Part 2

Vaccine Safety and Adverse Events Following Immunization

Vaccine Safety

Introduction

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

Health care providers have essential and pivotal roles to play in gaining and maintaining public confidence in the safety of vaccines These include providing evidence-based information on the benefits and risks of vaccines; helping clients and patients to interpret media and Internet vaccine safety messages; and identifying and reporting adverse events following immunization. Any single occurrence of an unusual event following immunization may be coincidental or caused by the vaccine. An accumulation of reports, sometimes as few as four or five, may signal a risk due to the vaccine. Thus, each and every report submitted by vaccine providers is important.

This new chapter has been added to the *Canadian Immunization Guide* for the following reasons:

- to highlight the critical importance of ongoing post-marketing vaccine safety surveillance by describing how vaccines are evaluated and regulated, and the scientific limitations of pre-marketing assessments;
- to provide an overview of Canada's vaccine safety surveillance system with specific information not only on how to report adverse events but also on how such information is used to ensure that immunization programs, in Canada and internationally, remain as safe as possible;
- to provide an overview of the type and quality of evidence available to inform vaccine safety;
- to summarize the current status of key vaccine safety issues;
- to provide a list of key resources and references on vaccine safety.

Vaccine evaluation and regulation

The development of a new vaccine starts with pre-clinical laboratory testing to ensure that vaccine candidates produce the immune response needed to prevent disease and have no toxicities that would prevent their use in people. Human studies then proceed through several phases involving progres-

sively more subjects. Table 1 describes the phases of vaccine evaluation in terms of how many subjects are studied and what is learned.

Depending on the specific vaccine, it may take years to decades to gather the scientific immunogenicity, safety and efficacy data needed to obtain authorization for marketing. However, pre-marketing vaccine studies do not have sufficient numbers of subjects to detect rare or very rare adverse events, the frequency of which is shown in Table 2. Furthermore, all potential target populations have not been fully studied prior to marketing approval. Thus, ongoing post-marketing studies of vaccine safety and effectiveness are essential, not only to gather data on new vaccines but also to monitor existing vaccines for any change in the frequency of known events that might occur if newly released vaccine lots do not perform as expected. Post-marketing data help to refine the benefit-risk assessment of a given vaccine as well as add to key information regarding contraindications, warnings and concomitant use with other vaccines.

The Biologics and Genetic Therapies Directorate (BGTD) of Health Canada is the regulatory authority responsible for establishing the safety, efficacy and quality of all biologics for human use, including vaccines (http://www.hc-sc.gc.ca/dhp-mps/brgtherap/index_e.html). BGTD reviews the clinical and chemistry/manufacturing information of vaccine submissions, and conducts on-site evaluations of manufacturing facilities and laboratory analysis of vaccines. The clinical information includes data from clinical trials, and post-marketing safety and efficacy information. BGTD will

Table 1. Stages of Clinical Vaccine Assessment and Detectable Adverse Events

Phase	Number of subjects	Key study objectives
I	10-<100	• Immunogenicity • Local/systemic reactions
II	50-500	• Optimal dose/schedule in target population(s) • Ongoing safety assessment
III	300-30,000	• Immunogenicity/efficacy in target population(s) • Ongoing safety assessment
Regulatory authorization for vaccine marketing		
IV	Varies with study objectives (100 to many thousands)	• Immunogenicity/efficacy in not yet studied populations • Possible interactions with other vaccines • Expanded safety assessment
Post-marketing passive or active surveillance	General population	• "Real world" effectiveness • Rare or unexpected adverse events ("signals")

grant a marketing authorization for the vaccine if the evidence to support the safety, efficacy and quality of the vaccine is considered adequate and sufficient.

Subsequently, if there are any changes in chemistry/manufacturing procedures or new clinical information pertaining to approved products, vaccine manufacturers must submit information for BGTD approval. The nature, extent and importance of the changes affecting the approved vaccine will determine whether additional clinical testing is required and whether the changes must be communicated to vaccine users through updated labeling and revisions of the product monograph.

A product monograph is the official labeling document for a vaccine and must be approved by Health Canada when the vaccine is first authorized for marketing and each time the information is updated. It is a factual, scientific document that, devoid of promotional material, describes the properties, claims, indications, conditions and any other information required for optimal, safe and effective use of the vaccine. It must accurately reflect important information and results from clinical trials and other relevant information submitted to Health Canada for evaluation. The product monograph consists of three parts:

- **Health professional information:** contains prescribing information, including indications, contraindications, warnings and precautions, adverse reactions, interactions, dosage, administration and storage instructions.
- **Scientific information:** contains a summary description of the preclinical, toxicological and clinical testing of the vaccine and any other pertinent scientific information with relevant references.
- **Consumer information:** contains an abbreviated summary, written in simplified language, to communicate essential information to the vaccine or product recipient/user.

Table 2. Description of Terms Used for the Frequency of Adverse Events Following Immunization

Related adjective	Detectable range*
Very common	> 1/10
Common	> 1/100 and < 1/10
Uncommon	> 1/1000 and < 1/100
Rare	> 1/10,000 and < 1/1,000
Very rare	< 1/10,000

* The units for the detectable range may vary depending on how the data were derived and may be doses of vaccine administered, number of subjects immunized or doses of vaccine distributed.

Product monographs may contain proprietary information and thus are not generally made available in their entirety, although many manufacturers now publish them on their Web sites. The package insert in marketed vaccines is an abbreviated form of the product monograph and usually contains the same prescribing information as is found in part 1 of the full monograph. Information on a specific vaccine found in other publications, including the *Compendium of Pharmaceuticals and Specialties* (CPS), is not controlled by Health Canada. The vaccine manufacturer may choose to include all, selected or modified parts of the information from the product monograph.

To further establish ongoing quality, safety and efficacy, all vaccines are released on a lot-by-lot basis. For each lot, BGTD reviews production protocols submitted by the manufacturer and performs selective confirmatory testing as appropriate to each vaccine.

Vaccine safety surveillance and assessment in Canada

In 2005 the name of Canada's vaccine safety surveillance system was changed from the Vaccine Associated Adverse Event Surveillance System (VAAESS) to the Canadian Adverse Event Following Immunization Surveillance System (CAEFISS). This change harmonizes Canadian terminology with what is used by the World Health Organization (WHO) and many other countries. Furthermore, it describes the nature of such events more accurately, in that adverse events do indeed follow immunization, but the temporal association is not proof that the event was caused by the vaccine.

In Canada a standard report form is available on the Internet (http://www.phac-aspc.gc.ca/im/aefi-form_e.html), through public health units and in the CPS. This form includes check boxes to facilitate the reporting of selected adverse events of special interest (e.g., anaphylaxis, injection site reactions, neurologic events) but also should be used to report all other severe, unusual or unexpected adverse events that are of concern to the vaccine provider, health care provider, vaccine recipient or his/her parent(s)/caregiver(s). Vaccinees and/or their parents/caregivers should therefore be advised to notify their health care provider about any adverse event of concern. Information on the report form facilitates monitoring and follow-up of adverse events at the local/provincial level, and causality assessment and signal detection at the national level. Confidentiality and privacy of health information are maintained throughout.

Surveillance

Monitoring vaccine safety in Canada involves passive and active surveillance and, as necessary, focused ad hoc studies.

- **Passive surveillance:** this encompasses all spontaneous adverse event reporting. Health care providers complete reports and submit them to

their local health unit or Medical Officer of Health. From there, reports are sent to the central provincial/territorial health department, which in turn forwards them to the Immunization and Respiratory Infections Division within the Centre for Infectious Disease Prevention and Control at the Public Health Agency of Canada (PHAC). This federal office is responsible for maintaining a national database of all reported adverse events. The database also includes reports from vaccine manufacturers, which are required by law to submit all adverse event reports to PHAC and, if serious, to do so within 15 calendar days of receipt (http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/00vol26/26s1/26s1e_e.html). In some jurisdictions, reports related to vaccines that are not publicly funded are submitted by vaccine providers directly to PHAC. If in doubt it is best to check with the provincial/territorial public health department as to where the report should be sent.

- **Active surveillance:** for severe adverse events following childhood immunizations this type of surveillance has been conducted in Canada since 1991 by the Immunization Monitoring Program ACTive (IMPACT). This is a pediatric, hospital-based network funded by PHAC and administered by the Canadian Paediatric Society. The 12 IMPACT hospitals encompass approximately 90% of tertiary care pediatric beds in Canada. Details on the network and lists of relevant publications can be found at http://www.cps.ca/english/proadv/IMPACT/IMPACT.htm. All serious adverse events detected by IMPACT are to be reported to the vaccinee's home provincial/territorial public health authorities, as well as to PHAC.
- **Ad hoc studies:** additional surveillance, as well as epidemiologic or clinical studies, may be undertaken by public health or academic investigators to further characterize adverse events of concern, assess whether or not there is a causal link between the vaccine and a given adverse event or learn about risk factors that increase the likelihood that an adverse event will occur. Examples of such studies include those done following the recognition of oculorespiratory syndrome (ORS) following influenza vaccination.

Causality assessment

Special review of serious and unusual adverse events (life-threatening, such as anaphylaxis or those associated with 3 or more days of hospitalization, congenital abnormality, residual damage or death) is conducted by the Advisory Committee on Causality Assessment (ACCA), which comprises pediatricians, immunologists, epidemiologists and other experts. In addition, any unusual events or cluster of events may be reviewed by ACCA. The primary mandate of ACCA is to evaluate the degree to which such events are linked to the implicated vaccine (for more information see http://www.phac-aspc.gc.ca/im/vs-sv/acca_e.html). The process of causality assessment requires sufficient case detail to be sure the adverse event diagnosis is accurate and to judge the potential contribution of underlying

disease, intercurrent illness or concomitant medication(s). Since details are often missing in the submitted report it is usually necessary to contact the original reporter for additional information before ACCA can review a case. Plausible biologic mechanisms, as well as the availability and strength of existing scientific evidence to support or reject a causal association between the vaccine and a given adverse event, are all taken into consideration. The findings of ACCA are communicated back to the provinces/territories from which the report originated.

Global partners in vaccine safety

Canada actively participates in several international endeavours to monitor and improve vaccine safety on a global scale. Adverse event reports are forwarded to the WHO Uppsala Monitoring Centre for entry into a global pharmacovigilance database (http://www.who-umc.org/DynPage.aspx?id=13140&mn=1514). These data are regularly scanned to identify any safety signals of potential concern. Canada is an active participant in the Brighton collaboration (http://www.brightoncollaboration.org), which seeks to standardize and harmonize adverse event definitions for use in all phases of vaccine testing, as outlined in Table 1. Canada is represented on the WHO Global Advisory Committee on Vaccine Safety (http://www.who.int/vaccine_safety/en/) and also participates in ad hoc consultations and committees set up by the WHO to review specific issues in vaccine safety. Canada also cooperates with the Council for International Organizations of Medical Sciences (CIOMS, http://www.cioms.ch/), which is an international, non-governmental, non-profit organization established jointly by WHO and UNESCO in 1949 to facilitate and promote international activities in the field of biomedical sciences, including making recommendations on the assessment and monitoring of adverse reactions.

Evidence pertaining to vaccine safety: where to find it, how to interpret it

Temporal associations

Since vaccines are usually given to healthy people, any event that follows soon after immunization may be perceived as being due to the vaccine. This is particularly true for events with no proven cause, such as autism, most encephalopathies and multiple sclerosis. Multiple immunizations are given during early childhood because that is the period of greatest human vulnerability to vaccine-preventable morbidity and mortality. However, it is also a critical period of growth and development during which damage due to genetic, in utero and/or other post-natal influences may first become apparent. Consideration should always be given to the possibility of an association between the vaccine and an adverse event. However, other possibilities must also be considered. These include infections and concomitant medications, as well as diseases due to genetic, environmental

or other factors. Adverse events due to these other causes may simply occur by chance after the administration of a vaccine.

Chance associations illustrate the greatest vulnerability of universal immunization programs. If a vaccine truly causes a given event, even if rare, the association can be proven by a well-designed study with sufficient subjects. In contrast, the absence of association or "zero risk" cannot be proven by epidemiologic methods. Even if no association is repeatedly shown in a number of studies, it is always possible to theorize that an association might be found in another group of individuals who have not been studied. It is not possible to demonstrate that there is a 100% certainty that no person has ever had the adverse event of interest. An element of doubt will always remain, although it can be stated that the risk is very close to zero.

Clinical trials have repeatedly shown that placebo recipients experience adverse events, which clearly cannot be due to the vaccine. In a randomized placebo-controlled trial of varicella vaccine among healthy children aged 1 to 14 years, the vaccinees (n = 491) and placebo recipients (n = 465) had a similar frequency of irritability (24% and 20%, respectively), tiredness (20%, 22%), headache (15%, 16%), cough (45%, 48%), common cold (63%, 65%), poor sleep (12%, 13%) and loss of appetite (11%, 13%) during the 8-week period after immunization. Rigorous trials such as this are very helpful because they allow the assessment of the degree to which adverse events are attributable to the vaccine as opposed to other factors.

Vaccine attributable risk

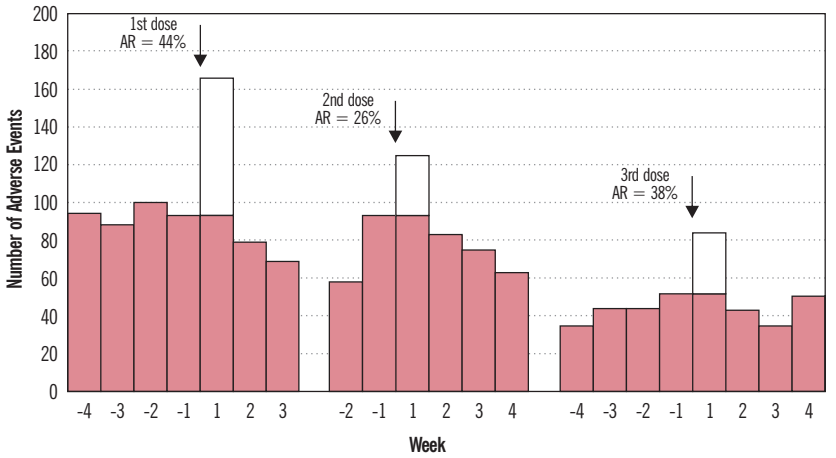
This is defined as the difference between the frequency of adverse events in otherwise comparable vaccinated and unvaccinated individuals. Figure 1 illustrates that not all health problems noted after immunization are caused by vaccine. In a population of immunized children, the number of illnesses or 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 [AR]).

As another example, in a Finnish study of cross-over design, each twin of 581 pairs was given either measles, mumps and rubella (MMR) vaccine or placebo in a blinded fashion, and 3 weeks later was administered the other substance. Adverse events were monitored for 21 days after immunization. Table 3 clearly shows that some children in the placebo group experienced fever throughout the follow-up period, but the only significant differences (AR) between placebo and MMR groups occurred from days 7 to 12.

Randomized, placebo-controlled trials

These trials provide the most reliable and valid evidence pertaining to vaccine safety. Unfortunately such trials are not done for all vaccines nor are they usually large enough to detect rare adverse events.

Figure 1. Total Number of Adverse Events in the Weeks Preceding and Following Each of the Three 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 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;1(8487):939-42

Population-based epidemiologic studies

Such studies use **cohort** (i.e., they compare the adverse event rate in immunized versus non-immunized populations) or **case-control** methodologies (i.e., they compare the proportion of cases with an adverse event and controls without an adverse event who were exposed to vaccine) to test hypotheses regarding a causal association between a given vaccine and an adverse event. However, the validity, generalizability and utility of data from such studies are highly dependent on study design. Since exposure to

vaccine is not random in the study populations, several sources of bias exist that may confound the results.

Ecologic studies

Ecologic studies take advantage of "natural experiments" to test hypotheses regarding vaccines and adverse events. For example, the occurrence of autism might be compared during two separate periods of time in a country that switched from thimerosal-containing to thimerosal-free vaccines. As another example, the prevalence of multiple sclerosis might be compared in a country that has never introduced hepatitis B vaccine to one that has been using the vaccine for decades. A major methodologic problem with such studies is the inability to control for multiple confounding factors that may not be equally distributed or applicable to the time periods or geographic areas being compared. For example, differences in diagnostic criteria, standards of health practice and/or health-seeking behaviour could confound the results in favour of or against the hypothesis.

Reports of single or multiple cases

These reports often represent the first evidence of a possible link between a vaccine and an adverse event. As discussed earlier, chance temporal associations between vaccine(s) and subsequent adverse events are relatively common occurrences given the frequency of disease that occurs in any given population. In certain rare instances, a well-documented case report can establish a causal relation such as death due to disseminated BCG or unrelenting measles infection following administration of BCG vaccine or measles vaccine, respectively, to a severely immunocompromised host. The vaccine strains are distinguishable from naturally circulating disease strains (commonly referred to as "wild type"). Thus recovery of the vaccine types from body tissue(s) in conjunction with histopathological changes consistent with severe infection is usually considered proof of causality. However, the vast majority of case reports represent unproven temporal associations that require confirmation using scientifically sound methodologies.

Spontaneously submitted reports to passive surveillance systems

Reports sent to CAEFISS or the Vaccine Adverse Event Reporting System (VAERS) in the United States provide the weakest evidence of a causal association between a vaccine and the reported adverse event. It is essential to understand that proving causality is not the intent of passive surveillance. Rather, such systems are put in place to identify signals of concern as early as possible. Subsequently, specific studies must be designed to test the hypothesis that the adverse event is truly caused by vaccine. Illustrative of this process is the recent US experience with rotavirus vaccine. Regular analysis of VAERS data revealed an increased frequency of reports of intussusception (the "signal") in infants following the introduction of live attenuated rotavirus vaccine. Subsequently, several case-control studies confirmed the hypothesis of a link between rotavirus vaccine and intus-

susception, and the vaccine was withdrawn from the market. In Canada oculorespiratory syndrome (ORS) following immunization with influenza vaccines used in 2000 was recognized through an increased frequency of reports to the passive surveillance system. Following those observations several studies were done to characterize the causes and determinants of ORS, and modifications were made to one of the implicated vaccines before the 2001 influenza vaccine campaign.

There is currently public access to data from VAERS. Public access to CAEFISS data is planned, with announcements to be posted at the PHAC vaccine safety web site, http://www.phac-aspc.gc.ca/im/vs-sv/index.html, as soon as it is initiated. This is essential, given the need for transparency and openness regarding reported adverse events in order to maintain public confidence in immunization programs. However, the data are frequently misinterpreted and used to draw inappropriate conclusions regarding risks associated with immunization. Since many of the allegations presented on the Internet and in mass media result from inappropriate use of such data, health care professionals need to clearly understand both the purpose (as described above) and the limitations of passive surveillance systems:

- lack of an appropriate control group
- reporting bias. This stems from several factors that increase the rate of reporting other than a true increased frequency of a given adverse event. Examples include the following:
  - major media focus on allegations such as a link between autism and MMR vaccine
  - markedly increased frequency of immunization such as occurs during mass vaccine campaigns for outbreaks of infection due to *Neisseria meningitidis*
  - enhanced awareness following recognition of clusters of specific adverse events such as ORS
- lack of use of and/or adherence to standard case definitions
- incomplete detail to support a given diagnosis and/or to consider other possible causes, such as intercurrent infection or concomitant medication
- underreporting
- inability to determine the frequency of association since the total number of persons immunized is unknown:
  - the Internet often contains allegations of "hot lots" based on data from VAERS, which publishes the lot numbers associated with adverse event reports. However, the number of actual vaccine doses distributed for a given lot can vary from thousands to millions. If the lot size is unknown it is impossible to determine the lot-specific incidence of a given adverse event.

Expert-based reviews of vaccine safety issues

Vaccine safety is an issue of global concern. Although there are variations in vaccine products used in different countries, the similarities in terms of immunogen are such that much can be learned from expert reviews of specific issues, including examination of published and unpublished data. Currently, there are three sources of such reviews: the WHO, the Institute of Medicine and the Cochrane Collaboration.

World Health Organization: Details of the many WHO initiatives involving vaccine safety are available on the Internet (http://www.who.int/immunization_safety/en/). Two initiatives deserve further mention here as sources of reliable information on vaccine safety issues. In 1999 the Global Advisory Committee on Vaccine Safety (GACVS) was established to provide prompt, scientific evidence-based responses to safety issues of global concern. The expert committee meets every June and December, and soon afterwards posts reports of its deliberations on the WHO Web site (http://www.who.int/vaccine_safety/en/) and publishes these in the Weekly Epidemiological Record (http://www.who.int/wer/en/). The Web site also has a "topics" page that not only summarizes committee conclusions and recommendations but also provides links to other key publications or information on the specific issue. The other initiative, Vaccine Safety Net (http://www.who.int/immunization_safety/safety_quality/vaccine_safety_websites/en/), has been developed by GACVS to promote and identify Web sites on vaccine safety that adhere to good information practices.

Institute of Medicine (IOM): Formed in 1970 by the U.S. National Academy of Sciences (NAS), the IOM functions as an independent, expert professional body that examines issues of relevance to the health of the public (http://www.iom.edu). From 1977 through 1994 the IOM committees reviewed childhood vaccines and other vaccine safety issues. In 2001 a new IOM Immunization Safety Review Committee was assembled and included 13 individuals with broad expertise. To avoid real or perceived conflict of interest, an absolute criterion for membership was lack of any association with vaccine manufacturers or their parent organizations and no prior function as a legal expert witness. From 2001 through 2004 the committee reviewed and published its findings on eight specific vaccine safety issues (http://www.iom.edu/; a search on <immunization safety> will lead to all activities since 2001). For each issue studied, the Committee reviewed all pertinent theoretical, experimental, clinical and epidemiologic evidence and heard presentations from the public and health professionals. The Committee started from a neutral position, with no prior assumption regarding a positive or negative connection between the vaccine and the issue at hand. The scientific evidence was then reviewed, and biologic mechanisms for a possible causal association were carefully considered. Prior to publication, each report was reviewed by an independent expert panel, chosen by the NAS and IOM but anonymous to the committee. Reviewer's comments are given due consideration, but ultimately the final published report represents the consensus of the IOM safety panel alone. To view

reports online and/or purchase copies see the National Academies Press site, http://lab.nap.edu, and search on vaccine or immunization safety.

The **Cochrane Collaboration** (www.cochrane.org) also conducts systematic reviews of vaccines, which may include information on vaccine safety. Since reviews are limited to randomized controlled trials, information regarding rare adverse events is unlikely to be covered.

Vaccine safety data in the Canadian Immunization Guide

In each chapter of this *Guide*, pre-licensure and post-marketing evidence-based safety data are presented for specific vaccines, as appropriate. At the time of publication of the *Guide* post-marketing surveillance of reports submitted to the CAEFISS has demonstrated continued vaccine safety and no unexpected serious adverse events. Detailed summaries of Canadian safety surveillance data for all reports by year, as well as for subgroups by vaccine and specific adverse event, will be published periodically on the Internet, in the *Canada Communicable Disease Report* and in peer reviewed publications as appropriate to the content. An updated list of published materials can be found at the PHAC Vaccine Safety Web site (http://www.phac-aspc.gc.ca/im/vs-sv/index.html, see "Safety data and publications").

Vaccine safety controversies

Space does not permit a detailed discussion of past or current controversies. Table 4 summarizes the conclusions of the IOM safety panel on several recent vaccine safety issues. Topical information on new, as well as past, controversies can be found at the PHAC's Vaccine Safety Web site. Additionally, in the suggested reading and resources given later, Web addresses are provided for the IOM's detailed reports as well as for meeting reports from the GACVS. Also, see the WHO Vaccine Safety Net Web site for a list of sites whose content on vaccine safety has been judged to meet the necessary criteria for credibility, content, accessibility and design.

Suggested reading and resources

Final report: National Immunization Strategy, 2003: http://www.phac-aspc.gc.ca/publicat/nat_immunization_03/index.html

WHO Global Advisory Committee on Vaccine Safety

Folb PI, Bernatowska E, Chen R et al. *A global perspective on vaccine safety and public health: the Global Advisory Committee on Vaccine Safety.* American Journal of Public Health 2004;94(11):1926-1931. This is an overview of the committee's role and activities. Downloadable pdf file at http://www.who.int/vaccine safety/about/en/vaccine.pdf.

GACVS. Bi-annual meeting reports, including summary lists of the topics discussed and full text details, can be found at http://www.who.int/vaccine_safety/reports/en/

Table 4. Events Judged Not To Be Linked to Vaccines*

Exposure	Events judged not to be causally linked with exposure	Year reviewed and National Academies Press site address for specific citation
Multiple immunizations	• Increased susceptibility to infection • Type 1 diabetes mellitus • Sudden infant death syndrome	2002 http://fermat.nap.edu/catalog/10306.html 2003 http://fermat.nap.edu/catalog/10649.html
• MMR vaccine • Thimerosal-containing vaccines	• Autism	2004 http://fermat.nap.edu/catalog/10997.html
Haemophilus influenzae type b conjugate vaccines	• *H. influenzae* infection shortly after immunization	1994 http://fermat.nap.edu/catalog/2138.html
Hepatitis B vaccine	• Incident cases/relapses of multiple sclerosis in adults	2002 http://fermat.nap.edu/catalog/10393.html
Influenza vaccine	• Relapses of multiple sclerosis	2004 http://fermat.nap.edu/catalog/10822.html
Diphtheria and/or tetanus toxoid containing vaccines	• Acute/chronic encephalopathy • Sudden infant death syndrome • Infantile spasms (hypsarrythmia)	2003 http://fermat.nap.edu/catalog/10649.html 1994 http://fermat.nap.edu/catalog/2138.html
Whole cell pertussis vaccines	• Sudden infant death syndrome	2003 http://fermat.nap.edu/catalog/10649.html

* Based on review of scientific evidence by an expert safety review panel of the IOM (see www.iom.edu or specific citation in Table)

WHO Vaccine Safety Net

http://www.who.int/immunization_safety/safety_quality/vaccine_safety_websites/en/

Institute of Medicine

To read and/or purchase reports on vaccine and immunization safety issues, see the National Academies Press site, http://lab.nap.edu, and search on vaccine or immunization safety.

Guidelines for preparing core clinical safety information on drugs – report of the Council for International Organizations of Medical Sciences (CIOMS) Working Group III. Geneva: *World Health Organization (WHO)*, 1995. (Chapter 5, Good Safety Information Practice).

Canadian Coalition for Immunization Awareness and Promotion

Tips for assessing Web sites (usually for health professionals and the public) can be found at the Canadian Coalition for Immunization Awareness and Promotion

English version: http://www.immunize.cpha.ca/english/poster/intip_e.htm
French version: http://www.immunize.cpha.ca/francais/posterf/intip_f.htm

BOX 1. The W5 of AEFI (Adverse Event Following Immunization) Reporting in Canada

- WHY to report:
  - to ensure that the vaccines used in Canada are safe
  - to maintain public confidence in Canada's immunization programs
  - it is a health care professional responsibility
  - it is a legal requirement in many Canadian jurisdictions
- WHO should report:
  - all vaccine providers
  - all health care professionals caring for patients who may have had an AEFI
  - all vaccine manufacturers to whom an AEFI report is submitted
- WHEN to report:
  - when an AEFI is
    - severe (death, hospitalization for > 3 days, congenital abnormality, residual abnormality, life threatening)
    - unexpected (in terms of type or frequency)
    - of concern (to the vaccinee, his/her caregiver(s) or AEFI reporter)
  - when an AEFI occurs within a timeframe that is generally consistent with one or more of the following:
    - immunizing agent: 30 days after live vaccine/7 days after killed or subunit vaccine
    - plausible biologic mechanism: up to 8 weeks for immune-mediated events
    - reporter suspects the AEFI may be linked to immunization
- WHAT to report: details regarding
  - vaccinee – unique identifier, date of birth and sex;
  - immunization event(s) – province/territory where given, date, all vaccines given including name, manufacturer, lot number, administration site and route, as well as the number in series of vaccine doses if relevant;
  - adverse event(s) – description, including time of first onset following immunization, duration, health care utilization, treatment and outcome;
  - relevant medical history – underlying disease, known allergies, prior AEFI;
  - concomitant event(s) – acute illness, current medication, injury, exposure to environmental toxins.
- WHERE to find the AEFI report form:
  - Web (http://www.phac-aspc.gc.ca/im/aefi-form_e.html)
  - Local public health units
  - *Compendium of Pharmaceuticals and Specialties*

General Contraindications and Precautions

Contraindications

A **contraindication** is a condition that significantly increases the chance that a serious adverse event will occur if the vaccine is given. In general, vaccines should not be given when a contraindication exists.

The only three contraindications to vaccines approved in Canada that may exist are the following:

- anaphylaxis to a component of the vaccine (can occur with any vaccine)
  - A patient who has had an anaphylactic reaction to a vaccine or who has a history of anaphylaxis to a component of a vaccine should not receive the same vaccine again. Such patients should be referred to an allergist to determine the specific cause of the allergic reaction and to assess which vaccines should be avoided and for how long. Anaphylactic reactions to vaccines are rare (approximately 2 per million doses administered) but can be life threatening. All vaccine providers should be prepared to respond to anaphylactic reactions to vaccines. For more information see the *Anaphylaxis: Initial Management in Non-Hospital Settings* chapter, page 80.
- significant immunosuppression (live vaccines only)
  - In patients significantly immunocompromised, live viral or bacterial vaccines may cause serious adverse events because of uncontrolled replication of the virus or bacteria. For more information see the chapter on *Immunization of Immunocompromised Persons*, page 117.
- pregnancy (live vaccines only) (see Table 5)
  - If a pregnant woman receives a live vaccine, the infection with the vaccine-strain virus or bacteria might affect the fetus. Although this has been confirmed to occur only for smallpox vaccine, safety data for other live virus vaccines in pregnant women are very limited. Thus women should not receive live vaccines during pregnancy unless their risk from the illness is clearly greater than the potential risk from the vaccine. For more information, see *Immunization in Pregnancy and Breast-Feeding* chapter, page 107.

Precautions

A precaution is a condition that may increase the chance of an adverse reaction following immunization or that may compromise the ability of the vaccine to produce immunity. In general, vaccines are deferred when a precaution is present. However, there may be circumstances when the ben-

efits of giving the vaccine outweigh the potential harm, or when reduced vaccine immunogenicity still results in significant benefit to a susceptible, immunocompromised host.

The precautions associated with each vaccine are discussed in detail in the chapters about specific vaccines. See also Table 6 regarding concerns associated with multiple vaccines.

Two precautions deserve further comment:

- Persons who have chronic underlying illness or who are immunocompromised, in whom there may be a reduced response to vaccines.
  - Even a less than optimal response may provide important benefit to such patients, who are also at high risk of morbidity and mortality due to vaccine-preventable infection. For more information please refer to the *Immunization of Immunocompromised Persons* chapter, page 117.
- Persons with a history of Guillain-Barré syndrome (GBS) with onset within 8 weeks of a previous immunization.
  - Subsequent doses of the same vaccine should only be given if the benefit of vaccination outweighs the potential risk of recurrence of the GBS if vaccine is given.

As noted in Table 6, children and adults with neurologic conditions other than GBS are not at increased risk of adverse events after vaccination and may be at greater risk of morbidity and mortality from vaccine-preventable diseases than healthy individuals. Recommended vaccines should not be avoided in children or adults with neurologic conditions. For more information, please refer to the *Immunization of Persons with Neurological Disorders* chapter, page 131.

Table 5. Contraindications and Selected Precautions for Vaccine Administration

Issue of concern **(see indicated page for more detailed discussion)**	Type of vaccine	
	Inactivated/ subunit	**Live**
Allergy to vaccine component (page 80)	Contraindication if the specific vaccine contains that particular component	
Severely immunocompromised (page 117)	Precaution	Contraindication
Pregnancy (page 107)	None	Contraindication
Recent administration of blood product containing antibodies (page 53)	None	Precaution
Recent administration of live virus vaccine (page 51)	None	Precaution
Severe bleeding disorder (page 134)	Precaution	Precaution

Not contraindications

There are a number of conditions or circumstances that some health care providers inappropriately consider to be contraindications to vaccination. This may result in missed opportunities for needed vaccination. Information about some of these conditions is provided in Table 6.

In particular, mild common illnesses (e.g., upper respiratory tract infections, otitis media, colds, diarrhea) or concurrent antibiotic therapy do NOT interfere with the immune response and are NOT a contraindication to vaccination. Almost no acute illness, however severe, interferes significantly with the immune response to vaccine. Some people argue that the occurrence of systemic adverse events may complicate the medical management of the other acute illness or that events associated with the acute illness may mistakenly be thought to be vaccine-related adverse events. These are both theoretical concerns. Almost invariably, this potential risk is much less important than the risk associated with missing an opportunity to give a recommended vaccine.

Table 6. Conditions that are NOT Contraindications to Immunization

Conditions	Comments
Concurrent condition in vaccinee	

Premature birth	• Premature infants
	  ◦ respond adequately to vaccines used in infancy
	  ◦ are not at significantly increased risk of adverse events.
	• Immunize on schedule, according to child's chronological age.
	• **EXCEPTION:** Hepatitis B vaccine for infants weighing < 2000 g
	  ◦ Mother HBV negative: defer vaccine until infant weighs > 2000 g or is 1 month of age.
	  ◦ Mother HBV positive: give infant hepatitis B immune globulin and first dose of hepatitis B vaccine immediately after birth. Will need 4th dose of HBV (see chapter *Immunization of Infants Born Prematurely*, page 113).

Breast-feeding	• After immunization of either a mother or her infant, during breast-feeding there is
	  ◦ no reduction in maternal or infant response to vaccines
	  ◦ no increase in the risk of adverse events for either mother or breast-feeding infant, following immunization of either.

Pregnancy (inactivated vaccines)	• All **inactivated vaccines** are safe in pregnancy and should be administered if indicated.

Table 6. Conditions that are NOT Contraindications to Immunization

Conditions	Comments
Concurrent condition in vaccinee	
Neurologic disorder	• No evidence of increased risk of any adverse event following immunization. • Such persons may be at increased risk of complications from vaccine-preventable diseases such as influenza and should be immunized appropriately. • **EXCEPTION:** precaution for repeat doses of any vaccine that was temporally associated with an episode of Guillain-Barré syndrome (onset within 8 weeks after immunization).
Cancer (inactivated vaccines)	• No increased incidence of adverse reactions to inactivated vaccines • No interference between treatment of cancer and inactivated vaccine • The immune response may be less than that of healthy adults and children, but any protection following immunization is important because of the increased risk of infection and associated complications
Minor acute illness (with or without fever of ≥ 39.5° C)	• No interference with response to vaccine. • No increase in risk of adverse event(s) following immunization.

Antibiotic therapy	• No effect on response to most inactivated or live vaccines used in Canada.
	• **EXCEPTIONS**
	  • **Live oral typhoid** vaccine should be delayed until 48 hrs after receipt of the last dose of antibiotics active against *Salmonella typhi* (penicillins, cephalosporins, trimethoprim-sulfamethoxazole, fluoroquinolones, azithromycin, tetracyclines).
	  • **Live attenuated varicella** vaccine may have reduced effectiveness if given concurrently with antivirals active against herpesviruses. If possible discontinue antivirals active against herpesvirus ≥ 24 hours before immunization and do not re-start until 4 weeks after vaccination.

Convalescence from or exposure to an infection	• No interference with response to vaccine. • No increase in risk of adverse event(s) following immunization.
Tuberculin skin testing	• Any vaccine can be given at the same time as, or at any time after, a tuberculin skin test. • Tuberculin skin tests can be given at the same time as, or any time after, any vaccine. However, MMR vaccine may suppress the tuberculin reaction and cause false-negative skin test results if skin tests are administered in the 4-6 weeks after vaccination. The effect of other live virus vaccines such as varicella and yellow fever vaccines on tuberculin reactivity is currently unknown, and no recommendations for postponement of tuberculin skin testing can be made at this time.

Table 6. Conditions that are NOT Contraindications to Immunization

Conditions	Comments
Concurrent condition in household contact of vaccinee	
Pregnant or immunosuppressed individuals living in household with vaccinee	• No risk from any vaccine marketed in Canada to household contacts of vaccinees. • Immunization of household contacts of immunosuppressed patients and neonates provides important protection against transmission of disease in the household. Vaccination opportunities in such persons should not be missed.
Concern regarding possible allergy in vaccinee	
Gastrointestinal intolerance to eggs	The inability to eat eggs for reasons other than allergy is not associated with an increase of adverse events to any vaccine.
Child, not yet exposed to egg protein	There is no reason to avoid any recommended vaccine. It is very unlikely that such children would have an egg allergy severe enough to cause them to react to the minute quantity of egg protein contained in some vaccines.

History of allergy that does not involve vaccine or component of vaccine	• It is safe to immunize people with any of the following:
	  ◦ non-specific allergies
	  ◦ environmental allergies
	  ◦ family histories of allergies
	  ◦ administration of allergy shots (desensitization therapy for allergy)
	  ◦ allergies to commonly used antibiotics
	• **EXCEPTION:** vaccines containing neomycin +/or polymyxin (see Table 1, General Considerations chapter, page 7 are contraindicated in individuals with IgE-mediated allergies to these antibiotics.

Concern regarding past adverse reaction	
History of large local reaction following immunization	• A large local reaction to one vaccine is not associated with an increased risk of local reactions to other vaccines. • A large local reaction to the fourth dose of DTaP-IPV-Hib does not predict a large reaction to the fifth dose booster (DTaP-IPV), which should be given on schedule. • In other circumstances, repeating a dose of a vaccine that previously gave a large local reaction may result in another large local reaction. However, there is no increased risk of systemic adverse events.
Febrile seizures	Childhood vaccines prevent serious diseases that pose a much greater risk to most children's health than seizures that might be associated with a febrile reaction after vaccination.

Table 6. Conditions that are NOT Contraindications to Immunization

Conditions	Comments
Concern regarding past adverse reaction	
Family history of adverse reactions to vaccines	• Adverse reactions to vaccines are not known to be inherited. • **EXCEPTION:** a family history of an overwhelming infection or fatality after administration of a live vaccine may suggest inheritable severe immunodeficiency, which should be ruled out before administering live vaccines.
Concern regarding capacity to respond to vaccine	
Concern about exposure to too many antigens	This concern is not substantiated given the following facts: • The vaccines used today are much more highly purified than those in the past, so that even though infants and children now receive more vaccines than they did 30 years ago, the total number of vaccine antigens to which they are exposed is much lower today than it used to be. • The human immune system has an enormous capacity to respond to antigens. • Infants can respond to about 10,000 different antigens at any one time. Immunization does not add, significantly, to the daily load of foreign antigens even for a 2-month-old baby. • The vaccines given at 2, 4 and 6 months of age in Canada engage less than 0.01% of an infant's immune response capacity.

Concern about too many needles	• A Canadian study has shown that
	  • immunization providers are more concerned about multiple injections than are parents
	  • most parents accept multiple injections if it means getting a vaccine with fewer side effects.

Pre-immunization screening for contraindications and precautions

Every patient should be screened for contraindications and precautions before receiving any vaccine dose. Checklists and routine screening questions are useful ways to ensure that this takes place. Effective screening requires only a few questions: sample questions for two circumstances are shown in the box. (Please refer to the *Vaccine Administration Practices* chapter, page 38.)

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Sample screening questions for the parents of children about to receive a dose of any vaccine:

- How is your child today?
- Does your child have any allergies to food or medication?
- Did your child have any problems after his or her previous vaccines/shots?

If the vaccine to be given is a live viral or live bacterial vaccine, add

- Does your child have any problems with his or her immune system?
- Has your child received any transfusions or blood products in the last year?

Sample screening questions for adults being offered influenza vaccine:

- Have you had influenza vaccine before? If yes, did you have any problems after the vaccine?
- Have you had any reactions to vaccines in the past?
- Have you ever fainted after a needle or vaccine?
- Do you have any allergies to food or medications?

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, medical office or similar non-hospital setting. For 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.

Since the publication of the 2002 *Canadian Immunization Guide*, the following changes have been made: 1) the management of an urticarial rash at the injection site has been outlined; 2) the use of self-injectors (Epipen® or Twinject™) has been reviewed; 3) and the use of diphenhydramine hydrochloride (Benadryl®) has been expanded and the dose reduced for some age groups.

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. According to the latest analysis of complete national data collected through passive surveillance, the estimated annual reported rate of anaphylaxis ranges from 0.4 to 1.8 reports per 1,000,000 doses of vaccines distributed in Canada.

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 observed 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, labored breathing and upper airway swelling (indicated by hoarseness and/or difficulty swallowing) possibly causing airway obstruction;
- hypotension, which generally develops later in the reaction and can progress to cause shock and collapse.

Gastrointestinal symptoms like nausea, vomiting and diarrhea may occur with anaphylaxis.

Swelling and urticarial rash at the injection site can occur but are not always caused by an allergic reaction. This reaction can be managed by observation. Ice can be put at the site of reaction for comfort. It can also be treated with diphenhydramine hydrochloride (Benadryl®, see step 7 in the next section) alone. If diphenhydramine is given to treat such a reaction, the patient should be kept under close supervision for 1 hour after the dose. If the hives or swelling disappear without additional treatment, the patient does not need to be kept under further observation. However, if any other symptoms arise, even if considered mild (e.g., sneezing, nasal congestion,

tearing, coughing, facial flushing) or if the hives progress despite the use of diphenhydramine, epinephrine should be given (see below). There is little risk to the unnecessary use of epinephrine, whereas delay in its administration when required may result in difficulty to treat anaphylaxis and in death.

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 1)**, which should not be delayed if earlier steps cannot quickly be completed.

1. **Promptly administer 0.01 mL/kg (maximum 0.5 mL) of aqueous epinephrine 1:1000 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 (see text below for discussion of epinephrine).
2. Call for assistance, including an ambulance.
3. Place the patient in a recumbent position, elevating the feet if possible.
4. Establish an oral airway if necessary.
5. If oxygen is available, it should be given to patients with cyanosis, dyspnea or any other severe reaction. Monitor with pulse oximetry if available.
6. If the vaccine was injected subcutaneously, an additional dose of 0.005 mL/kg (maximum 0.3 mL) of aqueous epinephrine 1:1000 can be injected into the vaccination site to slow absorption. This should be given shortly after the initial dose of epinephrine (Table 7) 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.
7. As an adjunct to epinephrine, a dose of diphenhydramine hydrochloride (Benadryl®) can be given. Oral treatment (oral dose: 1-2 mg/kg to a maximum single dose of 50 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 8.
8. If available, consider inhaled β-agonist if there is a bronchospasm resistant to an adequate dose of epinephrine (e.g., nebulized salbuta-

mol 2.5-5.0 mg in 3 mL of saline or 1 puff per 3 kg to a maximum of 10 puffs by metered dose inhalers).

9. Monitor vital signs and reassess the situation frequently, to guide medication use.

10. 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.

The subcutaneous or intramuscular route for epinephrine injection is appropriate. Epinephrine dosing can be repeated twice at 5-minute intervals if necessary, for a total of three doses, again avoiding the limb in which the vaccination was given. A different limb is preferred for each dose to maximize drug absorption.

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 1:1000 can be approximated from the subject's age (Table 7).

Table 7. Appropriate Dose of Epinephrine (1:1000) 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 years	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.

Table 8. Appropriate Dose of Diphenhydramine Hydrochloride

Age	Dose	
	Injected (50 mg/mL)	Oral or injected
< 2 years	0.25 mL	(12.5 mg)
2-4 years	0.50 mL	(25.0 mg)
5-11 years	0.50-1.00 mL	(25-50 mg)
≥ 12 years	1.00 mL	(50 mg)

An epinephrine self-injector (Epipen® or Twinject™) can also be used if the person who administers it is knowledgeable about proper use. The junior preparations contain 0.15 mL of epinephrine 1:1000, which is ideal for children weighing 15 kg. The regular preparations contain 0.3 mL of epinephrine 1:1000 and should be used for people weighing ≥ 30 kg. For those weighing below 15 kg or between 15 and 30 kg, judgement should be used to decide which, if any, self-injector should be used.

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

Epinephrine vials and other emergency supplies should be checked on a regular basis and replaced if outdated.

Recommended epinephrine kit contents

- Copy of the anaphylaxis procedures and doses recommended of epinephrine and diphenhydramine for weight and age
- 2–1 cc syringes with attached needles (1–25 gauge, 5/8" needle; 1–25 gauge, 1" needle)
- 2 vials of epinephrine 1:1000 (check expiry date monthly and replace once expired)
- 1 vial of diphenhydramine (pills or oral solutions optional, check expiry date monthly and replace once expired)
- 1 – 25 gauge, 5/8" needle (extra)
- 1 – 25 gauge, 1" needle (extra)
- 2 alcohol swabs (optional)

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Anaphylactic Hypersensitivity to Egg and Egg-Related Antigens

Changes since the publication of the 2002 *Canadian Immunization Guide* include the following: 1) no special precaution when administering measles, mumps, and rubella (MMR) vaccine to egg-allergic individuals; 2) information on the new rabies vaccine (RabAvert®), which is derived from virus grown in chick embryo cell culture; and 3) chicken allergy as a contraindication to vaccination with the yellow fever vaccine.

General considerations

In this chapter, egg or chicken allergy is defined as an IgE-mediated hypersensitivity causing symptoms like, but not limited to, urticaria, swelling of the mouth and throat, difficulty breathing or hypotension. Chicken allergy refers to allergy to chicken meat as opposed to allergy to feathers.

Egg allergy is one of the most common food allergies of childhood, with a prevalence of 1%-3% in children under 3 years of age. As most children outgrow their egg allergy, the prevalence in adulthood is much lower. Isolated chicken allergy is a very rare condition.

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. The yellow fever vaccines are prepared from virus grown in chick embryos and are the most likely to cause allergic reaction in egg- or chicken-allergic individuals. Allergic reactions can also occur to vaccines against influenza, which are prepared from viruses grown in embryonated eggs. In contrast, the MMR vaccine viruses most widely used in Canada and one of the rabies vaccines (RabAvert®) are grown in chick embryo cell culture. The final vaccine products *may* contain trace quantities of egg proteins, but the amount is not felt to be enough to cause an allergic reaction, especially for MMR. Some extra precautions are still recommended for RabAvert®. Egg proteins are not involved in the manufacturing process of the other rabies vaccine (Imovax® Rabies).

MMR vaccine

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. The minute quantity of egg proteins contained in the MMR vaccine seems to be insufficient to cause an allergic reaction in egg-allergic people.

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. Therefore the use of skin testing with MMR vaccines in egg-allergic individuals is no longer recommended.

The largest published review of the literature provides data on 1227 egg-allergic patients who received the MMR vaccine as a usual single dose. Only two had any symptoms suggesting an allergic reaction, and they were from the same case report, whereas in better studies no patient reacted. These combined data indicate that 99% of children who are allergic to egg can safely receive the vaccine (95% confidence interval (CI) 99.41%-99.98%). Four of the best studies from this review of the literature are summarized below.

- Fasano et al (1992) studied 140 children whose double-blind placebo-controlled food challenges to egg were positive or who had a convincing history of recent anaphylaxis to egg ingestion and a positive skin test to eggs. Seventy-one children were immunized prospectively and 69 children had already received the MMR vaccine. None had any reaction to the vaccine.
- James et al (1995) prospectively evaluated the administration of MMR vaccine to 54 children with positive skin test to eggs and either a positive food challenge to egg or convincing history of severe or recent anaphylactic reaction to egg. None had any reaction to the vaccine.
- Aickin et al (1994) described 242 children with documented allergic reaction after the ingestion of egg and positive skin test to egg. None had any reaction to the vaccine.
- Freigang et al (1994) described 500 children with convincing history of egg allergy and positive skin test to egg. None had any reaction to the vaccine.

In view of the cumulative data indicating the safety of MMR 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, the National Advisory Committee on Immunization (NACI) does not recommend routine MMR skin testing or any special precaution in these individuals. As for all vaccines, NACI recommends immunization by personnel with the capability and facilities to manage adverse events following immunization such as anaphylaxis.

Rabies vaccine

Immunization with rabies vaccine obtained by viruses grown in chick embryo cell culture (RabAvert®) is probably safe in egg-allergic individuals because the vaccine contains only a minute quantity of egg proteins; however, no safety data exist. An alternative vaccine, if available, should be used in egg-allergic individuals. If an alternative vaccine is not available, post-

exposure prophylaxis should be administered with strict medical monitoring in facilities where emergency treatment of anaphylaxis is available. For pre-exposure vaccination when no alternative vaccine is available referral to an allergy specialist prior to vaccination is recommended, as vaccination might be possible after careful evaluation, skin testing and graded challenge or desensitization.

Influenza vaccine

Allergic reactions have been reported in patients with egg allergy receiving the influenza vaccine. In the few studies evaluating immunization with influenza vaccine in egg-allergic children, allergic reactions ranged from 0%-40%.

Most influenza vaccines probably contain only a very small amount of egg proteins, but manufacturers do not report the egg content of their influenza vaccine. In some studies in which investigators have determined the egg content of some influenza vaccines, it was found that the egg protein content varied by several logarithmic factors from manufacturer to manufacturer and from year to year.

Egg-allergic individuals should not be routinely vaccinated with the influenza vaccine. Of these individuals, those who are at risk of the complications of influenza should be evaluated by an allergy specialist, as vaccination might be possible after careful evaluation, skin testing and graded challenge or desensitization. If such an evaluation is not possible, the risk of an allergic reaction to the vaccine must be weighed against the risk of influenza disease.

Yellow fever vaccine

The yellow fever vaccine has the greatest likelihood of containing sufficient amounts of egg or chicken proteins to cause an allergic reaction in egg- or chicken-allergic individuals. There have been several reports of anaphylactic reactions to the yellow fever vaccine in egg- or chicken-allergic individuals but no studies have been done in which the vaccine was administered to such individuals in order to monitor for the reaction. The yellow fever vaccine should not be routinely administered to egg- or chicken-allergic individuals. Referral to an allergy specialist is recommended, as vaccination might be possible after careful evaluation, skin testing and graded challenge or desensitization.

Summary of guidelines for vaccination of egg- or chicken-allergic individuals

- Individuals should be asked about allergy to egg prior to vaccination with influenza vaccine, yellow fever vaccine and the rabies vaccine RabAvert®.

- Individuals should be asked about allergy to chicken prior to vaccination with yellow fever vaccine.
- Prior egg ingestion should not be a prerequisite for immunization with egg-containing vaccine.
- Atopic diseases are not a contraindication to immunization with egg-containing vaccine.
- Egg allergy is not a contraindication to immunization with MMR. People with these allergies may be immunized in the routine manner without prior testing.
- Influenza vaccines that are prepared from viruses grown in embryonated eggs should not be given to egg-allergic individuals unless the risk of the disease outweighs the small risk of a systemic hypersensitivity reaction. Referral to an allergy specialist is recommended, as vaccination might be possible after careful evaluation, skin testing and graded challenge or desensitization.
- Yellow fever vaccines should not be given to egg- or chicken-allergic individuals unless the risk of the disease outweighs the small risk of a systemic hypersensitivity reaction. Referral to an allergy specialist is recommended, as vaccination might be possible after careful evaluation, skin testing and graded challenge or desensitization.
- When no alternative vaccines are available for egg-allergic individuals, post-exposure vaccination with RabAvert® should be performed in facilities where treatment for anaphylaxis is available. For pre-exposure vaccination when no alternative vaccine is available, referral to an allergy specialist is recommended as vaccination might be possible after careful evaluation, skin testing and graded challenge or desensitization.
- Re-immunization with MMR, yellow fever, influenza or rabies vaccine is contraindicated in an individual with a previous anaphylactic reaction to that vaccine. Referral to an allergy specialist is recommended to find out which component of the vaccine was responsible for the allergic reaction

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