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Practice Point

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Canada's eight-component vaccine safety system: A primer for health care workers

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Abstract

Concerns about vaccine safety make some parents hesitant about immunization. Health care providers are pivotal in helping parents understand that Canada is a leader in vaccine safety. The present practice point provides an update on the eight components of Canada's vaccine safety system: (1) an evidence-based pre-license review and approval process; (2) strong regulations for manufacturers; (3) independent evidence-based vaccine use recommendations; (4) immunization competency training and standards for health care providers; (5) pharmacovigilance programs to detect and (6) determine causality of adverse events following immunization (AEFIs); (7) a program for vaccine safety and efficacy signal detection; and (8) the Canadian Immunization Research Network's special immunization clinics for children who have experienced serious AEFIs.

Keywords: *AEFI; BGTD; CAEFISS; IMPACT; NACI; Vaccine safety*

Using vaccines to control serious infectious diseases has been one of the outstanding achievements of preventive medicine, yet a rise in parental hesitation about vaccination globally threatens this success (1). Some parents are so troubled by vaccine safety concerns that they choose not to have their child immunized (2). Although reasons for delaying or refusing vaccines are varied (1), one Canadian survey in 2011 revealed that concern about safety (at 17%) was the second-most-reported reason for not immunizing children, with "vaccines are not necessary" being the first (3).

Health care providers are pivotal in helping parents to understand that Canada has been a leader in vaccine safety and that our health system continues working to ensure the safety and efficacy of vaccines on an ongoing basis. The present practice point updates information for health care providers on Canada's vaccine safety system (4).

CANADA'S VACCINE SAFETY SYSTEM

The eight key components of Canada's vaccine safety system are summarized in Table 1. Vaccine development, licensing (notice of compliance) and post-licensure monitoring are parts of a highly regulated and inspected process that is even more stringent than for other drugs (5). The sequence outlined below describes the steps which are applied to all vaccines to ensure that they are safe.

1. Evidence-based pre-licensing review and approval

In North America, Europe and many other places around the world, the licensing of drugs and vaccines is highly regulated. In Canada, the Biologics and Genetic Therapies Directorate of Health Canada (BGTD) has this authority. Before any vaccine is approved for use in Canada, in-depth reviews of scientific product data on efficacy, stability, teratogenicity, toxicity and safety are required by the BGTD. Standards are in place to ensure that the data generated throughout all phases of testing are valid, reliable and obtained in an ethical manner (see Good laboratory and Good clinical practices, below). Pre-licensure vaccine trials can involve anywhere from 10,000 to several hundred thousand people. A separate data monitoring committee, independent from researchers, oversees each trial to ensure risks are minimized and the trial is stopped immediately if concerns arise. Every adverse event is thoroughly scrutinized to determine whether it is caused by the vaccine or not. Vaccine efficacy is determined either directly or by an agreed-upon surrogate marker established before starting the trial. Health Canada issues a notice of compliance (NOC) (i.e., "licenses" the vaccine) only if there is sufficient evidence of quality, safety and efficacy, with a positive benefit-to-risk profile (i.e., the predicted benefit from the vaccine outweighs the predicted risk of adverse events).

2. Good practice standards and regulations for manufacturers

A number of regulations and related guidelines ensure that vaccines are safe by requiring very high standards of consistency, validity and reproducibility in all aspects of pre-clinical and clinical testing of vaccines, as well as for each process step involved in their manufacture:

(a) **Good laboratory practices (GLPs)** are international standards that govern all aspects of laboratory data, providing regulators with assurance that the data on which they base their approval decisions are reliable. For details, see: www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/glp_bpl-eng.php.

(b) **Good clinical practices (GCPs)** are based on quality standards that are defined by the International Conference on Harmonisation (ICH: http://www.ich.org/home.html). Health Canada uses GCPs to review, approve

Table 1. The eight components of the Canada's vaccine safety system

1. Evidence-based pre-license review and approval process
2. Regulations for manufacturers:
   (a) Good laboratory practices (GLPs)
   (b) Good clinical practices (GCPs)
   (c) Good manufacturing practices (GMPs)
   (d) Vaccine lot assessment (before release)
   (e) Regular review of vaccine safety data submitted by the market authorization holder
3. Evidence-based vaccine use recommendations
4. Immunization competencies training for health care providers
5. Pharmacovigilance for adverse events following immunization (AEFIs):
   (a) AEFI post-marketing surveillance
   (b) AEFI monitoring (CAEFISS): passive, enhanced and active (IMPACT)
   (c) Global surveillance (Uppsala Monitoring Centre)
6. AEFI causality assessment
7. Safety and efficacy signal detection
8. Canadian Immunization Research Network special immunization clinics (SICs)

and monitor all clinical vaccine trials that are brought forward for licensing. For details, see: www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/ich/efficac/e6-eng.php.

(c) **Good manufacturing practices (GMPs)** are "a system for ensuring that products are consistently produced and controlled according to quality standards". GMPs cover all aspects of production: from the starting materials, premises and equipment to the training and personal hygiene of staff. Vaccine manufacturing facilities in Canada are monitored by government inspectors to verify adherence to GMPs. Imported vaccines approved for marketing in Canada must also be made in facilities that meet GMP standards.

(d) **Vaccine lot assessment before release.** Health Canada regulators conduct this program to ensure that every newly manufactured lot of vaccine matches those used to generate the original product safety and efficacy data needed to obtain the NOC or license: www.phac-aspc.gc.ca/publicat/cig-gci/p02-01-eng.php#evaluation. Manufacturers must conduct, document and submit results of key quality control tests for each new lot. Health Canada carefully reviews these data and often performs their own confirmatory tests before issuing a release for the lot to be sold.

(e) **Review of vaccine safety data submitted by the market authorization holder.** Safety data submitted by the company holding the NOC also undergoes regular review (see Pharmacovigilance and Causality assessment, below) to detect safety signals or concerns (see Signals, below).

3. Evidence-based vaccine recommendations

For an approved vaccine to be recommended for routine use in Canada, a formal independent review separate from the licensing review is done by the National Advisory Committee on Immunization (NACI). For details, see: http://www.phac-aspc.gc.ca/naci-ccni/. NACI is comprised of independent experts in infectious diseases, public health, vaccine safety, epidemiology, paediatrics, nursing and internal medicine. They review all safety and efficacy data on both old and new vaccines to make recommendations for their use in Canada. A NACI member is precluded from making recommendations for any vaccine if she/he has a conflict-of-interest. NACI recommendations are based on careful scrutiny of disease epidemiology, vaccine efficacy, vaccine safety and alternative prevention and treatment options. As new efficacy and safety data are reported post-licensure (see Pharmacovigilance, below), recommendations are updated. NACI is independent of vaccine manufacturers and government with respect to decision-making. All NACI guidelines, literature reviews and evidence tables are published online, along with the *Canadian Immunization Guide* (see http://www.phac-aspc.gc.ca/publicat/cig-gci/index-eng.php). Because health is a provincial/territorial responsibility, public health authorities in each jurisdiction review NACI recommendations before possible implementation in their own program.

4. Immunization competencies for health care providers

In 2008, a handbook entitled *Immunization Competencies for Health Professionals* (www.phac-aspc.gc.ca/im/ic-ci/index-eng.php) was published to better equip immunization providers in the application of NACI immunization guidelines (www.phac-aspc.gc.ca/publicat/cig-gci/index-eng.php) for vaccine delivery.

5. Pharmacovigilance for adverse events following immunization

Vaccine pharmacovigilance oversees the science and activities related to the detection, assessment, understanding, prevention and communication of adverse events following immunization (AEFIs) or any other vaccine- or immunization-related issues (6). Very rare side effects (<1/10,000 exposures) are not always detected before a vaccine is approved. Pharmacovigilance acknowledges the need for ongoing safety assessment of products after they have been marketed and used in vaccination programs.

Requirements for post-market vaccine safety studies and surveillance

Canada's Food and Drug Act and Regulations set out many requirements for the market authorization holders of vaccines, regarding post-market safety monitoring, reporting and, in some cases, specific safety studies to fill in recognized knowledge gaps. At periodic intervals specified by Health Canada, they must submit safety update reports that contain all global data related to the use of their product.

The Canadian Adverse Events Following Immunization Surveillance System

Many countries have post-market AEFI reporting systems in place for both old and new vaccines. The Canadian Adverse Events Following Immunization Surveillance System (CAEFISS) is a public health-federal/provincial/territorial collaboration that has been in place since 1987. The CAEFISS has five objectives: (1) To continuously monitor the safety of marketed vaccines in Canada; (2) To identify increases in the frequency or severity of recognized AEFIs; (3) To identify previously unknown AEFIs that may possibly be related to a vaccine; (4) To identify areas that require further investigation and/or research (see Signal detection, below); and (5) To provide timely information for analysts and policy-makers on AEFI profiles for vaccines marketed in Canada. For details, see www.phac-aspc.gc.ca/im/vs-sv/.

The system includes passive reporting. Anyone—families, patients, the general public—can report if they suspect an AEFI has occurred (see www.phac-aspc.gc.ca/im/aefi-essi_guide/index-eng.php). Government health authorities encourage both enhanced reporting (when several AEFIs are listed on a national report form and are considered to be of special public health importance) and active reporting (when specific serious events are sought among hospitalized children and reported if found to have followed immunization).

The active surveillance component, which has been in place for over two decades, is conducted by the Immunization Monitoring Program ACTive (IMPACT), overseen by the Canadian Paediatric Society and funded by the Public Health Agency of Canada (PHAC) (7). IMPACT uses specially trained nurse monitors to actively and systematically search all hospital admissions for selected AEFIs (e.g., neurological conditions, thrombocytopenia, local or allergic complications of vaccination, intussusception), for vaccine-preventable diseases (including cases where vaccine failure might be a factor), and for selected infectious diseases in children that are (or will soon be) vaccine-preventable. The program is conducted in 12 paediatric hospitals across Canada that collectively capture over 90% of all paediatric tertiary care admissions. IMPACT's summary reports are available to health care practitioners and the public on the Canadian Paediatric Society website (www.cps.ca/en/impact).

International surveillance

Because serious AEFIs are so rare, sharing AEFI information from around the world is crucial to ensuring vaccine safety. Canada and many other countries share AEFI data with the WHO through the Uppsala Monitoring Centre (www.who-umc.org/). In 1999, the WHO created the Global Advisory Committee on Vaccine Safety to respond to issues of potential global importance in a prompt, efficient and scientifically rigorous manner (8). Canada has brought signals to this committee for discussion (such as oculorespiratory syndrome associated with influenza vaccine in 2002). For details, see: www.who.int/vaccine_safety/committee/topics/influenza/oculorespiratory_syndrome/Dec_2002/en/.

6. AEFIs: Causality assessment

Simply because an adverse event follows immunization does not mean the vaccine or vaccination caused that adverse event. A causality assessment must be done to determine whether the AEFI was related to the vaccine or vaccination (i.e., was vaccine product-related, vaccine quality defect-related, immunization error-related [e.g., a drug was administered, not the vaccine, or a vaccine was administered by the wrong route], or immunization anxiety-related), or was a coincidental event unrelated to the vaccine or vaccination. In Canada, this causality assessment is carried out by the PHAC, using internationally accepted principles. For details, see: www.who.int/vaccine_safety/publications/aevi_manual.pdf?ua=1.

In some instances, there is insufficient information to perform a causality assessment and the AEFI remains unclassifiable. To minimize this occurrence, it is incumbent upon the reporting clinician to provide as much clinical information as possible to support a proper causality assessment. The communication of assessment outcomes is an important component of the process, with quarterly reports posted on the PHAC website (www.phac-aspc.gc.ca/im/vs-sv/index-eng.php). It is worthy of note that the WHO's user manual, *Causality assessment of an AEFI*, had its roots in the AEFI causality assessment program pioneered in Canada in the mid-1990s (9).

7. Vaccine safety and efficacy signal detection

Canada has laws and procedures in place to support the immediate recall of a vaccine and/or nondistribution of a vaccine lot when a significant safety issue is detected. For example, in late 2007, Health Canada placed three lots of measles, mumps and rubella (MMR) vaccine on hold while five cases of suspected anaphylaxis in Alberta patients who had received vaccine from these lots were investigated (10). The review found no link between the MMR vaccine lots and these adverse events. A review or signals investigation from British Columbia of an AEFI "cluster" between November 2007 and July 2014 detected two fatalities (both due to sudden infant death syndrome and not vaccine-related) and 13 other AEFI clusters. The clusters were predominately local injection site reactions (at 54%) or allergic events (at 39%) but none were found to be associated with a specific vaccine or lot. One cluster of severe local reactions following influenza immunization was determined to be a result of improper injection technique and was addressed through training. Such examples demonstrate the importance and effectiveness of this safety system.

Vaccine failure signals are also searched for. When a vaccine-preventable disease outbreak occurs, the immunization status of people affected is checked to detect whether a vaccine failure has occurred, and if so, whether the failure rate is above that expected for a specific vaccine. For example, see the 2011 Quebec measles outbreak report (11). The IMPACT network (described above) actively searches for children hospitalized with a vaccine-preventable disease to help detect possible vaccine failures. When a case is found, the child's immunization status is checked. If the child has been fully immunized, testing can sometimes be done to determine whether the infection is due to a vaccine failure or would have occurred despite vaccine because of an underlying immunodeficiency.

8. Canadian Immunization Research Network special immunization clinics

Following an AEFI, not only must causality be determined but an assessment of the safety of further immunizations must also be done (12). Not surprisingly, parents, patients and health care workers might be reluctant to continue administering a particular vaccine, especially if an AEFI required hospitalization. To address this, the Canadian Immunization Research Network established 13 special immunization clinics (SICs) in 2013, staffed by paediatric and adult infectious disease specialists and allergists experienced in dealing with "challenging" AEFIs (12). Patients with underlying conditions that may put them at higher risk of an AEFI (e.g., compromised immunity) are also seen in SICs. Referred patients are assessed and managed using a standardized approach. With consent, these cases are logged into a central registry to enable review of further immunization outcomes for people with similar AEFIs, as well as to better evaluate management protocols.

CONCLUSION

Vaccines were developed to protect people who are, for the most part, healthy. As a result, the public rightly expects vaccines to be safe and effective. Concerns about vaccine safety can foster vaccine hesitancy. Education about the breadth, depth and rigour of Canada's vaccine safety system, including our ability to rapidly detect and act on potential vaccine safety alerts, may help to overcome this hesitancy. This knowledge will support vaccine acceptance resiliency among health care workers and the general public when anti-vaccine safety concerns are raised in the media or by encounters with parents in immunization clinics and doctor's offices. The many checks and signal-detectors built into Canada's vaccine safety system make the system as a whole, and its eight components, very trustworthy.

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