informed consent and the number of approved vaccines is growing, the continued success of immunization programs will depend on a very high level of public confidence. Widely trusted as a source of information among parents and adult patients, health care providers have a vital role to play in keeping the success of vaccine programs strong.

Appropriately, more and more questions are being asked about the vaccines being offered. Unfortunately, however, a small minority of people actively oppose immunization, and their messages are often dramatic, misleading and widely disseminated. On television and radio, on the Internet, in public libraries and print media, parents and adult patients are often confronted with conflicting information about immunization. In their genuine concern for the safety of their children, parents especially may give undue weight to reports of vaccine-related concerns. The "good news" —

about the safety and effectiveness of vaccines in controlling diseases that once disabled or killed in large numbers — can be much harder to find.

I. Communication issues in immunization

Communication skills play a vital role in the proper implementation of immunization programs at several levels. The advice of a trusted health care provider is recognized as an important factor in determining whether a person is immunized or not. Physicians and other health care workers are viewed as reliable sources of information about immunization issues. Public health officials are called upon to address the public during outbreaks of infectious diseases.

Dialogue with patients and guardians

Provider behaviour may be the most important determinant of parents' acceptance of immunization for their children, but a minority of parents will require more detailed explanations. Adherence to recommendations made by medical personnel has been found to be directly related to the degree to which their discussions are patient-centred. When preventive measures and health promotion are being dealt with, the patient-centred approach means listening to concerns with respect, answering any questions forthrightly and arriving at a common understanding as to the goals and roles of both patient and care provider. It is important to have relevant information readily at hand in a number of formats and languages. The reading level of this information must be appropriate for various levels of education. There are a variety of sources for accurate information about vaccines in printed format and on the World Wide Web (see Selected References).

Good risk communication requires that we understand how risks are perceived and that we recognize the inherent biases of both the public and health care providers. It has been demonstrated that perceptions of risk are not based strictly on a numerical evaluation of risks and benefits. Risk perception reflects an individual's previous experience as well as religious and cultural contexts. Risks perceived as uncontrollable or those involving children are, generally, more feared than other types of risks; man-made risks are considered in a more negative light than those that are perceived as natural. Parents are unlikely, then, to undertake immunization for their children unless they perceive a serious threat as well as some control over the risk. It is important to recognize that people use heuristics or shortcuts to arrive at decisions and rarely resort to simple cost-benefit determinations. This means that the framing of the risk is very important i.e., framing a vaccine in terms of its benefits and not only its risks. The goals of communication include advocacy, education and the development of a decision-making partnership. The method and the content of the communication should reflect these goals.

There are four components to effective risk communication:

1. Communicating existing knowledge, taking into account what an individual already knows. Examples of sources of immunization information are the information sheets provided by provincial/territorial ministries of health or the book

Your Child's Best Shot, published by the Canadian Paediatric Society. It is useful to have varied information formats (visual, audio, printed) tailored to a range of educational levels and languages appropriate to the wide variety of cultures in our society.

2. Respecting differences of opinion about immunization and taking time to understand them. Some parents will express reluctance or refusal to have their children immunized, and it is necessary that the health care worker come to an understanding of the personal (sources of information, prior experiences), cultural and religious background to this. Parents need to be educated about the risks of the diseases and be participants in the immunization decision so that they are given the necessary sense of control.
3. Physicians and other health care workers should be on guard against their own personal opinions and should represent the risks and benefits of vaccines fairly. Such workers are a trusted source of information and are ideally suited to discuss these issues.
4. Effective decision making is best done in a partnership between the vaccinator and the parent or patient. Central to this is the understanding that parents have some input into the decision to immunize and retain responsibility for their child's health.

Communicating with the media

Public health officials, practitioners and other health care professionals are called upon to communicate with the public in a number of instances, such as dealing with media reports of those opposed to immunization or informing people of outbreaks of vaccine-preventable diseases.

It is important to identify a single spokesperson regarding any particular issue. This should be someone who is informed, empathetic and sincere, and can be available to the media. There should be a back-up person identified as well. In larger organizations it is very helpful to have a media coordinator to organize and identify important information, and help the media meet any deadlines. In the case of breaking news, such as the occurrence of an outbreak, it is important to involve the media proactively and early, as part of the total response.

In preparing to deal with the media there are 10 important items to keep in mind:

1. Prepare key messages in advance. There should be a limited number (three is ideal, five the maximum) of clear, concise messages. These should be backed up by facts, statistics and examples.
2. Identify your audience.
3. Understand any controversial issues, for example, the views of those who object to immunization, and deal with these concerns in an honest and forthright manner.

4. Never guess. If you do not know the answer, say so, but offer to find it.
5. Be polite; never lose your temper.
6. Stick to your areas of responsibility.
7. Keep in mind that the goal is to be message-driven, not question-driven.
8. Prepare and rehearse with your media advisor or someone experienced in working with media.
9. Keep your personal opinions out of your communications.
10. When speaking to the media, nothing is off the record.

II. Questions and answers about immunization

The questions and answers that follow, adapted from a number of sources (see Selected References and the list of helpful Web sites on the inside back cover), are intended to assist in counselling about immunization; the wording and style are targeted at a general audience. The answers expand on the key messages about vaccine safety listed in Box 1 while addressing the common misconceptions listed in Box 2.

Box 1: Key messages on vaccine safety in Canada

- The vaccines used in Canada are extremely effective and extremely safe.
- Serious adverse reactions are rare. The dangers of vaccine-preventable diseases are many times greater than the risks of a serious adverse reaction to the vaccine.
- Health authorities worldwide take vaccine safety very seriously. Expert committees in Canada investigate reports of serious adverse events.
- There is no evidence that vaccines cause chronic diseases, autism or sudden infant death syndrome. Alleged links – for example between hepatitis B vaccine and multiple sclerosis – have been disproved by rigorous scientific study.

Box 2: Common misconceptions about vaccines

- Vaccines are not safe.
- Vaccines cause serious side effects. Vaccines are linked to chronic diseases.
- Vaccines are not necessary. The diseases are gone.
- Vaccines contain poisonous substances.
- Vaccines weaken the immune system.
- Natural medicines provide safer protection.
- There are greater risks from the vaccines than from the illnesses they can prevent.

Do vaccines work?

Yes. Vaccines work very well in preventing specific diseases. They are so effective that most of the diseases they prevent are now rare in Canada.

Some people do not develop full immunity after being vaccinated. This is why some immunization programs include a second or third dose of a vaccine. For some diseases, we need "booster" doses because the protection of the vaccine wears off over time. However, no vaccine will work for 100% of the people who receive it. How often a vaccine might fail to work varies with each type of vaccine and each vaccine product. For more details, please see the chapters on specific vaccines in this *Guide*.

Some vaccines also work by creating "herd immunity". When most people in a community have received a vaccine for a particular disease, the chance of an outbreak of that disease is greatly reduced. This "herd immunity" protects the small number of people who cannot be immunized for medical reasons or for whom the vaccine did not work. For herd immunity to be effective, however, as many people as possible must be vaccinated.

Are vaccines safe?

Yes. Vaccines are among the safest tools of modern medicine. Serious side effects are rare. For example, severe allergic reactions can occur, but they very rarely do. In Canada, this kind of reaction has occurred less than once in every 1 million doses of vaccine, and there are effective treatments for this condition. The dangers of vaccine-preventable diseases are many times greater than the risks of a serious adverse reaction to the vaccine.

For information on who should not receive specific vaccines, please see the Contraindications and Precautions section of each vaccine chapter in this *Guide*.

Minor side effects from vaccines, on the other hand, are common. Many patients get a mild fever after immunizaton or soreness where they receive the injection. These reactions are a nuisance but do not usually last long. They can be part of the body's normal response to the vaccine.

No one in the field of public health takes the safety of vaccines for granted. Vaccine safety is an international concern. Information on possible safety concerns is communicated very rapidly among different countries. This careful monitoring ensures that public health authorities can act quickly to address concerns. In addition, research continues to improve vaccines. Some examples follow:

- In 1999, some babies in the U.S. developed a rare form of bowel obstruction after receiving a new vaccine to prevent rotavirus infection (a cause of diarrhea, sometimes severe, in infants). Pre-licence studies had suggested that there might be an increased risk of this condition, and monitoring effectively picked up the problem. (In the first 1.5 million doses of rotavirus vaccine, 15 cases of bowel obstruction were reported.) Use of this vaccine was stopped in the U.S., and the manufacturer withdrew its request to license the vaccine in Canada.

- The oral polio vaccine (OPV), introduced in the 1950s, prevented hundreds of thousands of polio cases. It was also found to cause a form of paralysis once in every 3 million doses. A vaccine that uses inactivated virus (IPV) is now used almost exclusively throughout the world and cannot cause even this rare adverse event.
- The original whole-cell pertussis (whooping cough) vaccine sometimes caused high fever, seizures or collapse. A vaccine was developed that uses only part of the cell of the pertussis bacterium. This vaccine has fewer side effects and is now used instead.

In considering the safety of vaccines, it is important to look at both risks and benefits. If there were no benefit from a vaccine, even one serious side effect in a million doses could not be justified. If there were no vaccines, however, there would be many more cases of disease, more serious side effects from disease, and more deaths. The examples from countries that have stopped or decreased their immunization programs have illustrated this fact many times in recent years. The diseases we can prevent with vaccines can lead to pneumonia, deafness, brain damage, heart problems, blindness and paralysis in children who are not protected. We are fortunate in Canada to have vaccines for diseases that still kill and disable children throughout the world every day. The risks of *not* getting immunized are a lot greater than any risk of immunization itself.

How are vaccines made and licensed in Canada?

Vaccines for humans are regulated in Canada by the Biologics and Genetic Therapeutics Directorate of Health Canada. Like all medicines, vaccines must undergo several stages of rigorous testing before they are approved for use. The Bureau also supervises all aspects of vaccine production by the manufacturers. Before any vaccine is licensed and approved for use in Canada, the factory where it is manufactured must be inspected to ensure that all stages of production meet the requirements for safety, sterility and quality control. Before release by the manufacturer, each batch of vaccine is tested for safety and quality under guidelines specified by the Biologics and Radiopharmaceuticals Evaluation Centre. Most safety tests are carried out by both the manufacturer and, independently, by the laboratory of the Bureau.

Once vaccines are in use, Canada has several systems in place to ensure that they are carefully monitored and that any problems are dealt with quickly. These systems are described in the section "Adverse Events" in this *Guide*.

What would happen if we stopped immunizing?

Experience from other countries shows that diseases quickly return when fewer people are immunized:

- Ireland saw measles soar to more than 1,200 cases in the year 2000, as compared with just 148 the previous year, because immunization rates fell to around 76%. Several children died in this outbreak.

- A large outbreak of rubella (German measles) occurred in Nebraska in 1999. All 83 cases in this outbreak involved adults who had not been immunized. Most of them came from countries where rubella immunization is not routine. The outbreak spread from a meat-packing plant to the general community, including several pregnant women and two day care centres. The greatest danger from rubella is to infants, who may be born with congenital rubella syndrome if their mothers are infected during pregnancy.
- In 1994, there were 5,000 deaths due to diphtheria in Russia after the organized immunization system was suspended. Previously, Russia (like Canada) had had only a few cases of diphtheria each year and no deaths. Diphtheria toxoid came into routine use in the 1930s, but even today diphtheria remains a severe disease. About one person in 10 with diphtheria still dies in spite of medical treatment.
- In the U.K., a major drop in rates of immunization against pertussis (whooping cough) in 1974 was followed by an epidemic of more than 100,000 cases and 36 deaths in 1978.
- Japan had 13,000 cases and 41 deaths from whooping cough in 1979, after only 30% of children received pertussis immunization. In earlier years, when most children received vaccine, Japan had only a few hundred cases of whooping cough and no deaths.
- Sweden had a similar experience with pertussis. When vaccination programs restarted, the number of cases fell once again.

Why do we still need vaccines if the diseases they prevent have disappeared from our part of the world?

It is important to continue vaccine programs for four basic reasons:

- First, unless a disease has completely disappeared, there is a real risk that small outbreaks can turn into large epidemics if most of the community is not protected. The only disease that has been entirely eliminated in the world so far is smallpox. Some diseases, such as tetanus, are caused by bacteria that live naturally in the soil. The risk of diseases like tetanus will never disappear, so continued immunization is important.
- Second, no vaccine is 100% effective. There will always be some people who are not immune, even though they have had their shots. This small minority will be protected as long as people around them are immunized.
- Third, there are a small number of people who cannot receive vaccines. These may be people who have previously had a severe allergic reaction to a component of the vaccine, or they have a medical condition that makes receiving vaccines too risky for them. These people are not protected from disease, and for some diseases it is very important that people around them are immune and cannot pass disease along to them. By protecting themselves, immunized people can also protect those around them who are vulnerable to disease.

- And fourth, most vaccine-preventable diseases are still common in other parts of the world. Travellers can carry them from country to country. If we are not protected by immunization, these diseases will quickly spread. For example, most cases of measles in Canada today can be traced to someone who travelled here from a country where measles is more common.

Why can't I take a chance that my child won't get sick, as long as most other people are vaccinated?

Unvaccinated children have a much greater chance of getting disease than children who have received the vaccine.

Two recent studies of disease outbreaks in the U.S. illustrate this concern. Children whose parents chose not to have them immunized against measles were 22 to 35 times more likely to get measles than were immunized children. Children who did not receive the vaccine for pertussis (whooping cough) were almost 6 times more likely to get whooping cough than immunized children; the risks were even higher for the younger children (children < 11 years old), who were 62 times more likely to get measles if they were not immunized and 16 times more likely to get pertussis in these outbreaks.

Unimmunized children also add to the risk for children who cannot receive vaccinations or for whom the vaccine did not provide full protection from disease. People who are not immunized can be carriers of disease and pose a risk to those around them, even if they do not get sick themselves.

Do vaccines weaken the immune system?

No. Vaccines strengthen the immune system to protect children and adults from specific diseases. This is true even for newborn infants. Infants and children are exposed to many kinds of germs every day, through normal eating, drinking and playing. Scientists estimate the immune system can recognize and respond to hundreds of thousands, if not millions, of different organisms. The vaccines recommended for children and adults use only a small portion of the immune system's "memory".

Infants need to be protected with vaccines because they are more likely to get very sick from the diseases that vaccines can prevent, such as diphtheria, whooping cough and meningitis due to *Haemophilus influenzae* type b (Hib). The recommended immunization schedule for infants in Canada is carefully timed to ensure that newborns and older babies get safe and effective protection from the diseases that are most likely to seriously harm them.

Can giving a child several vaccines at the same time overload the immune system?

No. Only vaccines that have been shown to be safe and effective when given together are administered at the same time. When new vaccines go through the extensive testing process, they are given along with all of the recommended childhood vaccines. Scientific studies assess the effect of giving these vaccines at the same time.

Children may receive several vaccines during the same clinic visit, but only after studies have shown that this is a safe practice. In order to receive a licence to combine vaccines, the manufacturer must also prove that the combined product does not make any of the vaccine components less effective or raise new safety concerns.

Giving several vaccines at one time keeps children safe by protecting them against more diseases sooner. As an added benefit, it also reduces children's discomfort by reducing the number of injections they receive, and it saves parents the time and expense of additional office visits.

Can natural infection or a healthy lifestyle be effective alternatives to vaccines?

Vaccines create immunity to specific diseases without causing the suffering of the disease itself. Children do develop immunity to many different germs through their everyday exposure to these infections. However, the diseases we can prevent with vaccines kill and disable children. For some diseases (e.g. tetanus and meningitis) the vaccine creates stronger immunity than natural infection does.

Boosting the immune system in general through herbs or vitamins does not offer specific protection from the viruses and bacteria that cause vaccine-preventable diseases. For infants, breast-feeding offers protection against some infections, such as colds, ear infections and diarrhea, because the infant receives immune-boosting proteins in the mother's milk. Despite its many benefits, however, breast-feeding does not protect infants from the specific diseases we can prevent with vaccines.

Vaccines also use a natural mechanism to keep us healthy by taking advantage of our natural immune response. A vaccine stimulates antibodies so that if we are exposed to that specific virus or bacterium in the future, our immune system can mount an effective attack.

Why do we need vaccines if we have better hygiene and sanitation to help prevent disease in Canada?

Better living conditions have been important in controlling some kinds of infectious diseases, such as diseases spread by dirty water. For the specific diseases that vaccines can prevent, however, disease rates only began to drop dramatically after the vaccines for those diseases were licensed and came into widespread use:

- Measles vaccine was first approved in Canada in 1963. Sanitation and living conditions in Canada have not changed greatly since that time. Before immunization, almost everyone got measles. For many children, the disease was serious: about 5,000 were hospitalized every year, and 50 to 75 children died. Today, because the vaccine is in wide use, there are few cases of measles in all of North and South America, including communities where living conditions are much poorer than in Canada.
- Meningitis (infection around the brain) and other severe infections due to Hib were common until just a few years ago. About one in every 300 Canadian chil-

dren developed Hib disease by age 5. About 100 infants died each year from Hib meningitis, and many more suffered brain damage or deafness. Immunization against Hib became routine in the early 1990s. Since then, Hib disease has almost disappeared in Canada, from about 2,000 cases a year to less than four cases in the year 2000. Sanitation is no better now than it was in 1990, so it is hard to credit anything but the widespread use of Hib vaccine for this dramatic improvement.

- Many children in Canada still get very sick from pertussis (whooping cough) each year, and every year one child dies from this disease. Nearly all of the children affected got the disease because they were not immunized against pertussis.

What about reports that vaccines are linked to chronic diseases or problems such as sudden infant death syndrome (SIDS)?

Vaccines are sometimes blamed for conditions that are poorly understood. A child's first year of life is a time of tremendous growth and development, and it is a time when serious problems may start to appear. It is also the time when most vaccines are given, but this does not mean that vaccines cause these problems. Many of our vaccines have been in use for decades with no evidence of long-term adverse effects. Still, research to ensure the safety of vaccines continues.

Anti-vaccine books and web sites claim that vaccines cause autism, seizure disorders, multiple sclerosis (MS) or Crohn's disease, among other health problems. These connections have never held up to scientific scrutiny. Recent research using the best scientific methods and reviews of studies from around the world provide very strong evidence that

- MMR vaccine does not cause autism or inflammatory bowel disease.
- Hepatitis B vaccine does not cause multiple sclerosis or relapses of pre-existing MS.
- Pertussis vaccine does not cause brain damage.
- Childhood vaccines do not increase the risk of asthma.
- Vaccines do not cause SIDS. (Fortunately, we have learned that other factors, such as sleeping position and second-hand smoke, *are* linked with SIDS, and successful public education campaigns about these factors have helped to reduce the rate of SIDS in Canada.)

More extensive discussion of specific vaccine concerns is available in the resources for patients and parents listed at the end of this chapter (see Selected References).

Do vaccines contain toxic ingredients?

The main ingredient in most vaccines is the killed or weakened germ (virus or bacterium), which stimulates our immune system to recognize and prevent future disease. Some newer vaccines are made from only part of the germ's cell (for example, a purified sugar or a purified protein).

- In addition, vaccines usually contain sterile water or salt solution.
- Some vaccines are prepared with a preservative or antibiotic to prevent bacterial growth.
- Some vaccines also contain substances known as stabilizers, to help maintain quality during storage.
- Some vaccines contain an "adjuvant." These substances work to boost our immune response to the vaccine and make it more effective.

The amount of any of these ingredients in a vaccine is extremely small, and every batch of vaccine is tested for safety and quality in Canada before it is released for public use.

A preservative called thimerosal received attention in the U.S. in 1999 because it contains mercury and it is used in some vaccines for children. As a precaution, U.S. authorities recommended that the use of vaccines containing thimerosal be reduced or eliminated. In 2001, an independent panel of the U.S. Institute of Medicine conducted an extensive review of this concern. The panel found no evidence that the amount of mercury in childhood vaccines causes damage to a child's nervous system.

In Canada, the only routine vaccine for children that contained thimerosal was the hepatitis B vaccine. Canadian infants were never subject to the same level of mercury exposure from vaccines as U.S. infants. A new formula for hepatitis B vaccine, with no thimerosal, is now available. Meanwhile, research into whether thimerosal in vaccines is truly a risk to infants is continuing.

The ingredients for each vaccine in use in Canada is described in the specific vaccine chapters in this Guide.

Can vaccines transmit animal disease to people?

Because vaccines are a natural product, they sometimes require the use of animal cells during production. This process is strictly controlled so that it does not pose a risk to people. No brain cells are used in manufacturing vaccines in Canada. During the manufacturing process, the vaccines are purified, and all animal cells are removed. However, each batch of vaccine is tested to ensure that it is free from infectious agents.

For some vaccines in Canada, material derived from cows (for example, gelatin and lactose) have been used in the manufacturing process, and this has raised the question of whether vaccines can transmit "mad cow disease" to humans. Scientists in several countries have studied this risk and estimated that, in theory, there could be a risk of one person in 40 billion being exposed to the disease through a vaccine. Even though the risk is extremely small, vaccine manufacturers are working to find alternatives to these components. Meanwhile, Canada is making sure that any vaccine ingredients derived from cows come only from countries that are free from mad cow disease.

Is immunization compulsory in Canada? Does my child have to be immunized?

Immunization is not compulsory or "forced" in Canada, but we do have regulations that help ensure that as many people as possible are protected by vaccines from the diseases they prevent. Some provinces require certain vaccines to be given before a child can enter school, but these are not mandatory in the usual sense of the term. Rather, parents (or children, if they are old enough to give consent) are required to declare a choice of whether to have their child (or themselves) immunized or not. If they choose not to, the child may be told that he or she must stay home from school if there is an outbreak of disease. This rule is designed to keep unimmunized children from getting sick and to keep the outbreak from spreading. School entry regulations also give parents an opportunity to bring their child's immunizations up to date.

Health care workers may also be required to have certain vaccinations, such as hepatitis B vaccine and an annual 'flu shot. If they refuse, they may be required to stay away from work during an outbreak. This practice protects their patients, who could be in grave danger if they became ill with a communicable disease.

Conclusion

Because the diseases that vaccines can prevent are so rarely seen by the general public today, it is understandable that vaccine safety concerns have such a high profile. Careful and timely counselling can help patients weigh the benefits of vaccines and the risks of disease, as well as the small risk of the vaccine itself. By providing vaccines in a climate of appropriate informed consent, including discussion of the common misconceptions that are circulating, immunization will maintain its status as one of the most effective preventive measures in the history of medicine.

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Resources for parents and patients

Canadian Health Network web site. *Immunization/frequently asked questions*. <www.Canadian-health-network.ca/html/faq/chntopiccategory_13.html>

Canadian Immunization Awareness Program web site <www.immunize.cpha.ca> (CIAP is supported by a coalition of Canadian organizations including the Canadian Institute of Child Health, Canadian Medical Association, Canadian Nurses Association, Canadian Nursing Coalition for Immunization, Canadian Paediatric Society, Canadian Pharmacists Association, Canadian Public Health Association, College of Family Physicians of Canada, Conférence des Régies régionales de la santé des services sociaux du Québec, Council of Chief Medical Officers of Health, and Health Canada.)

Canadian Paediatric Society. *Your child's best shot: a parent's guide to vaccination*. Ottawa: Canadian Paediatric Society, 1997. (CPS web site <www.cps.ca> contains ordering information and the Questions and Answers about Immunization section of this book: www.cps.ca/english/carekids/immunization/ImmunizationFacts.htm)

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National Network for Immunization Information. *Communicating with patients about immunization: a resource kit*. 2000. (NNII is a U.S.-based initiative of the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, the American Academy of Pediatrics, and the American Nurses Association. The Resource Kit is available on the NNII web site www.immunizationinfo.org)