

Canada's eight-step vaccine safety program: Vaccine literacy

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Immunization to control serious infectious diseases has been one of the outstanding achievements of preventive health medicine. But hand in hand with the growing success of vaccine prevention of major scourges such as polio, measles, invasive *Haemophilus influenzae* type b disease and hepatitis B has come a rise in parental concerns regarding the safety of vaccines in a number of countries (1,2). Some parents are now so troubled by vaccine safety that they are choosing not to have their children immunized, sometimes with tragic results (3-5). Fear engendered by the purported links between vaccines and conditions such as autism, sudden unexpected death in infancy, demyelinating disorders and neurodevelopmental disorders is a symptom of mistrust in the safety of the vaccine system as a whole. Every new allegation of a vaccine safety concern fuels the mistrust. A growing number of parents simply do not believe that the vaccine system is safe.

Erosion of public trust in vaccines seems to be occurring despite more than two decades of effort to educate the public about the risks of vaccine-preventable diseases and the benefits and excellent safety profiles of the recommended childhood vaccines. An expanded approach to ensure and, if necessary, restore public confidence in vaccines is needed. Health care providers who are involved in immunization delivery have a key role to play. The present Paediatric Infectious Disease Note outlines a strategy for helping health care providers increase public trust in vaccines.

HOW CAN WE ADDRESS THIS FUNDAMENTAL PROBLEM OF MISTRUST IN THE VACCINE SYSTEM?

Trust is built on a combination of caring and competence. Both are needed. We have not done a good job in explaining the high degree of regulation and safety monitoring that ensure that the vaccine system is as safe as possible, nor have we always addressed vaccine safety concerns in a compassionate manner. Hence, it should come as no surprise that some parents are not reassured by the health care professional simply saying: "The vaccine is safe, do not worry". Perhaps what is needed to increase public trust in vaccines is an improvement in vaccine literacy – a better understanding of the many built-in safety monitoring components that ensure that vaccines are as safe as possible.

In Cuba, for example, trust in the vaccine system is high, partly because health care and education for all are much valued 'jewels' of the revolution (6). Education for all has led to high levels of literacy, including a focus on health literacy. The

average Cuban knows why vaccines benefit both individuals as well as the community as a whole, and also is familiar with components of the Cuban vaccine safety system from bench to arm and beyond (Noni MacDonald, personal experience).

WHAT ARE THE COMPONENTS OF CANADA'S VACCINE SAFETY SYSTEM?

Vaccine development, licensing and postlicensure monitoring is a highly regulated and inspected process that is even more stringent than for other drugs. The eight components of the Canadian vaccine safety system are summarized in Table 1 and described below.

1. Prelicensure review and approval process

In Canada, Europe and the United States, as in many other countries, licensing of drugs and vaccines is highly regulated. The Biologics and Genetic Therapies Directorate of Health Canada holds this authority in Canada (this authority is held by the Food and Drug Administration in the United States). In addition to the stringent routine prelicensure testing requirements for drugs, biologics including vaccines require more detailed chemistry and manufacturing information. For approval, in-depth reviews of scientific product data on vaccine efficacy, stability, teratogenicity, toxicity and safety are performed. Prelicensure vaccine trials now always involve thousands and even tens of thousands of people. Each trial undergoes rigorous scientific and ethical scrutiny before being allowed to proceed. Separate data monitoring committees independent of the researchers oversee the trial to ensure that risks are minimized and the trial stopped immediately if concerns arise. Every adverse event noted in the prelicensure studies is scrutinized carefully and assessed to determine whether the vaccine is the cause. Vaccine efficacy is determined either directly or by an agreed-upon surrogate marker established before starting the trial for diseases that have a low incidence. If the manufacturer's application is inadequate in any one area, such as a lack of convincing data for safety or efficacy, then approval for licensure is withheld. The regulatory bodies also determine labelling for the vaccine and the content information in the product monograph.

2. Current good manufacturing practices

Good manufacturing practices (GMPs) is a term recognized worldwide for the control and management of manufacturing and quality control testing of foods, pharmaceutical products and medical devices. For a company to be licensed to produce

TABLE 1
Components of the Canadian vaccine safety system

1. Prelicensure review and approval

The government regulator conducts a thorough review of all the scientific product data for each vaccine before it can be sold

- review of vaccine efficacy, stability, teratogenicity, toxicity and safety data

2. Current good manufacturing practices

Manufacturers must follow strict, globally recognized manufacturing procedures that include regular and random onsite checks of the manufacturing plants by government inspectors

3. Lot assessment before release

Manufacturers test every lot (small quantities, all made at the same time) of vaccine for potency, safety and purity before release. Government inspectors may test lots when conducting an inspection

4. Independent expert review of national vaccine recommendations

A committee of independent experts reviews all safety and efficacy data on vaccines, and recommendations for use are published

5. Postmarketing surveillance for adverse events

Reporting adverse events is mandatory for health care providers and vaccine manufacturers

- These reports are analyzed by independent experts
- Active search is also performed in 12 Canadian children's hospitals for adverse events following immunization, vaccine failures and admissions due to vaccine-preventable infectious diseases
- Analysis of the data is published

6. Rapid response to vaccine performance concerns

Detection of any concern about the safety of a vaccine triggers an immediate recall of a vaccine, and/or nondistribution of a suspected lot of vaccine

7. Expert causality assessment of serious adverse events following immunization

Serious adverse events following immunization, such as deaths or hospitalizations, undergo rigorous scrutiny by a group of independent experts to determine the cause. Reports from this expert group are published

8. International collaboration

Data on adverse events following immunization, and detection of any concerns in the vaccine system, are sent to the World Health Organization where it is shared with all countries

a drug or vaccine, the plant must meet current GMP (cGMP) standards. Adherence to cGMP standards is required of all vaccine manufacturers, ensuring that vaccines are consistently produced and controlled to meet the quality standards appropriate to their intended use, as required by the regulator. Government inspectors verify adherence to these quality standards. cGMP guidelines can be downloaded from the Health Canada Web site <www.hc-sc.gc.ca>. In several instances in the past decade, a vaccine supply issue arose because a manufacturing plant on inspection had not met cGMP standards. Therefore, no vaccine was accepted from the plant until it again met the required standards, demonstrating that this regulation (ie, ensuring quality vaccine manufacturing) is enforced.

3. Vaccine lot assessment before release

Each lot of vaccine manufactured is tested by the manufacturer for potency, safety and purity before it can be released. The lot must meet standards set by the government before release for use and can be retracted if a problem is identified later. Manufacturing, testing and plant inspection histories also are reviewed by government regulators. Manufacturers may be

required at any time to submit samples of each vaccine to the regulator for independent testing. Inspectors appear regularly and randomly to ensure lots are being tested and accurate records kept. Drugs do not undergo such rigorous lot-by-lot assessment.

4. Independent expert review of vaccine use recommendations

For a 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 <<http://www.phac-aspc.gc.ca/naci-ccni/>>. Similar committees are present in other countries, eg, the United States Advisory Committee on Immunization Practices <<http://www.cdc.gov/vaccines/recs/acip/default.htm>>. These committees are composed of independent experts in infectious diseases, public health, vaccine safety, epidemiology, paediatrics, nursing and internal medicine. They have the responsibility to review all safety and efficacy data on vaccines, both old and new, and to make and publish recommendations for the use of these vaccines in Canada and the United States, respectively. All recommendations are based on careful scrutiny and evaluation of disease epidemiology, vaccine efficacy, vaccine safety, and alternative prevention and treatment options. As new vaccine efficacy and safety data are reported postlicensure, these committees revise and update their recommendations. Both committees are independent of vaccine manufacturers and government with respect to decision making. Each committee member must declare any competing interests relevant to vaccines at each meeting and are not permitted to vote if a conflict exists. Public health authorities in each province and territory and practitioners generally consult publications from these committees before they recommend immunization.

5. Postmarketing surveillance for adverse events following immunization

Rare adverse events that only occur at a rate of one per 100,000 immunizations or one per 1,000,000 immunizations would not be detected in the prelicensure studies. Therefore, following licensure of a new vaccine, vaccine manufacturers are required to conduct surveillance studies to determine whether there are any exceedingly rare but important serious adverse events of the vaccine that were not detected before licensure.

Beyond these formal postlicensure vaccine studies, Canada and many other countries have surveillance systems in place to detect serious adverse events following immunization for both old and new vaccines. In Canada, the passive surveillance system in which anyone – including families, patients and the general public – can voluntarily submit a report is the Canadian Adverse Events Following Immunization Surveillance System (CAEFISS) run by the Public Health Agency of Canada (7). Health care professionals and manufacturers are required to report all serious adverse events following immunization using a standardized reporting form to CAEFISS (CAEFISS form: <http://www.phac-aspc.gc.ca/im/aeif-form-eng.php>). In the United States, the passive surveillance system called Vaccine Adverse Event Reporting System (VAERS) is jointly administered by the Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration (8).

In addition to the passive surveillance system, Canada has had an active surveillance system in place for more than 17 years, the Immunization Monitoring Program, ACTive (IMPACT) run by the Canadian Paediatric Society with funding from the Public Health Agency of Canada (9). IMPACT uses specially trained nurse monitors to actively and systematically search all hospital admissions to the 12 children's hospitals across the country for adverse events following immunization, for vaccine failures and for selected infectious diseases in children that are, or are soon to be, vaccine preventable. IMPACT summary reports are available to the practitioners and the public on the Canadian Paediatric Society's Web site <www.cps.ca>. In the United States, the Vaccine Safety Datalink (VSD) project, created in 1990 by the CDC with eight large managed care organizations, uses large-linked databases to analyze vaccine-related and clinical information pertaining to more than seven million people including both children and adults (10). This VSD system is used for planned immunization studies such as detecting rare adverse events when selected new vaccines are licensed or safety issue questions arise, as well as allowing determination of vaccine-preventable disease rates and detection of rare adverse events above baseline rates (11).

Review of data from these surveillance systems means the immunization safety branches at the Public Health Agency of Canada and the CDC can more readily detect vaccine safety alert and vaccine effectiveness signals. For example, in 1999, a spike in reports to VAERS of intussusception following the rotavirus vaccine RotaShield (Wyeth-Ayerst Laboratories, USA) in the USA (12) led to its voluntary recall by the manufacturer within three months of its licensure. With the introduction of the next-generation rotavirus vaccine RotaTeq (Merck Frosst, Canada) in 2006, using both VAERS and the VSD project data over a one-year period, the CDC was able to show that surveillance data showed that RotaTeq was not associated with an increased risk of intussusception (13).

6. Rapid action if vaccine performance concerns arise

Both Canada and the United States have laws and systems in place that support the immediate recall of a vaccine and/or nondistribution of a lot of vaccine if there is a safety alert or detected problem. In December 2007, Health Canada placed three lots of measles, mumps and rubella (MMR) vaccine on hold while the Department investigated five suspected cases of anaphylaxis in Alberta patients who had received vaccine from these lots (14). The review found no link between the MMR vaccine lots and the adverse event. The rapid response post-licensure to reports of intussusception following RotaShield immunization in the United States in 1999 and the MMR vaccine in Canada noted above demonstrates how effectively these systems work.

7. Expert causality assessment review of serious adverse events following immunization

Serious adverse events following immunization, such as deaths or hospitalizations, undergo rigorous scrutiny to determine causality. In Canada, this review is done by the Advisory Committee on Causality Assessment, a committee composed of independent experts in infectious diseases, public health, vaccine safety, epidemiology, pathology, neurology and

paediatrics (15). When needed, additional expertise is sought for complex cases. The committee's decisions are independent of government and vaccine manufacturers. The results of these assessments are followed up by the Centre for Immunization and Respiratory Infectious Diseases of the Public Health Agency of Canada. They are used to detect signals of rare, vaccine-attributable adverse events as well as being used for vaccine recommendation adjustments and education purposes in collaboration with the National Advisory Committee on Immunization and with the provincial and territorial immunization programs.

8. International collaboration

Canada, the United States and many other countries share their data on adverse events following immunization and signal detection with the World Health Organization that gathers data on vaccine adverse events from around the world. The World Health Organization created the Global Advisory Committee on Vaccine Safety in 1999 to respond to vaccine safety issues of potential global importance in a prompt, efficient and scientifically rigorous manner (16).

CONCLUSION

Given that immunization is not mandatory for school entry in Canada, vaccine uptake is a direct result of access to vaccines and a receptive public that understands the benefits of vaccines and trusts the vaccines and the system that ensures vaccine safety. Despite best efforts to bolster trust through the provision of up-to-date vaccine safety and efficacy data, trust is continually being challenged by the ever-growing onslaught of accusations about vaccine safety. Our attempts to refute these claims one by one through scientific studies, while important and necessary, have not always been sufficient to maintain and enhance public trust.

Given the breadth, depth and rigour of our vaccine safety system including our ability to rapidly detect potential vaccine safety alerts, and the lack of knowledge about this on the part of both health providers and the general public, it is time to aggressively address this knowledge deficit. Health care workers, especially those who immunize, need to know about and share with the public and families the many checks and built-in alarm systems in the Canadian vaccine safety program that make the system trustworthy.

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COMMENTAIRE SUR LES MALADIES INFECTIEUSES EN PÉDIATRIE

Le programme d'innocuité vaccinale canadien en huit étapes : des notions en matière de vaccination



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La vaccination pour contrôler de graves infections est l'une des réalisations remarquables de la médecine préventive. Toutefois, conjointement avec le succès croissant de la prévention vaccinale de grands fléaux comme la polio, la rougeole, l'*Haemophilus influenzae* de type b envahissante et l'hépatite B, dans plusieurs pays, on constate une augmentation de l'inquiétude parentale envers l'innocuité des vaccins (1,2). Désormais, certains parents s'inquiètent tellement de l'innocuité vaccinale qu'ils décident de ne pas faire vacciner leurs enfants, ce qui donne des résultats parfois tragiques (3-5). La peur engendrée par les liens présumés entre les vaccins et des troubles comme l'autisme, la mort subite du nourrisson, les troubles de démyélinisation et les troubles neurodéveloppementaux est symptomatique de la méfiance envers l'innocuité de l'ensemble du système vaccinal. Chaque nouvelle allégation d'inquiétude à l'égard de l'innocuité vaccinale alimente cette méfiance. De plus en plus de parents ne croient tout simplement pas en la sécurité du système vaccinal.

L'érosion de la confiance du public envers les vaccins semble se poursuivre malgré plus de 20 ans d'efforts pour informer le public des risques des maladies évitables par un vaccin ainsi que des bienfaits et de l'excellent profil d'innocuité des vaccins recommandés pour les enfants. Une démarche élargie s'impose pour assurer et, au besoin, rétablir la confiance du public envers les vaccins. Les dispensateurs de soins qui participent à l'administration des vaccins ont un rôle essentiel à y jouer. Le présent commentaire sur les maladies infectieuses en pédiatrie

expose une stratégie pour aider les dispensateurs de soins à accroître la confiance du public envers les vaccins.

COMMENT FAIRE FACE À CE PROBLÈME FONDAMENTAL DE MÉFIANCE ENVERS LE SYSTÈME VACCINAL?

La confiance se bâtit à partir d'un ensemble de soins et de compétences. Ces deux éléments sont nécessaires. Nous n'avons pas réussi à expliquer le fort degré de réglementation et de surveillance de l'innocuité qui garantit le système vaccinal le plus sécuritaire possible et nous n'avons pas toujours fait preuve d'empathie envers les préoccupations en matière d'innocuité vaccinale. Nous ne devrions donc pas être surpris si certains parents ne se sentent pas rassurés lorsque les professionnels de la santé se contentent de leur dire : « Ce vaccin est sécuritaire, ne vous inquiétez pas. » Pour accroître la confiance du public envers les vaccins, il faudrait peut-être améliorer les connaissances au sujet des vaccins, c'est-à-dire faire mieux comprendre les nombreux éléments intégrés à la surveillance de l'innocuité, qui garantissent que les vaccins sont les plus sécuritaires possible.

À Cuba, par exemple, on fait beaucoup confiance au système vaccinal, en partie parce que les soins de santé et l'éducation pour tous constituent des « trésors » très prisés de la révolution (6). L'éducation pour tous a favorisé des taux élevés d'alphabétisation, qui accordent une place importante aux connaissances en santé. Le Cubain moyen sait pourquoi les vaccins sont bénéfiques tant pour les individus que pour

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