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In this supplement: Vaccine Safety

Canada has one of the best vaccine safety surveillance systems in the world yet few people appreciate how it works. Read about the adverse events that were tracked in 2012, and the early detection and response system we have in place to identify vaccine safety issues. See the Useful links section to see how our capacity has been recently strengthened with the funding of the Canadian Immunization Research Network.

Invited Editorial

Surveillance

Commentaries

Useful links

Canadian Immunization Research Network (CIRN). Strengthening Canada's Immunization Research Capabilities. www.cirnetwork.ca/

Public Health Agency of Canada. Canadian Immunization Guide. Part 2: Vaccine Safety
http://www.phac-aspc.gc.ca/publicat/cig-gci/p02-eng.php

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Vaccine vigilance in Canada: Is it as robust as it could be?

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Abstract

Canada has been known to have one of the better vaccine safety surveillance capacities in the world, but in the early 2000s, it was noted there was still room for improvement. How has Canada done over the last decade and is there more to be done? Canada has done well. First, there has been significant progress made by the Vaccine Vigilance Working Group to enhance the passive vaccine safety monitoring system and address potential issues arising from the review of surveillance data and cases or clusters of concern. Second, there has been an increased investigative capacity for clusters of adverse events and other vaccine safety issues, including an assessment and referral system for individuals with adverse events following immunizations (AEFIs). Third, the use of the Brighton Collaboration definitions and other international standards has facilitated international collaboration and represents the best standard of practice.

Despite all these improvements, however, there is more that could be done. The sensitivity of Canada's passive surveillance system still varies from one province and territory to another. The timeliness of the data exchange flow could improve. The AEFI Signal Response Protocol, which identifies the processes and required actions for timely management of any newly detected or emerging vaccine safety signals, is a critical piece of a robust vaccine safety system but it is still in the making. It is commendable that Canada has decided to expand its focus on evaluation research from influenza vaccines to vaccine-preventable diseases more broadly, with the establishment of the Canadian Immunization Research Network (CIRN). CIRN's newly developed Provincial Collaborative Network and the move toward record linkages is excellent. These new investments are welcome in light of the rich vaccine development pipeline, the increased pool of available vaccines, and the growing set of technologies for vaccines production, delivery, and safety monitoring. What would round this all out would be a stronger capacity to monitor the implementation of vaccination programs and vaccine coverage, and better documentation of the reduction of the disease burden attributable to vaccination programs. Canada's investment in vaccines for the health of all deserves no less.

Introduction

This special theme issue on vaccine safety is indeed important and welcome. First, it is opportune to review the situation and progress in sustaining and further developing one of the critical elements of the National Immunization Strategy (1) 11 years after its establishment. Second, it is desirable to review how Canada is delivering on one of the key elements of the Global Vaccine Action Plan 2011−2020 of the Decade of Vaccines (2), approved by the World Health Assembly in May 2012, that highlights the importance to detect and promptly analyze serious adverse events following immunization (AEFI). Third, it is essential to inform health care professionals and the public about the processes and activities that are continuously in place to ensure vaccine safety, but often go unnoticed. Fourth, it is useful to consider if the current system is now optimal or if there is more to be done to fill the remaining needs and gaps.

Background

The six papers presented in this supplement on vaccine safety (3,4,5,6,7,8) have been specially selected to collectively represent a series of complementary aspects of what goes into vaccine vigilance: monitoring, signal generation, investigation and response, together with the role of research networks that allow for quick implementation of vaccine research and clinical trials. They highlight the best assets of Canadian vaccine vigilance and provide examples of provincial/territorial resources, activities and capacity. Among the strengths of the Canadian vaccine vigilance program is its ability for crisis communication and informing health professionals and the public of emerging risks.

Although these papers identify quite a few of the elements needed to ensure vaccine safety, even more goes into this. There are additional elements that work to ensure vaccine safety in Canada. These include: the international norms and standards and processes for the development, production and quality control of vaccines; the role of the national regulatory authority; the role of the public health advisory bodies on decision making such as the National Advisory Committee on Immunization (NACI), the Canadian Immunization Committee (CIC), and provincial advisory bodies such as the Comité sur l'immunisation du Québec; the supply chain and health delivery infrastructure; and the role of pre- and post-curriculum training and standards set by professional bodies that lead to the following of best practices by health care professionals delivering immunization.

Canada strengthened its vaccine safety monitoring capabilities in the 1990s (9),with a passive surveillance system, the Immunization Monitoring Program, ACTive (IMPACT), signal generation, and the ability for public health response that included investigative ability and review/follow-up of AEFIs by the then Health Canada's Advisory Committee on Causality Assessment (ACCA) (10).

Indeed, Canada's vaccine vigilance was (11) and continues to be highly regarded at the global level. Canada is a major contributor to global vaccine safety not only through its surveillance systems and investigative capacity, but also through ongoing contributions by its vaccinology and vaccine safety experts to global vaccine pharmacovigilance activities, including the strengthening of the capacities of developing countries. The Global Vaccine Safety Blueprint highlighted in the Global Vaccine Action Plan calls for the establishment of a global vaccine safety support structure (12). There is no doubt that Canada has contributed vastly to this initiative; in turn, this global structure complements the Canadian vaccine vigilance program.

Despite its strength, in 2003, the National Immunization Strategy (1) noted some limitations of the vigilance system and highlighted the need for it to be optimized to maintain professional and public confidence and address growing anti-immunization concerns. The National Immunization Strategy called for improvements in both the monitoring system and the public health response. So, how has Canada done?

Progress to date

To date, Canada has delivered on some of the elements called for in the 2003 National Immunization Strategy. One major indicator of progress has been the formalization of a network of dedicated federal/provincial/territorial vaccine safety contacts in all jurisdictions Health Canada's Biologic and Genetic Therapies Directorate (the regulator) and the IMPACT network through the Vaccine Vigilance Working Group (3). This Working Group identifies potential issues through the review of surveillance data and cases/clusters of concern, enhancing the passive system of ongoing vaccine safety monitoring. This facilitates the production of timely national surveillance reports on adverse events following immunization. Second is the improvement of public health response with the establishment of a clinical assessment/referral system to assess and follow up with individuals who have suspected AEFIs (7). Third is the noticeable improvement of the investigative capacity both for clusters of adverse events and for vaccine safety issues that may emerge from surveillance signals through the various clinical and research networks (7,8). Finally, another positive development is the use of the Brighton Collaboration definitions

and harmonization of tools with international standards that not only facilitate international collaboration but also represent the best standard of practice in vaccine vigilance (6,13,14).

Optimization

So is Canada's vaccine vigilance system optimal or is there more that could be done? Although robust, the current Canadian system could be improved further. Sensitivity still varies from one jurisdiction to another. Furthermore, despite the regular release of quarterly public safety postings, the timeliness of the data exchange flow could be improved (6, 15). Over the next three years, the plan for IMPACT to transition to electronic reporting will enable faster transmission and follow-up of information (5). While IMPACT captures approximately 90% of paediatric tertiary care beds in Canada, it would be useful to improve the representation in Ontario and, ideally, capture all paediatric admissions in the country (5). Finally, the work of the Vaccine Vigilance Working Group to create an AEFI Signal Response Protocol that will describe the critical processes and required actions for timely management of any newly detected or emerging vaccine safety signals is still ongoing, long after the establishment of the Working Group itself (3).

To date, there has been limited focus of active surveillance of the adult population. One welcome development is the transformation of the Public Health Agency of Canada and Canadian Institutes of Health Research Influenza Research Network (PCIRN), with its focus only on influenza, into the broader Canadian Immunization Research Network (CIRN) that has capacity for rapid clinical trials to investigate vaccine safety issues. The provincial collaborative network created under CIRN and its evolution to move toward record linkages is excellent (7). It is worth noting that in 2007 Belize, with Canadian technical assistance, deployed a country-wide fully integrated patient-centred health information system (which required vaccine bar coding) with embedded disease management for $4 (CAD) per citizen with definite positive outcomes (16). The Canadian Paediatric Surveillance Program, established nearly 20 years ago, is one of the other tools that Canada enjoys and that was and could still be used for completing its vaccine vigilance armamentarium (17).

Vaccine safety is one of the elements of vaccination decision making and one must keep in mind the benefit-risk assessment that needs to be maximized. Given the focus of this supplement on vaccine safety, the IMPACT report does not do justice to the very valuable contribution of the network in assessing the reduction of the disease burden attributable to vaccination programs and complementing Canada's disease surveillance system. Of course this goes hand in hand with the monitoring of the implementation of the vaccination programs. A similar look into Canada's capacity for timely monitoring of vaccine coverage in all age groups would be of interest. It is clear from the articles presented in this supplement that vaccine vigilance in Canada has been strengthened over the last decade, but it could be even more robust.

Conclusion

As a country, Canada has one of the best vaccine safety surveillance capacities in the world. So why should we continue to optimize our vaccine vigilance system? As Ward noted in 2000, we need a strong vaccine safety system that stays in step with the accelerating pace of vaccine development (18). Now, almost 15 years later, it is even more important that vaccine safety monitoring keep pace with the advances that have been made. There are an increasing number of vaccines currently in use, a rich vaccine development pipeline, and a growing set of technologies in place for vaccines production and delivery. Today, the total cost of all vaccines required to complete the national immunization schedule for one person is in excess of $1,000 (CAD). This merits an optimal investment in a vaccine safety monitoring system—Canada's investment in vaccines for the health of all deserves no less.

Declaration

The opinions expressed in this article are those of the author and do not necessarily represent the decisions, official policy or opinions of the World Health Organization. From 1989 through 1991, Philippe Duclos served as Head, Vaccine-Associated Adverse Event Section, Laboratory Centre for Disease Control, Health Canada; and from 1991 through 1998, served as Chief, Division of Immunization, Laboratory Centre for Disease Control, Health Canada, in Ottawa, Canada.

Conflict of interest

None

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Canadian Adverse Events Following Immunization Surveillance System (CAEFISS): Annual report for vaccines administered in 2012

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Abstract

Background: To describe the adverse event following immunization (AEFI) reporting profile for vaccines administered in Canada during 2012 and surveillance trends relative to reports for vaccines administered from 2005 through 2011.

Methods: Analysis of data based on AEFI reports received by the Public Health Agency of Canada by April 30, 2013, for vaccines marketed in Canada and administered from January 1, 2005, through December 31, 2012.

Results: The AEFI reporting rate was 10.1 per 100,000 population in Canada for vaccines administered in 2012 and was inversely proportional to age. There was a trend of declining rates from 2005 (14.8) to 2012 overall and by age group. The vast majority of reports (94%−95%) were non-serious involving reactions at or near the vaccination site, rash and febrile events.

Conclusion: Canada has a strong pharmacovigilance system for vaccines with one of the highest AEFI reporting rates in developed countries. Vaccines marketed in Canada have a very good safety profile. This report enables comparisons across jurisdictions in Canada and globally.

Introduction

The Canadian Adverse Events Following Immunization Surveillance System (CAEFISS) is a collaborative effort of federal, provincial and territorial (F/P/T) public health authorities that dates back to 1987 (1,2). At the national level, CAEFISS is managed by the Public Health Agency of Canada's (PHAC's) Vaccine Safety Section, within the Centre for Immunization and Respiratory Infectious Diseases. National reports on vaccine safety have been published periodically (2,3,4,5,6,7,8,9,10,11). The last published report focused on safety surveillance data for vaccines administered in 2004 along with annual reporting trends back to 1992 (11). The primary purpose of this report is to summarize the adverse event following immunization (AEFI) reports received at PHAC for vaccines administered in 2012 and provide annual comparative data for vaccines given from 2005 through 2011. It also introduces a standard format for future annual reports that will facilitate year-to-year comparison for the national report as well as comparison to reports from other jurisdictions in Canada (12) and globally (13,14).

The objectives of CAEFISS are to: continuously monitor the safety of marketed vaccines in Canada; identify increases in the frequency or severity of previously identified vaccine-related reactions; identify previously unknown AEFIs that could possibly be related to a vaccine; identify areas that require further investigation and/or research; and provide timely information on AEFI reporting profiles for vaccines marketed in Canada that can help inform immunization-related decisions (15).

To achieve these objectives CAEFISS includes enhanced passive as well as active syndromic surveillance. The former includes all systems in place to monitor and report AEFIs in Canada's provincial/territorial and federal immunization programs and is considered enhanced because emphasis has always been placed on reporting designated adverse events of special public health importance which are listed as checkboxes on the national AEFI report form (16). All provinces and territories actively promote reporting within their regions (17).

Active syndromic surveillance has been conducted since 1991 by the Immunization Monitoring Program ACTive (IMPACT) (18). IMPACT is funded by the Agency through a contract with the Canadian Paediatric Society and currently includes 12 paediatric centres across Canada representing over 90% of all paediatric tertiary care beds in the country (19,20). IMPACT screens hospital admissions for neurologic events (e.g., seizures, encephalitis, acute flaccid paralysis, including Guillain-Barré syndrome, aseptic meningitis), thrombocytopenia, vaccination site abscess/cellulitis, and other complications that may have followed immunization. Any found to be temporally linked to immunization without clear explanation are reported as AEFI.

All F/P/T and IMPACT AEFI reports have personal identifiers removed and are then forwarded to PHAC for national collation, signal detection and report generation. From 1987 through 2010 Market Authorization Holders also reported to PHAC. In January 2011, a change in reporting regulations required Market Authorization Holders to report directly to Health Canada; since then, several of them have stopped reporting to PHAC.

A more complete explanation of the respective roles and responsibilities for post-market pharmacovigilance of Health Canada, PHAC, and F/P/T immunization authorities can be found in the "Vaccine Safety" chapter of the *Canadian Immunization Guide* (21) and at the CAEFISS web page (15).

Methods

CAEFISS report processing

All AEFI reports are entered into the CAEFISS database and coded using the international Medical Dictionary for Regulatory Activities (MedDRA). A systematic Medical Case Review is also done by trained health professionals to classify each report by the single most important reason for reporting (Primary AEFI, **Table 1**) and severity (**Table 2**).

Table 1: Medical Case Review adverse event following Immunization (AEFI) categories and sub-types used for purposes of classification

Category	AEFI category sub-types
Reactions at or near the vaccination site	Abscess (infected or sterile) Cellulitis Extensive limb swelling Pain in the vaccinated limb of 7 days or more Other local reaction
Allergic or allergic-like events	Anaphylaxis Oculo-respiratory syndrome (ORS) Other allergic events
Neurologic events	Encephalitis/Acute Disseminated Encephalomyelitis(ADEM)/Myelitis Cerebellar Ataxia Aseptic Meningitis Guillain-Barré syndrome (GBS) Bell's palsy Other paralysis lasting >1 day Seizure Other neurologic event

Rash only	Generalized, localized, or location not specified
Other events specified on the CAEFISS report form	Arthritis Hypotonic-hyporesponsive episode (HHE) Intussusception Paraesthesia/Anaesthesia Parotitis Persistent crying Thrombocytopenia
Systemic events not specified on the CAEFISS report form	Fever alone Infection Influenza-like illness Other general symptom(s) Rash with fever and/or other illness Syndrome
Vaccination anxiety-related events	(no subtype)
Miscellaneous other events	Gastrointestinal disorders Vaccine failure Other events
Vaccination error without an associated AEFI	(no subtype)

Table 2: Severity classification for primary adverse event following immunization (AEFI) in the Medical Case Review

Severity	Criteria
Serious	• Fatal outcome • Results in hospitalization or prolongation of hospitalization for ≥24 hours • Results in persistent or significant disability/incapacity • Congenital anomaly or birth defect • Life-threatening
High impact	• Results in hospitalization for <24 hours • Requires medically supervised observation outside of hospital • Requires ≥3 separate physician assessments during acute AEFI episode • Requires outpatient intravenous therapy (e.g., for antibiotics or rehydration) • Prevents performance of daily activities for ≥4 days
Moderate impact	• Results in 1−2 unscheduled urgent or non-urgent physician assessments • Requires emergency medical services to come to immunization clinic • Results in a new drug prescription or increased dose of an existing drug • Prevents performance of daily activities for 1 to 3 days
Low impact	• Requires treatment limited to immunization clinic setting by on-site staff • Requires health professional advice/reassurance without a scheduled visit • Requires non-prescription medication for symptomatic relief • Prevents performance of daily activities for <24 hours • No discernible impact

Key definitions

An adverse event following immunization (AEFI) is “any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the usage of the vaccine. The adverse event may be any unfavourable or unintended sign, abnormal laboratory finding, symptom or disease” (22).

In 1994 the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use defined seriousness criteria for expedited reporting of AEFIs (23). A serious AEFI (SAE) is one that results in death, is life-threatening, requires in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect (23). Expedited reporting is defined as no later than 15 calendar days after initial recognition of the AEFI and preferably as soon as possible. At PHAC, all SAE reports are reviewed by a physician.

An unexpected AEFI is an adverse event, the nature or severity of which is not consistent with domestic labelling or expected from the characteristics of the vaccine (23).

For purposes of Medical Case Review classification, national case definitions were used where available, including published Brighton Collaboration case definitions (24,25,26,27,28,29,30,31,32,33,34,35,36,37), and CAEFISS User Guide definitions for Oculo-Respiratory syndrome (ORS), Bell's palsy, arthritis, parotitis, anaesthesia and paraesthesia (38).
Additional definitions included:

- Extensive limb swelling of an entire proximal and/or distal limb segment with segment defined as extending from one joint to the next (39).
- Cerebellar ataxia: sudden onset of truncal ataxia and gait disturbances (40). Of note, this assumes absence of cerebellar signs appearing with other evidence of encephalitis or Acute Disseminated Encephalomyelitis (ADEM), in which case it would be classified according to the Brighton case definition (28).

Data extraction and analysis

All AEFI reports received by April 30, 2013, where the date of vaccine administration was between January 1, 2005, and December 31, 2012, were extracted from CAEFISS. Reports where the only administered vaccine was one of the pandemic H1N1 vaccines were excluded since these products were used exclusively in 2009−2010, confounding comparison of reporting trends for vaccines administered in 2012 versus 2005−2011.

All data analyses were conducted using the statistical software system, SAS 9.3. Reporting rates per 100,000 were calculated using annual population estimates for 2005–2012 by age, sex, province/territory (41).

Information on total vaccine doses distributed in 2011 and 2012 was provided by the Market Authorization Holders and is considered proprietary information. To enable presentation of total AEFI and SAE reports for vaccines administered in 2012 and reporting rates per 100,000 doses distributed without making it possible to calculate specific annual doses distributed, the rates were calculated using combined 2011 and 2012 data. Vaccines were grouped by antigenic content for purposes of analysis.

Results

Total reports and reporting rates

Of 38,364 extracted AEFI reports, 5,204 involving pandemic vaccine given alone were excluded since this vaccine was used only in 2009−2010. Of the 33,160 reports for analysis, the distribution of AEFI (% SAE) reports by year vaccine administered was: 2005: 4,792 (4.5%); 2006: 4,417 (4.8%); 2007: 4,258 (5.3%); 2008: 4,482 (4.7%); 2009: 4,099 (5.8%); 2010: 4,046 (5.9%); 2011: 3,558 (5.8%); 2012: 3,508 (5.4%).

Age-specific reporting rates per 100,000 population by year vaccine administered for all of Canada are shown in **Table 3**. For all years of vaccine administration, the highest reporting rates were observed for 1- to <2-year-old children followed closely by infants <1 year old with a sharp drop-off for 2 to <7 year-olds, 7 to <18 year-olds, and adults aged 18 years and older. There was a consistent downward trend in reporting rates throughout the period, most noticeable in children <7 years and for AEFI as opposed to SAE rates.

Table 3: Annual age-specific AEFI[1] and SAE[2] reporting rates per 100,000 population for vaccines administered from 2005 through 2012

Age group	AEFI (SAE) reporting rates per 100,000 population							
	2005	2006	2007	2008	2009	2010	2011	2012
<1 year	176(16)	161(16)	169(18)	134(12)	152(19)	150(20)	136(15)	130(12)
1 to <2 years	305(22)	290(24)	276(22)	283(22)	238(18)	217(18)	202(17)	152(16)
2 to <7 years	47.1(1.2)	36.7(1.1)	31.5(1.2)	31.0(1.2)	27.8(1.0)	28.7(1.0)	28.8(1.4)	25.2(1.2)
7 to <18 years	11.9(0.5)	11.4(0.4)	9.5(0.4)	15.1(0.6)	12.3(0.5)	12.0(0.4)	9.7(0.6)	11.2(0.4)
18 to <65 years	6.5(0.2)	6.0(0.1)	6.0(0.1)	5.6(0.1)	4.9(0.2)	4.7(0.1)	4.2(0.1)	5.0(0.1)
65+ years	8.0(0.3)	6.6(0.2)	6.3(0.2)	6.8(0.2)	4.3(0.3)	7.1(0.5)	5.3(0.3)	5.8(0.3)
All ages	14.8(0.7)	13.5(0.6)	12.9(0.7)	13.4(0.6)	12.1(0.7)	11.9(0.7)	10.3(0.6)	10.1(0.6)

[1] Adverse event following immunization (AEFI)
[2] Serious adverse event (SAE)

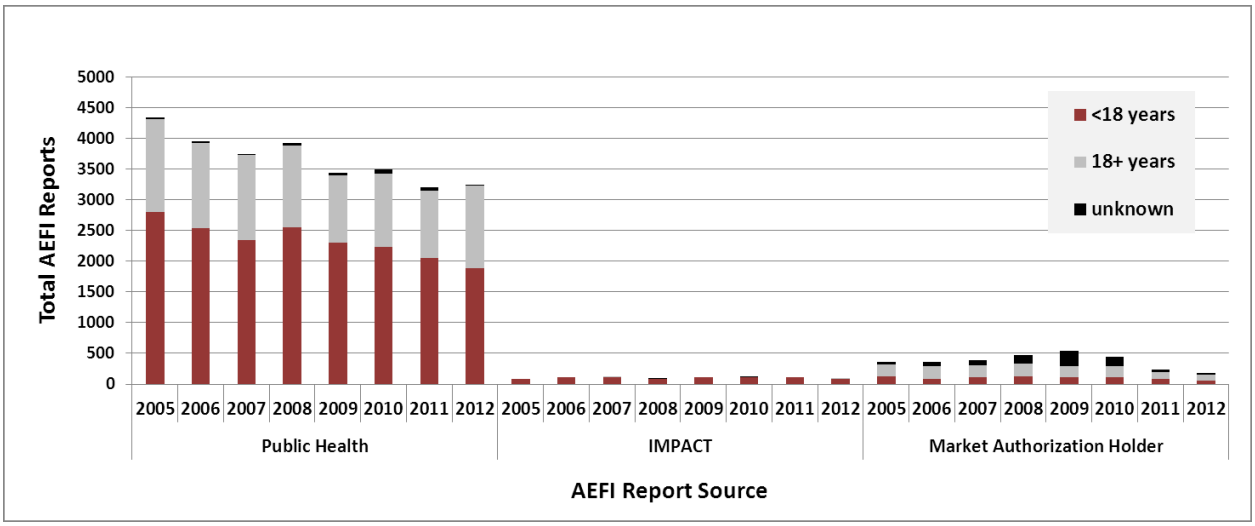
The explanation for the observed drop in reporting rates overall and by age group is likely multi-factorial based on changes in publicly funded immunization programs as well as guidelines for AEFI reporting. Several P/Ts introduced universal meningococcal conjugate and varicella immunization programs for infants from 2004 to 2006 and HPV (human papillomavirus) programs for school girls from 2007 to 2010. Several associated age-specific catch-up campaigns were also conducted; most of these were completed by 2011 or 2012. Additionally, several provincial jurisdictions now discourage the reporting of expected milder events such as most vaccination site reactions. Another important caveat is that there has been less time to receive reports for vaccines administered in 2012 than other years. The April 30th cut-off for including reports was based on the observation that over 80% of reports for vaccines administered in a given calendar year will have been received within four months of the end of the calendar year. The numbers for 2012 will be updated as part of the annual report for vaccines administered in 2013.

A total of 46,481,347 doses of vaccine were distributed in Canada in 2011 and 2012, giving reporting rates per 100,000 doses distributed of 15.2 for all AEFI and 0.85 for SAE.

Reporting sources

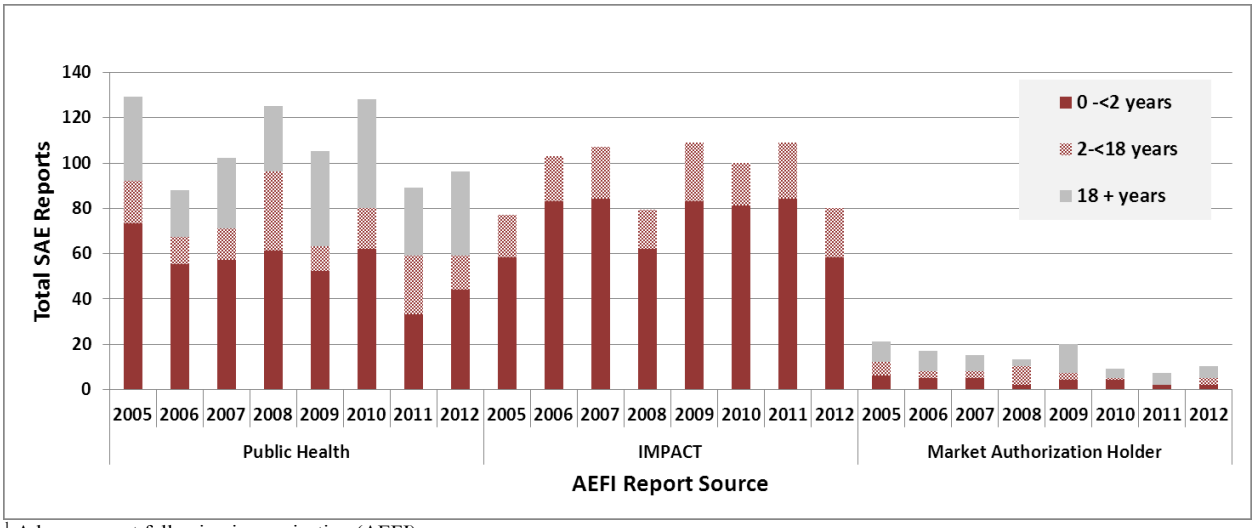
Figures 1A and **1B** show AEFI and SAE reporting source distribution, stratified by age group, for vaccines administered from 2005 to 2012. Notably, for children aged <18 years IMPACT submitted, on average, 4.1% of all AEFI reports, but generated 54.3% of all SAEs. A noticeable trend is the drop off in the number of Market Authorization Holder (MAH) reports following the 2011 change in regulatory reporting. From 2005 through 2010 MAH reports made up 9.8% of all AEFI and 7.1% of all SAE reports. For 2011 and 2012 the relative contribution decreased to 6.0% of all AEFI reports and 4.3% of all SAE reports. Given the volume of reports from F/P/T immunization programs and IMPACT, this change has not been substantial for CAEFISS reporting trends; furthermore, the reports are collected and reviewed by Health Canada's Marketed Health Products Branch so information is not lost.

Figure 1A: AEFI[1] reporting sources for children and adults by year vaccine administered, 2005–2012



[1] Adverse event following immunization (AEFI)

Figure 1B: Serious AEFI[1] (SAE)[2] reporting sources for children and adults by year vaccine administered, 2005–2012



[1] Adverse event following immunization (AEFI)
[2] Serious Adverse Event (SAE)

Age and gender distribution

For vaccines administered in 2012, the age distribution among AEFI (SAE) reports was: <1 year: 14% all AEFIs (24% all SAEs); 1 to <2 years: 16% (32%); 2 to <7 years: 14% (12%); 7 to <18 years: 14% (9%); 18 to <65 years: 32% (14%); 65+ years: 9% (8%); and unknown age: 1% (1%). The distribution has remained fairly constant over time (data not shown). The higher proportion of serious reports among younger children reflects the contribution of active syndromic surveillance by IMPACT.

With respect to gender, the female to male ratio remained fairly constant for vaccines administered from 2005 through 2012 for children under 7 years (range 0.8−0.9) and for all adults (range 3.4−4.1). In contrast, the ratio for children aged 7 to <18 years rose steadily from 1.1 in 2005 to 1.6 in 2007, peaked at 2.3 in 2011, and then dropped to 1.8 in 2012. The changes were consistent with the introduction of female targeted universal HPV vaccination programs, starting with Ontario in 2007, all other provinces by 2008 and the territories by 2010, along with catch-up programs for older school-aged girls which were largely completed before 2012.

AEFI health care utilization and outcomes for vaccines administered in 2012

The distribution of associated health care utilization was: none for 24.5%; health professional advice for 5%; non-urgent medical assessment for 35.9%; urgent medical assessment for 17.9%; hospital admission for 5.2%; prolongation of an existing hospital stay for 0.1%; and unknown for 11.4% of reports. The only temporal reporting trend was that utilization was specified for an increasing proportion of reports along with slight increases in the proportion receiving urgent or non-urgent medical assessment (data not shown).

The distribution of outcome status was: 67.8% fully recovered; 16.2% not yet recovered; 0% with permanent disability; 0.1% fatal outcome; and 15.8% unknown. There were no significant temporal trends for vaccines administered from 2005 through 2012 (data not shown). Fatal outcomes and permanent disability are rarely reported (yearly range of 5−14 and 0−11 total reports, respectively).

Reported adverse events

Table 4 shows the MedDRA System Organ Class distribution of all reported AEFIs for all vaccines administered in 2012, along with comparative distributions for vaccines administered in 2011, and from 2005 through 2010. The only System Organ Class category with a sizable steady temporal increase was “immune system disorders”: from 5.8% for vaccines administered from 2005 to 2010, to 8.9% for 2011, and 14.0% for 2012. The 490 reports for vaccines administered in 2012 were all related to allergic AEFI preferred terms (mostly hypersensitivity, some anaphylaxis and two type III immune complex disorder); only 11 (2.2%) were serious. When cross-referenced with the primary AEFI classification, the majority were other allergic (198), rash alone (153), anaphylaxis (50), or vaccination site reactions (43). There was a single case of arthritis, one erythema multiforme, one serum sickness, and no immune disorders of concern. The reports of anaphylaxis were distributed across multiple ages and vaccines and there were no lot-specific clusters.

Table 4: System Organ Class distribution for all reported AEFI[1] and SAE[2] for vaccines administered from 2005−2012 (the average % distribution is shown for 2005−2010)

System Organ Class	% of AEFI reports with at least one SOC term[3]		
	2005−2010	2011	2012
Blood and lymphatic system disorders	2.1	2.7	1.9
Cardiac disorders	1	1.4	1.6
Congenital, familial and genetic disorders	0	0	0
Ear and labyrinth disorders	0.6	0.9	1.1
Endocrine disorders	0	0	0.1
Eye disorders	5.7	6.7	6.6
Gastrointestinal disorders	14.9	19.3	20.2
General disorders and administration site conditions	61.2	66.6	66.7
Hepatobiliary disorders	0.1	0.1	0.1
Immune system disorders	5.8	8.9	14.0
Infections and infestations	7.0	10.1	11.5

Injury, poisoning and procedural complications	1.8	3.3	3.1
Investigations	6.9	4.6	2.9
Metabolism and nutrition disorders	3.4	3.9	3.9
Musculoskeletal and connective tissue disorders	8.4	10.6	10.3
Neoplasms benign, malignant and unspecified (including cysts and polyps)	0	0	0
Nervous system disorders	19.5	20.4	21.6
Pregnancy, puerperium and perinatal conditions	0.1	0	0
Psychiatric disorders	2.6	2.2	2.1
Renal and urinary disorders	0.2	0.3	0.4
Reproductive system and breast disorders	0.2	0.1	0.3
Respiratory, thoracic and mediastinal disorders	9.3	11.8	11.4
Skin and subcutaneous disorders	35.2	40.0	37.6
Social circumstances	0.2	0.1	0.1
Surgical and medical procedures	0.1	0.1	0
Vascular disorders	3.1	3.4	4.2

[1] Adverse event following immunization (AEFI)
[2] Serious Adverse Event (SAE)
[3] Each AEFI report can have multiple AEFI terms falling into different System Organ Class (SOC) categories so the total for each vaccination period will exceed 100% of reports.

Primary reason for reporting

Table 5 shows the results of the Medical Case Review classification of the 3,508 AEFI reports following vaccines administered in 2012 including, for each main category, the AEFI and SAE reporting rates per 100,000 doses distributed and the proportion of specific AEFI types.

Table 5: AEFI[1] distribution, seriousness, and reporting frequency based on Medical Case Review

Adverse events following immunization (AEFI) category	Total AEFI/ Serious adverse events (SAE)	Reporting rate per 100,000 doses distributed		Category distribution by specific type of AEFI	Type % SAE
		All cases	SAE		
Reactions at or near the vaccination site	1,238/20	5.25	0.08	1.5% Abscess	5
				17% Cellulitis	7
				14% Extensive limb swelling	2
				1.5% vaccinated limb pain >7 days	0
				66% Other local reaction	0.1
Allergic or allergic-like events	443/10	1.88	0.04	11.7% Anaphylaxis	12
				8.6% Oculo-respiratory syndrome	3
				79.7% Other allergic event	0.5
Neurologic events	147/64	0.62	0.27	6.1% Encephalitis/Myelitis	67
				0.7% Ataxia/Cerebellitis	100
				1.4% Aseptic meningitis	100
				3.4% Guillain-Barré syndrome	80
				9.5% Bell's palsy	7
				1.4% Other paralysis of >1 day duration	50
				67.3% Seizure	43
				10.2% Other neurologic event	40
Rash alone	694/0	2.94	0		
Other events specified on	153/21	0.65	0.09	11.8% Arthritis	0

CAEFISS report form				19.6% Hypotonic Hyporesponsive Episode	33
				2.6% Intussusception	50
				41.8% Paraesthesia	0
				5.2% Parotitis	0
				11.1% Persistent crying	0
				7.8% Thrombocytopenia	75
Systemic events not otherwise specified on the CAEFISS report form	390/52	1.65	0.22	14.9% Fever only	7
				22.9% Infection	20
				7.7% Influenza-like illness	3
				28% Other general symptoms	7
				21.8% Rash with fever/other symptoms add 1 which was SAE	11
				4.7% Syndrome	**61**
Immunization anxiety	**38/2**	**0.16**	**<0.01**		
Miscellaneous other events	**337/20**	**1.43**	**0.08**	**50.7% Gastrointestinal disorder (not intussusception)**	**3.5**
				1.2% Immunization failure	**50**
				48.1% Other	**7**
Immunization error, no AEFI	**68/0**	**0.29**	**0**		

[1] Adverse event following immunization (AEFI)

Table 6 shows the severity and age group distribution within and across the primary AEFI categories. Reactions at or near the vaccination site and rash alone made up 55.1% of all reports received for vaccines administered in 2012 but only 11.2% of SAE reports. In contrast neurologic events accounted for only 4.2% of all reports for 2012 but 43.5% of SAE reports. The IMPACT network, which actively looks for neurologic events, reported 45 (70%) of the 64 serious neurologic events.

Table 6: Primary AEFI category profiles by severity and age group

		Primary AEFI category (total case reports in category)								
		V-site (1,238)	**Allergic (443)**	**Neuro-logic (147)**	**Rash alone (694)**	**Other speci-fied (153)**	**System-ic (390)**	**Anxiety (38)**	**Misc. other (337)**	**V-error (no AEFI) (68)**
Severity distribution by AEFI category[1]	Serious	1.6	2.2	43.5	0	13.7	13.3	5.3	5.6	0
	High impact	1.1	3.6	4.1	0.7	4.6	4.4	10.5	2.7	0
	Moderate impact	57.2	50.8	40.8	47.6	41.8	45.1	63.2	39.8	0
	Low impact	28.2	32.3	5.4	40.9	31.4	25.6	21.1	30.9	55.9
	Unspecified	11.9	11.3	6.1	10.8	8.5	11.5	0	21.1	44.1
AEFI category distribution by level of severity[2]	Serious	10.7	4.8	34.2	0.5	11.2	27.3	1.1	10.2	0
	High impact	17.9	20.5	7.7	6.4	9.0	21.8	5.1	11.5	0
	Moderate impact	41.1	13.1	3.5	19.2	3.7	10.2	1.4	7.8	0
	Low impact	32.3	13.2	0.7	26.2	4.4	9.2	0.7	9.6	3.5
	Unspecified	33.4	11.4	2.0	17.0	3.0	10.2	0	16.1	6.8
Age group distribution by AEFI category[1]	<1 year	3.9	7.7	17.7	18.4	35.3	23.6	0	30.6	20.6
	1 to <2 years	11.4	6.8	40.1	28.8	4.6	28.2	0	5.3	19.1
	2 to <7 years	23.6	7.2	8.2	11.5	0.7	11.5	7.9	4.5	2.9
	7 to <18 years	12.0	20.8	9.5	15.3	7.8	8.5	55.3	12.8	11.8
	18 to <65 years	34.2	48.8	19.7	22.5	46.4	22.1	28.9	35.0	20.6
	65+ years	14.5	8.1	4.1	3.2	4.6	5.4	7.9	8.9	1.5

	Unknown	0.4	0.7	0.7	0.3	0.7	0.8	0	3.0	23.5
AEFI category distribution by age group[2]	<1 year	9.6	6.8	5.2	25.7	10.8	18.4	0	20.6	2.8
	1 to <2 years	24.4	5.2	10.2	34.6	1.2	19.0	0	3.1	2.2
	2 to <7 years	60.6	6.6	2.5	16.6	0.2	9.3	0.6	3.1	0.4
	7 to <18 years	31.2	19.2	2.9	22.2	2.5	6.9	4.4	9.0	1.7
	18 to <65 years	37.7	19.2	2.6	13.9	6.3	7.6	1.0	10.5	1.2
	65+ years	58.7	11.8	2.0	7.2	2.3	6.9	1.0	9.8	0.3
	Unknown	35.3	12.6	4.2	19.8	4.4	11.1	1.1	9.6	1.9

[1] Column totals are 100% for each primary AEFI category.
[2] Row totals are 100% for severity level or age group.

Children aged 1 to <2 years contributed the largest proportion of reports in the neurologic, rash alone, and systemic primary AEFI categories. Children aged 7 to <18 years accounted for 55.3% of the vaccination-related anxiety reactions. Adults aged 18 to <65 were the most prevalent age group for vaccination site, allergic, other specified, and miscellaneous primary AEFI categories. Within each age category the most frequent primary AEFI group reported was vaccination site reactions for all ages 2 years and older versus rash alone for those aged <2 years.

Vaccines administered in 2012

Table 7 lists the vaccines for which at least one AEFI report was received for vaccine administered during the 2012 calendar year, grouped by antigenic content as well as whether or not they were included in Canada's publicly funded immunization programs for routine or limited use, or sold primarily on the private market. For each antigenic grouping, the table provides data on the proportion of reports where there was only a single vaccine given, the total count for AEFI and SAE reports following vaccines administered in 2012, as well as combined 2011−2012 reporting rates per 100,000 doses distributed. Caution is needed in interpreting variation in reporting rates. One notable example is the nearly 4-fold higher rate observed for DTaP-IPV-HB-Hib relative to DTaP-IPV-Hib vaccines, both of which are used for infants at 2, 4 and 6 months of age. The HB containing product is used predominantly in British Columbia which has a significantly higher reporting rate than other provinces (data not shown). Also the doses distributed information does not account for returned or wasted dosages and at best it is a poor proxy for reporting rates for vaccines administered, which are not presently available across Canada.

Table 7: Vaccine abbreviations and groupings used for annual report[1]

Targeted infections	Vaccines marketed in Canada trade name (MAH[2])	Vaccine group abbreviation	% only vaccine given	2012 AEFI	2012 SAE (% AEFI)	Combined 2011−2012 AEFI reporting rate per 100,000 doses distributed
Vaccines used in publicly funded immunization programs						
Diphtheria, Tetanus, Pertussis	Adacel® (SP) Boostrix™ (GSK)	Tdap	67	334	3(0.9)	20.0
Diphtheria, Tetanus, Pertussis, Polio	Quadracel® (SP), Infanrix™-IPV (GSK)	DTaP-IPV	53	176	6(3.4)	101.0
	Adacel®-Polio (SP), Boostrix®-Polio (GSK)	Tdap-IPV	57	60	1(1.7)	15.2
Diphtheria, Tetanus, Pertussis, Polio, H. influenzae type b	Pediacel® (SP), Infanrix™-IPV/Hib (GSK),	DTaP-IPV-Hib	42	498	38(7.6)	37.6

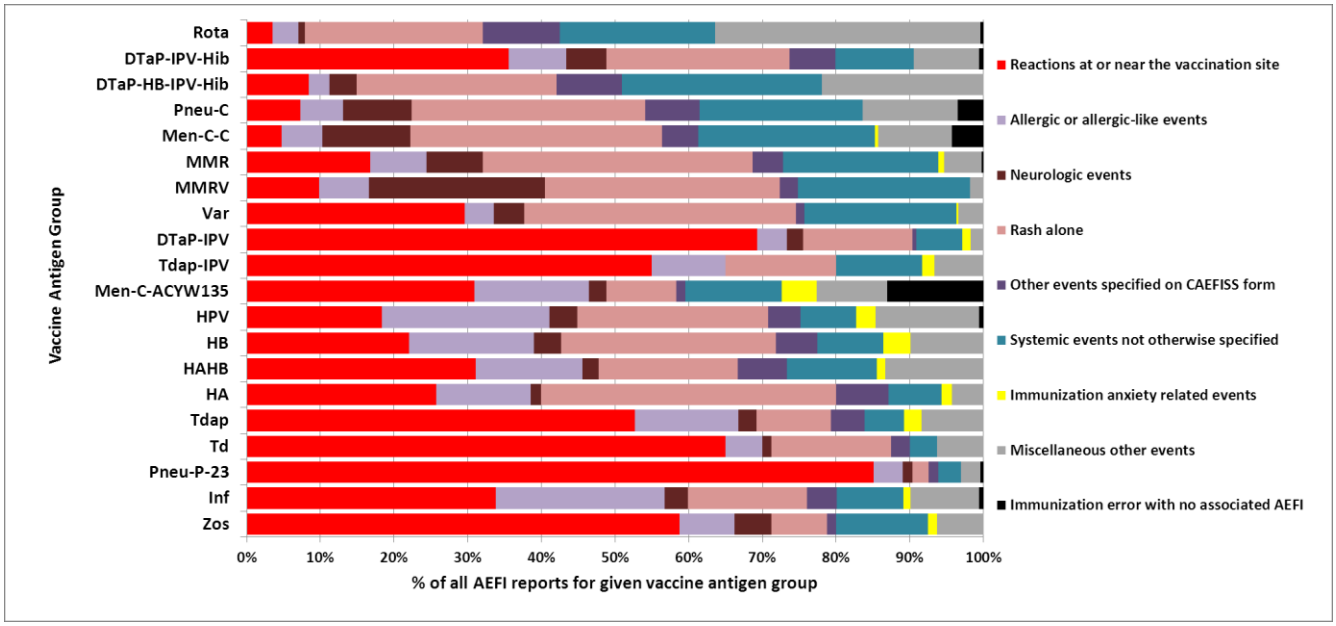
Diphtheria, Tetanus, Pertussis, Polio, H. influenzae type b, Hepatitis B	Infanrix hexa™ (GSK)	DTaP-HB-IPV-Hib	16	214	12(5.6)	148.2
Diphtheria, Tetanus, Polio	Td Polio Adsorbed (SP)	Td-IPV	47	15	1(6.7)	22.1
Diphtheria, Tetanus	Td Adsorbed (SP)	Td	54	80	2(2.5)	10.3
Invasive pneumococcal disease	Prevnar® (Pfiz), Synflorix™ (GSK), Prevnar®13 (Pfiz)	Pneu-C	6	682	78(11.4)	56.8
	Pneumo® 23 (SP), Pneumovax® 23 (MF)	Pneu-P-23	50	228	18(7.9)	38.0
Invasive meningococcal disease	Meningitec® (Pfiz), Menjugate® (NP), Neis Vac-C® (GSK)	Men-C-C	6	468	61(13.0)	85.2
	Menactra® (SP), Menveo™ (NVD), Nimenrix™ (GSK)	Men-C-ACYW-135	48	84	2(2.4)	23.7
	Menomune® - A/C/Y/W-135 (SP)	Men-P-ACYW-135	0	2	0	NC[3]
Hepatitis B	Engerix® -B (GSK), Recombivax HB® (MF)	HB	38	213	11(5.2)	22.0
Hepatitis A, Hepatitis B	Twinrix® & Twinrix® Junior (both GSK)	HAHB	56	90	3(3.3)	10.1
Hepatitis A	Avaxim® & Avaxim®-Pediatric (both SP), Havrix®1440 & Havrix®720Junior (both GSK), Vaqta® (MF)	HA	24	70	2(2.9)	14.1
Hepatitis A, Typhoid	ViVAXIM™ (SP)	HA-Typh-I	46	11	0	20.8
Measles, Mumps, Rubella	M-M-R® II (MF), Priorix® (GSK)	MMR	20	393	29(7.4)	68.2
Measles, Mumps, Rubella + Varicella	Priorix-Tetra™ (GSK)	MMRV	17	163	42(25.8)	53.7
Varicella	Varilrix® (GSK), Varivax® III (MF)	Var	22	358	16(4.5)	74.0
Influenza	Fluviral® (GSK), Vaxigrip® & Intanza™ (both SP), Agriflu® (NVD), Fluad® (NP), [D]Influvac® (API) Flumist® (AZC)	Inf	82	913	36(3.9)	8.5
Human Papillomavirus	Gardasil® (MF), Cervarix™ (GSK)	HPV	65	185	9(4.9)	29.8
Rotavirus	Rotarix™ (GSK), RotaTeq® (MF)	Rota	11	228	21(9.2)	30.5

Special use vaccines (publicly funded in selected situations)						
Tuberculosis	BCG (SP)	BCG	100	5	0	NC[3]
Rabies	Imovax® Rabies(SP), RabAvert® (NP)	Rab	85	39	0	135.1
Non-publicly funded vaccines						
Herpes Zoster	Zostavax® (MF)	Zos	91	80	2(2.5)	27.7
H. influenza type b	ACT-HIB® (SP), Hiberix® (GSK), Liquid PedvaxHib®(MF)	Hib	6	16	3(18.8)	63.8
Polio	Imovax® Polio (SP)	IPV	3	29	0	28.2
Cholera	Dukoral® (CV)	Chol-Ecol-O	77	26	1(3.8)	10.5
Japanese Encephalitis	IXIARO® (NP)	JE	57	7	1(14.3)	NC[3]
Tickborne Encephalitis	FSME-IMMUN™ (Bax)	TBE	100	1	0	NC[3]
Typhoid	Typherix™ (GSK), Typhim Vi® (SP), Vivotif ® (CV)	Typh-I/O	42	43	1(2.3)	18.4
Yellow Fever	YF-Vax® (SP)	YF	24	25	0	33.5

[1] Note: only those vaccines marketed in Canada for which at least one AEFI report was received by April 30, 2013, for vaccines administered in 2012.
[2] Market Authorization Holders, including: API—Abbott Laboratories Ltd.; AZC—AstraZeneca Canada Inc.; Bax—Baxter Corporation; CV—Crucell Vaccines Canada; GSK—GlaxoSmithKline Inc.; MF—Merck Canada Inc.; NP—Novartis Pharmaceuticals Canada Inc.; NVD— Novartis Vaccines and Diagnostics, Inc.; Pfiz—Pfizer Canada Inc.; SP—Sanofi Pasteur Ltd.
[3] NC—not calculated because of small sample (<10 reports over two years)

Figure 2 shows the total distribution of primary AEFI by vaccine group. Reactions at or near the vaccination site made up over 50% of reports involving DTap-IPV, Tdap-IPV, Td, Pneu-P-23, and Zos vaccines. Neurologic events made up 24% of all reports for MMRV but a much smaller fraction of other vaccines including MMR.

Figure 2: Primary adverse event following immunization (AEFI) distribution by vaccine group



Serious adverse events by primary reason for reporting

Among 188 serious AEFI reports received for vaccines administered in 2012, the reason for seriousness was hospital admission for 183 and fatal outcome for 5. None of the deaths were considered related to vaccine, as discussed further below.

Three deaths occurred in adults 3 minutes, 35 minutes, and five days following inactivated influenza vaccines (two different manufacturers and one unidentified product) for an overall reporting rate of 0.3 per 1 million influenza vaccine doses distributed). All were sudden in onset involving cardiac arrest and all had pre-existing cardiac disease as the likely cause of death.

One death followed a second dose of MMR vaccine given to a school-aged child (reporting rate of 1.45 per million doses distributed). No other vaccines were given. There was an acute onset of fever within one day of vaccination and an afebrile seizure three days later which progressed to status epilepticus and resulted in a refractory coma. Death occurred several weeks later. Neuro-imaging revealed a right temporal focal abnormality but no etiology was found despite extensive investigation. The timing of onset did not support a vaccine-associated cause of illness.

Finally, there was one death in a toddler within one day after immunization with DTaP-IPV-Hib alone (reporting rate of 0.7 per million doses distributed). A coroner's investigation revealed an acute respiratory infection as the cause of death.

There were 64 serious neurologic events of which 43 were seizures, mostly febrile. Of 42 where outcome was known, all but one had full recovery; the exception was a known case of tuberous sclerosis with infantile spasms. Six cases followed a single vaccine (MMR, HPV, Inactivated influenza, DTaP-IPV-HB-Hib, Var, HAHB) and the remainder followed administration of two or more vaccines. All but eight cases involved MMR or MMRV usually given with pneumococcal and/or meningococcal conjugate vaccines. The reporting rate per 100,000 doses distributed for measles-containing vaccines where time to onset after vaccination was in the expected risk interval of 5−12 days was 1.08 for MMR and 4.83 for MMRV. The increased risk of febrile seizure following MMRV relative to MMR is now well known and has been documented recently in Canada (42).

The remaining 21 serious neurologic events involved several different entities. There were 11 cases of possible demyelinating disease. Guillain-Barré syndrome was reported four times, three of which followed 10, 11 and an unknown number of days after Td-containing vaccines, and one that onset 24 hours after pneumococcal polysaccharide vaccine. There were two cases of acute encephalitis; one with an onset 11 days after MMRV given alone, and the other with an onset 22 days after MMRV was given with pneumococcal and meningococcal conjugate vaccines. Causality was not proven for either case, but live attenuated vaccine virus could have caused the illness. Both cases had full recovery. There were two reports of acute disseminated encephalomyelitis: one following 1 day and 29 days after the second and first doses of JE vaccine, respectively; and the other following 13 days after the first dose of HPV and HB vaccines. Neither case met the Brighton criteria for diagnostic certainty, so causality could not be assessed. There was one case of transverse myelitis that onset five days after MMR but there was a concurrent viral infection that was the likely cause. In addition, there was one case of optic neuritis that onset seven days after the second dose of HPV vaccine. No other explanation was apparent and vaccine may have contributed. Finally, there was a single case of encephalomyelitis that onset within one day of DTaP-IPV-Hib and Pneu-C. The timing did not fit a vaccine cause of illness and an enteroviral infection was the suspected cause. The other serious neurologic cases followed a variety of different vaccines none of which were considered likely causes of the reported events that included: two aseptic meningitis; one Bell's palsy; one other paralysis lasting longer than one day; one cerebellar ataxia; one stroke; two temporary cases of confusion; and one conversion disorder.

There were 20 SAE reports involving reactions at or near the vaccination site, including: 15 cellulitis; three extensive limb swelling; one abscess; and one that could not be sub-classified. In all cases, the reason for

seriousness was hospital admission, primarily for intravenous antibiotic therapy. Implicated vaccines included: pneumococcal polysaccharide (14 reports, 7 with no other vaccine); inactivated influenza (nine reports, three with no other vaccine); and two DTaP-IPV-Hib (one with no other vaccine). The time to onset following immunization was within 24 hours for 16 reports and two days for four reports.

Among ten serious allergic events, six were reported as anaphylaxis (one Brighton Level 1, two Level 2, and three Level 4), one as ORS, and three as other allergic reaction. Onset was within 30 minutes for six events, 1 hour to <24 hours for two events, 17 days for one event, and unknown for one other. The implicated vaccines for anaphylaxis included two HB given alone, two inactivated influenza given alone, and two DTaP-IPV-Hib, one given alone, and one with Men-C-C and Pneu-C. The only unusual event was a case diagnosed as type IV hypersensitivity with secondary hepatitis in a middle-aged adult that onset 17 days after administration of a second dose of Chol-Ecol-O, and 39 days after HAHB and Typh-I/O. Causality could not be further assessed given lack of sufficient detail, but the individual made a full recovery.

Among other events specified on the CAEFISS form, SAE reports included ten HHE, nine thrombocytopenia, and two intussusception. None of these were unexpected, given known associations although several had alternate explanations.

The remaining SAE reports classified by the Medical Case Review as systemic (52 cases), miscellaneous other (20 cases), or immunization anxiety (two cases) events covered a broad range of specific diagnoses, vaccines and age groups. There was no significant clustering of any one type of event or vaccine group and nothing considered to be of concern.

Discussion

This report represents the first annual safety report for vaccines administered in Canada in a given calendar year using a uniform presentation format. Several caveats must be understood in interpreting CAEFISS data. Surveillance does not capture all events nor are there reliable denominators for vaccines administered, so AEFI incidence cannot be calculated or extrapolated from the data. Reports vary in terms of completeness and adherence to national case definitions. Reporting rates are affected by many factors including age, geographic jurisdiction, newness of a given vaccine program, and degree of public controversy over real or perceived safety concerns. While this report summarizes our experience over the last eight years, the information provided to CAEFISS is reviewed regularly during the year to identify any unusual or unanticipated increases in SAEs and acted upon accordingly.

The main purpose of post-market surveillance is to detect new or unusual safety concerns that may signal previously unknown associations between a given vaccine and event or changes in expected safety profiles in terms of frequency or severity of selected adverse events. Thus, while reporting of suspected associations is encouraged, it must be remembered that a report is not proof that vaccine(s) caused a given event. AEFIs by their very name are a temporal association whereby an event follows immunization. The cause of that event could be due to an inherent property of vaccine, a manufacturing quality problem, an error in one or more steps involving the immunization process, anxiety related to immunization, or a coincidental event completely unrelated to vaccine or immunization (22). It is rarely possible to determine a specific cause based on what is reported to national systems such as CAEFISS. Further investigation is always required when a signal is detected to determine causality—both at the individual and at the population level. Nevertheless, the data presented in this report do provide a profile over time that can be used to make general conclusions regarding CAEFISS as a surveillance system and the safety of vaccines administered in Canada.

First, Canada has a strong vaccine safety surveillance system as a result of decades of synergistic collaboration between regional and federal public health authorities in collaboration with key partners, described more fully elsewhere in this supplement. Canada's overall annual AEFI reporting rate of 10.1 per 100,000 population is high

relative to most other countries with similar immunization schedules, including the United States (rate of 4.4 for vaccines administered 1991−2001) (13), Europe (2005 rates under 5 for France, Germany, Great Britain, Italy and Spain, 6−7 for Netherlands and Norway, 9.8 for Sweden, and 18.5 for Finland) (43), and appear comparable to Australia (10.4 in 2011) but are likely higher (14). Canada and most other countries use individual case reports as the numerator for population-based rates whereas Australia uses individual adverse events which often exceed one per case report. Given similar immunization programs the higher AEFI reporting rates in Canada reflect the high degree of vigilance by Canada's public health immunization authorities to report AEFI as well as the active surveillance component by IMPACT.

Second, the safety profile of vaccines administered in Canada is very good. The vast majority of reported AEFIs are of low severity and resolve fully. The only notable cluster of serious events for vaccines administered in 2012 were febrile seizures during the second year of life, most likely the result of measles-containing vaccines, with the highest rate associated with MMRV. These are expected, albeit frightening, events for all concerned. It is essential that realistic risk-benefit information be provided to parents and caregivers along with advice for what to do should such an event occur.

Finally, the Medical Case Review classification, initiated nationally by the Vaccine Safety Section of the Public Health Agency of Canada in 2011, provides an additional framework for presenting AEFI data that is hoped to be more useful for public health, clinical and public stakeholders than previous report summaries based on regulatory coding frameworks such as MedDRA. Both frameworks are useful and thus are included in this report. The System Organ Class data provide a means to compare this report to those published by national regulatory agencies and Market Authorization Holders. The Medical Case Review classification is closely aligned with the CAEFISS report form and is also used for PHAC's web-based quarterly summaries of AEFI reports received (44). The Medical Case Review also provides an important added tool for timely expert review of all SAE reports received at PHAC and facilitates quality assurance activities.

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Conflict of interest

None

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Behind the scenes in public health: Adverse events following immunization (AEFI) signal investigation in British Columbia

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Abstract

Background: In British Columbia, vaccine safety is monitored through a passive surveillance system with voluntary reporting of adverse events following immunization (AEFIs) from immunizers to five regional health authorities and onward to the British Columbia Centre for Disease Control (BCCDC).

Objective: To review and summarize all documented AEFI cluster or signal investigations carried out by BCCDC between November 2007 and July 2014.

Method: Documented cluster or signal investigations were reviewed to summarize year, alerting mechanism, event type and vaccine, investigative analysis approach, results, and public health actions. The findings and public health actions of two cluster investigations are described in detail.

Results: There were two fatality investigations and thirteen cluster investigations. The two fatalities were found to be due to sudden infant death syndrome and were not vaccine-related. Clusters were predominantly identified through notification from regional medical health officers or public health nurses, and the majority were local injection site reactions (54%), or allergic events (39%). Most investigations did not identify a specific association to a vaccine or a lot of vaccine, and no public health actions were taken. Two recent investigations—reports of hypotonic-hyporesponsive episodes with or without severe vomiting and diarrhea following receipt of a single lot of DPT-IPV/Hib/hepatitis B vaccine, and reports of severe pain past nearest joint following administration of a single lot of influenza vaccine—were thought to be vaccine-related. The former investigation did not find an association to vaccine, while the severe local reactions post-influenza immunization were determined to be a result of improper injection technique. Public health actions included communication to federal/provincial/territorial vaccine safety partners and additional injection technique training.

Conclusion: This investigative aspect of public health immunization programs is often not in the public eye but is an important component of behind the scenes activities that serve to protect public safety.

Introduction

Vaccination has been shown to greatly reduce the burden of disease, disability, death, and inequity worldwide (1); making immunization programs an invaluable component of population health. Post-marketing pharmacovigilance of vaccine safety, therefore, is critical for timely identification and response to safety concerns and to support public confidence in vaccines. British Columbia has a population of 4.6 million and an infant cohort of 45,655 (in 2013) (2). Vaccine safety is monitored largely through a passive surveillance system with reporting to five regional health authorities (RHAs) and thereon to the British Columbia Centre for Disease Control (BCCDC) under a

voluntary scheme. The processes in place are similar to those in other provinces/territories; these processes and the immunization schedule are described elsewhere (3).

When a cluster of similar events associated with one vaccine or one lot of vaccine is identified, it may be investigated locally and/or by BCCDC. BCCDC also identifies potential clusters using the Public Health Intelligence for Disease Outbreak (PHIDO) aberration detection software developed at BCCDC and also used for weekly analysis of notifiable disease data. This paper provides a summary of adverse event following immunization (AEFI) cluster investigations conducted at BCCDC between November 2007 and July 2014, with a focus on two recent and distinct investigations, to highlight provincial vaccine safety monitoring activities in BC.

Methods

All documented cluster or signal investigations recorded between November 2007 and July 2014 were reviewed to identify year, alerting mechanism (how the alert was detected), event type and vaccine, analytical approach, results/findings, and public health actions.

Two recent investigations that highlighted different cause-specific categorization of AEFIs, and that were brought to provincial attention through different processes, are described in more detail.

Results

Between November 2007 and February 2014, many cluster investigations were documented. However, only 13 investigations for which complete documentation could be retrieved are included in this summary (**Table 1**). In addition to cluster investigations, two reports of infant deaths were investigated (not described in **Table 1**); both were attributed to sudden infant death syndrome (SIDS), which is a recognized entity unrelated to vaccination that occurs at a frequency of 0.09 to 0.8 per 1,000 infants in industrialized nations (4,5).

Clusters were predominantly identified through notification from medical health officers (MHOs) or public health nurses (PHNs) to ask whether similar findings could be seen in provincial data. One cluster was reported at a provincial communicable disease meeting, and one was queried by the Vaccine Evaluation Center based at BC Children's Hospital. Occasionally PHIDO alerted a frequency of reported events above expected.

Documented clusters were predominantly local injection site reactions (seven clusters or 54%) primarily associated with the same vaccine or same lot of vaccine. Next most frequent were allergic events (five clusters or 38%), with most of these events managed as anaphylaxis, and one cluster of oculo-respiratory syndrome (ORS) across multiple RHAs associated with influenza vaccine. One cluster of "neurological event—hypotonic-hyporesponsive episode (HHE) and/or severe vomiting and diarrhea" was investigated.

Cluster investigations typically compared frequencies and reporting rates of AEFIs for the vaccine or lot(s) of interest (LOI) to other lots of the same vaccine or similar vaccines. Where relevant, trends in AEFI reports by sociodemographic characteristics (age, gender, geography) and clinical characteristics (interval to onset, dose number, and administration in conjunction with other vaccines) were also examined. Rates were calculated using denominator estimates from one of two sources: the number of doses administered in the immunization registry, or doses distributed adjusted downward for the most recent shipment issued to accommodate for lag time to administration. The former is limited to childhood vaccines, as few adult immunizations are recorded. On occasion, doses administered were estimated from the immunization schedule, size of the target population, and available data on coverage, and rarely on estimated coverage.

Anaphylaxis case reports were classified using the Brighton case definition when sufficient details were reported about signs and symptoms (6). Investigation of the ORS cluster following influenza immunization involved review of each influenza vaccine-associated report received during that influenza season to abstract signs and symptoms indicative of ORS.

Most investigations did not find significant relationships between LOIs or vaccine type and the reported events, and no public health action was taken. When examining subcutaneous administration versus intramuscular (IM) administration of polysaccharide 23-valent pneumococcal vaccine (PPV-23), analysis using proportionate reporting ratios indicated the former may be associated with increased local reactions compared to IM, but did not show a change over time in frequency of these events. In one investigation of severe local reactions following second dose of varicella vaccine in Grade 6 students, the observed increase was attributed to reporting of events within expected parameters. When appropriate, a report of the investigation was provided to the health authority and/or to the Public Health Agency of Canada's (PHAC's) Vaccine Safety Unit, the Vaccine Safety Working Group of the BC Immunization Committee, and/or the manufacturer(s).

Table 1: Summary of 13 clusters investigated from November 2007 to July 2014, British Columbia

Type	Description	Results	Public Health Action(s)
Local	1. Large local reactions past the nearest joint following subcutaneous administration of PPV-23 vaccine[1]	BC[1] surveillance data indicated that subcutaneous administration of PPV-23 may be associated with increased local reactions compared to intramuscular administration; however, the data did not indicate a recent increase in AEFI[2] reports following PPV-23 administration.	Investigation report shared with the RHA[3]. No further action required.
	2. A cluster of significant local reactions (n=2) following same lot of tetanus diphtheria toxoid	The lot in question had fewer overall reports of local reactions compared to other lots recently distributed in the province.	Investigation report shared with the RHA[3]; recommendation was to continue immunization with lot of interest.
	3. Sore arms lasting 48 hours to seven days following influenza vaccine[4]	Analysis did not find an increase in events reported in this season.	Investigation report shared with the RHA[3]. No further action required.
	4. Wheals at injection site following MMR[5] vaccine (n=37)	At the provincial level did not appear to be any evidence of an increase in rate of these events over time.	Investigation report shared with the RHA[3]. No further action required.
	5. Local reactions (n=9) presenting in children within minutes of immunization with a particular lot of DPT-IPV/Hib (Pediacel) vaccine	No indication of increased reporting of local or allergic reactions following administration of Pediacel lot of interest.	Investigation report shared with the RHA[3]. No further action required.
	6. Severe local reactions among Grade 6 students (n=25) after receipt of second dose varicella vaccine in a single RHA[3]	The investigation did find an increase in reporting rates of local reactions associated with the lot of interest; however, when examined by geography, the increase was determined to be localized to one region. No other RHA[3]s reported similar events, both before or after notification of this alert. Clinical trials described in the product monograph indicated that increased rates of local events are associated with second dose varicella vaccine.	Investigation report and information about higher expected rates shared with the RHA[3]. Reporting rates declined to expected levels. No further action required.
	7. Severe arm pain following administration of one lot of influenza vaccine (AGRIFLU®) (n=4)	This was determined to be due to incorrect immunization technique and not due to the lot of interest.	Investigation report shared with the RHA[3] and the Public Health Agency of Canada. Clinician involved self-identified a need for additional

			immunization training prior to completion of investigation.
Allergy/ Anaphylaxis	8. A cluster of anaphylaxis cases (n=3) following immunization MMR[5] vaccine at immunization clinic	One report was classified as Level 2 Brighton, the other two were classified as "certainty unclear." Was determined not to be related to the lot of interest.	Information provided to the RHA[3]. No further action required.
	9. Events managed as anaphylaxis (n=2) following MMR[5] post change in vaccine manufacturing procedures	In BC[1], there was no difference found in the frequency and type of AEFI[2] reports before and after product change. In Alberta, six cases of anaphylaxis had resulted in a temporary quarantine of several lots of MMR[5].	A simultaneous review occurred federally in response to issues observed in other provinces. Several lots of vaccine were quarantined by Health Canada but subsequently released for use. No changes were made to the product monograph.
	10. AEFI reports of symptoms compatible with anaphylaxis (n=4) among Grade 9 students after receipt of a single lot of Tdap (Adacel)	The lot of interest was not associated with higher rates of AEFI[2] or anaphylaxis/allergy.	The alert was posted to the Canadian Network for Public Health Intelligence website for national notification. The lot in question was suspended for use until investigation determined there was not a safety concern, and that vaccination should resume. Notification of the event and investigative findings were communicated to RHA[3]s.
	11. AEFI[2] reports of ORS[6] (n=6) following influenza immunization	The reports of ORS[6] were found to be within expected rates of this condition.	Findings communicated to the RHA[3]. No further action required.
	12. Serious allergic reactions (n=4), including two cases of anaphylaxis following Grade 6 meningococcal C conjugate and hepatitis B vaccines	There was no difference in event frequency by vaccine combinations across multiple years.	Findings communicated to the RHA[3]. No change in immunization was recommended and product was not recalled.
Neurologic	13. Reports of one or both of hypotonic-hyporesponsive episode and severe vomiting or diarrhea (n=6) following immunization with DPT-IPV/Hib/HepB (INFANXIR hexa®) in conjunction with voluntary recall of a specific lot of vaccine by the manufacturer	The reporting rates of any AEFI following the lot of interest were similar to other lots.	Collaboration with F/P/T[7] vaccine safety partners was initiated to query for similar reports. The Health Canada Regulatory Biologics and Genetic Therapies Directorate and manufacturer were informed of the issue. Investigative reports were sent to the Public Health Agency of Canada, the RHA[3]s, the Vaccine Vigilance Working Group, and the manufacturer.

[1] BC = British Columbia
[2] AEFI = adverse event following immunization
[3] RHA = Regional Health Authority
[4] Number of cases not explicitly documented
[5] MMR = Measles, Mumps, Rubella
[6] ORS = oculo-respiratory syndrome
[7] F/P/T = federal, provincial and territorial

Spotlight on DPT-IPV/Hib/HepB (INFANRIX hexa®) investigation

INFANRIX hexa® is a cornerstone of the BC childhood immunization schedule and provides protection against six disease entities. At the time of this alert, BC was the only province using this vaccine.

On August 31 2012, PHIDO identified two alerts: two reports of HHE and four reports of severe vomiting/diarrhea over seven days. The alerts involved five infants: one with HHE, severe vomiting/diarrhea and excessive somnolence; the other four reported a single event each: three severe vomiting/diarrhea events and one HHE. In addition to receiving other vaccines, all five had received INFANRIX hexa® lot A21CB242A.

Collaboration with federal, provincial and territorial (F/P/T) partners in vaccine safety was immediately initiated to determine if similar events had been reported in other jurisdictions using this product, and if the national Canadian Adverse Events Following Immunization Surveillance System (CAEFISS) had received similar reports. The Health Canada Regulatory Biologics and Genetic Therapies Directorate and the manufacturer were also informed of the issue.

Analysis of passive surveillance data found that neither overall rates of AEFI reports nor rates of specific reaction types were statistically significantly higher for lot A21CB242A compared to other lots. Two events (screaming episode/persistent crying and severe vomiting/diarrhea) had odds ratios larger than 1.0 for lot A21CB242A, but this increase was not statistically significant. A review of national surveillance data conducted by PHAC had suggested that the higher rates of vomiting/diarrhea may have been attributable to co-administration with ROTARIX®, for which this side effect is described (7); however, in the BC analysis which included immunization registry data and compared the events following the recalled lot to events reported over the same time period for other lots to account for seasonal variations in gastrointestinal illness (mainly of viral etiology), the proportion who received ROTARIX® at the same visit was similar among those who received the recalled lot compared to other lots.

Coincidentally, beginning in early October 2012, GlaxoSmithKline issued a precautionary recall for lot A21CB242A, citing identification of bacterial contamination in the environment where the bulk of the vaccine was stored, but without evidence of contamination in the vaccine and absence of reports of adverse events received globally compatible with vaccine contamination (8). An important finding in the BC analysis was that none of the adverse events reported were compatible with bacterial contamination of the vaccine, which would be expected to result in events such as cellulitis, abscess at injection site, bacteremia or sepsis.

Investigative findings, once complete, were shared with F/P/T partners through the pan-Canadian Vaccine Vigilance Working Group (VVWG). BCCDC also provided the conclusive findings to RHAs, in conjunction with the manufacturer-issued recall.

Spotlight on severe pain past nearest joint following administration of a lot of influenza vaccine

On February 18, 2014, an RHA contacted BCCDC to report severe arm pain in four recipients aged 50−70 years, following administration of AGRIFLU® lot 132701 between November 21, 2013, and January 7, 2014. All four experienced severe prolonged pain in the shoulder resulting in inability to lift the arm and resulting in work absenteeism. Some of the reactions remained unresolved at the time of the investigation. All had been immunized by the same clinician. While this association immediately suggested a problem with injection technique, due diligence warranted investigation into other hypotheses.

Both quantitative analysis and qualitative screening of individual case reports of these four, as well as twelve other AEFIs reported for the same lot of vaccine, was carried out to identify similarities in reported signs or symptoms.

Quantitative analysis did not identify a significant relationship between frequencies of local reports following this lot compared to other lots of the same or different influenza vaccine, and qualitative review of other cases did not find other similar events. It was concluded that these events were attributable to incorrect immunization technique.

Erroneous administration of intramuscular vaccines, particularly too high on the deltoid, can result in serious shoulder injury (9, 10, 11, 12). Suggested mechanisms of injury include injection of antigenic material into synovial tissues, including the subdeltoid bursa resulting in an immune-mediated inflammatory reaction, subacromial bursitis, bicipital tendonitis and adhesive capsulitis. The conclusion and supporting literature were reported to the RHA. The clinician involved, new to immunization practice, self-identified a need for additional training in immunization.

Conclusions and Future Directions

Vaccine safety surveillance is an integral component of safety assurance for vaccines and immunization programs throughout Canada. This paper highlights the signal detection and investigative component of the provincial vaccine safety program in BC. While activities in other countries may be the first to detect a safety signal and many vaccine products are used throughout the world, safety issues may be lot-specific with a given lot released for use in a single country, and not all products used in BC are used in all Canadian jurisdictions. British Columbia, as the third most populous province in Canada, plays an important role in contributing to vaccine safety monitoring. While AEFIs are voluntarily reported, BC has higher per capita reporting than any other province in Canada, an AEFI management and reporting guideline for public health workers in the province, and carries out surveillance and monitoring of serious AEFIs on a routine basis. Current limitations of the surveillance system include potential for misclassification or reporting bias, and lack of access to real-time provincial background rates of events of interest for appropriate analytical comparison.

We were motivated to describe these activities conducted by the public health infrastructure, which are often invisible to the outside world. BCCDC is taking steps to report out results of surveillance to stakeholders, as confidence in vaccines is as important for health care providers as it is for potential vaccine recipients. Surveillance activities at the provincial level should be transparent to encourage accurate and reliable reporting of adverse events and to promote education and awareness of vaccine safety in a scientifically accurate context. In addition to passive surveillance, active surveillance for select populations and events such as those conducted through the Immunization Monitoring Program ACTive (IMPACT) and the PHAC-CIHR Influenza Research Network (PCIRN) contribute to safety assurance in Canada. Future efforts should also aim to establish partnerships for multi-country data pooling to facilitate detection of both rare and possibly currently unrecognized vaccine event associations (13).

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Conflict of interest

None

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Analyzing and strengthening the vaccine safety program in Manitoba

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Abstract

Background: The emergence of a novel influenza A virus in 2009 and the rapid introduction of new pandemic vaccines prompted an analysis of the current state of the adverse events following immunization (AEFI) surveillance response in several provinces.

Objectives: To highlight aspects of the situational analysis of the Manitoba Health, Healthy Living and Seniors (MHHLS's) AEFI surveillance system and to demonstrate how common business techniques could be usefully applied to a provincial vaccine safety monitoring program.

Method: Situational analysis of the AEFI surveillance system in Manitoba was developed through a strengths-weaknesses-opportunities-threats (SWOT) analysis and informed by the National Immunization Strategy vaccine safety priorities. Strategy formulation was developed by applying the threats-opportunities-weaknesses-strengths (TOWS) matrix.

Results: Thirteen strategies were formulated that use strengths to either take advantage of opportunities or avoid threats, that exploit opportunities to overcome weaknesses, or that rectify weaknesses to circumvent threats. These strategies entailed the development of various tools and resources, most of which are either actively underway or completed.

Conclusion: The SWOT analysis and the TOWS matrix enabled MHHLS to enhance the capacity of its vaccine safety program.

Introduction

In late April of 2009, the World Health Organization (WHO) announced the emergence of a novel influenza A virus (1). In response, new vaccines against the pandemic strain had to be rapidly introduced with limited safety information in humans. At that time, Canada activated its Pandemic Influenza Plan for the Health Sector (2). Although this document addressed issues concerning vaccines, vaccine safety was only sparingly dealt with.

At the end of the pandemic, the Vaccine Vigilance Task Group- an expanded version of the Vaccine Vigilance Working Group (3) that included more medical and epidemiological expertise- commissioned an evaluation of the federal, provincial and territorial adverse event following immunization (AEFI) surveillance response (4). In line with this work, commencing in October 2010, Manitoba Health, Healthy Living and Seniors (MHHLS) signed a memorandum of agreement with the Public Health Agency of Canada (PHAC) to embark on a vaccine safety best practice model (BPM) pilot project. The BPM pilot was intended to bridge the gaps between current practice and the vaccine safety priorities or specific objectives enunciated in the National Immunization Strategy (5) to optimize

the vaccine safety system, to maintain professional and public confidence in the safety of vaccines, and to address growing anti-immunization concerns.

Two common business tools were used to determine the way to bridge those gaps: the SWOT (strengths-weaknesses-opportunities-threats) analysis, and the TOWS (threats-opportunities-weaknesses-strengths) matrix.

The SWOT analysis is a simple way of conducting an audit of the factors that affect an organization. It facilitates the assessment of the internal strengths and weaknesses of an organization—in this case, MHHLS. Likewise, the SWOT analysis facilitates examination of the opportunities and threats, which are factors in the external environment. It is imperative to make a distinction between internal and external factors as the organization naturally has more control over the former than the latter. Any appraisal of an organization's current situation should take into account the issues that are extrinsic as well as intrinsic to it.

The TOWS matrix is a useful tool for generating strategies or action steps in health management (6) and continues where the SWOT analysis leaves off (7). It allows for systematically matching or aligning the different elements itemized in the SWOT analysis, showing the relationships among the internal and external factors, thereby helping planners formulate measures that use strengths to either take advantage of opportunities or avoid threats, that exploit opportunities to overcome weaknesses, or that rectify weaknesses to circumvent threats.

A literature review of MEDLINE using the search terms "SWOT," "TOWS," "immunization," and "vaccine" revealed that, although these techniques have been used worldwide in strategic planning for immunization programs, only a handful of scholarly articles have actually been published that give an account of their application in this area. For example, one or both tools were utilized to address issues with vaccine shortage policies in the United States (7) and to guide a smallpox revaccination program in Israel (8).

The objectives of this study were to highlight aspects of the situational analysis of MHHLS's AEFI surveillance system and to demonstrate how common business techniques could be usefully applied to a provincial vaccine safety monitoring program.

Method

As part of the situational analysis of the current state of MHHLS's AEFI surveillance program at the early stages of this pilot project, the SWOT analysis was applied to map out the different factors affecting the organization. These factors were identified based on responses to questionnaires mailed out to various health professionals involved in AEFI surveillance, including managers of hospital emergency rooms, managers of long-term care facilities, epidemiologists, regional medical officers of health (MOHs) and other physicians, and immunization coordinators. Subsequently, the TOWS matrix was applied to generate or prioritize strategies identified in consultation with a vaccine safety advisory group composed of provincial AEFI surveillance personnel and infectious disease experts.

Results

A list of strengths, weaknesses, opportunities and threats was developed (see **Table 1**). Application of the TOWS matrix to this list enabled identification of strategies, which necessitated the development of various tools and resources.

Table 1: List of strengths, weaknesses, opportunities and threats (SWOT) for the MHHLS[1] best practice model for vaccine safety

INTERNAL	EXTERNAL
Strengths • Existing reporting form • Availability of administrative databases • Existing risk assessment procedure for public health alerts • Ubiquitous provincial government website • Provincial mandate and credibility	**Threats** • Erratic reporting • Illegible and incorrectly filled out forms • Lack of awareness by regional health authorities as to what reviews occur at the provincial level • Poor communication among stakeholders
Weaknesses • No clearly defined and documented surveillance aims and objectives • Available standard operating procedure (SOP) lacks description of roles and responsibilities of key surveillance personnel • No process to classify or apply case definition • No defined process for follow-up and reporting of outcomes for serious events • Lack of feedback from the province to the regions on the reports submitted • No system in place for completing a robust and meaningful analysis of data • No direction about data validation • Database's printing function is not very useful • Fragmented immunization information system • Database not regionally accessible • No evidence of guidance document on review process • No provincial reference resource for medical officers of health (MOHs)	**Opportunities** • Availability of provincial legislation mandating reporting • Awareness by provincial stakeholders of their surveillance duties • Awareness by most health care providers (HCPs) of where to obtain and submit reporting forms • Experience of most HCPs with reporting • Preference by stakeholders for electronic reporting • Advent of Panorama • Availability of standard case definitions • Availability of causality assessment algorithms • Interest and capacity for research by various provincial stakeholders • Availability of third party online training program • Good cooperation among provincial stakeholders • Existing inter-P/T networks • Supportive national agencies

[1] MHHLS—Manitoba Health, Healthy Living and Seniors

Resources identified from the strengths-opportunities strategy

Online education program for AEFI. By leveraging the credibility afforded to it by its mandate as the official policy-making body for the province's public health system, MHHLS is able to arrange with a provider of online continuing professional education free access for health care providers (HCPs) to an existing online immunization training course (9). This course includes a module on AEFI.

Resources identified from the weaknesses-opportunities strategies

AEFI surveillance roles and responsibilities document. This relies on the fact that Manitoba has provincial legislation mandating HCPs to report AEFIs. This also counts on the cooperation and good will of provincial stakeholders.

Brighton assessment tool. This was developed by PHAC, and adapted by MHHLS, based on AEFI case definitions established by the Brighton Collaboration (10).

Provincial AEFI causality assessment guide. This lays out a provincial process for follow-up of serious event outcomes by providing a standardized procedure specific to Manitoba for ascertaining the certainty of any potential causal association of vaccine administration with an AEFI that meets one or more of the seriousness criteria. It adheres to the Clinical Immunization Safety Assessment algorithm (11) and is currently being actively

utilized for assessing individual AEFIs. It is concurrently being continuously developed, guided by the revised WHO AEFI causality assessment user manual (12), mainly to expand the algorithm to include how to deal with population-level AEFIs.

AEFI signal detection methodology. This will depend on the outcome of research being conducted by the University of Manitoba on behalf of MHHLS with respect to AEFI background rates and signal validation. Additionally, the Public Health Intelligence for Disease Outbreaks, a statistical tool developed by the British Columbia Centre for Disease Control (BCCDC), which MHHLS is already using for alerting outbreaks of certain reportable diseases, could be tapped.

Online AEFI tool linked directly to database. Given the preference by stakeholders for electronic AEFI reporting, tapping of the Pan-Canadian Public Health Communicable Disease Surveillance & Management Project (Panorama) is being explored to rectify a fragmented immunization information system by having a single database for client immunization, vaccine inventory and AEFI surveillance records.

AEFI management aid. This would address the lack of a provincial reference resource to guide MOHs in making AEFI management recommendations and could emulate examples from other jurisdictions, such as the AEFI section of the BCCDC's Immunization Manual (13).

Resources identified from the strengths-threats strategies

Improved AEFI reporting form. A modified layout of the reporting form that is deemed more intuitive for health professionals was considered to prevent or minimize certain errors commonly made when filling out the form.

AEFI risk assessment tool. This will be used to assess risk and potential impact of an AEFI alert on the immunization program. It is based on an existing MHHLS risk assessment procedure for public health alerts that provides a structured approach to coordination of initial actions and communications following receipt of an alert indicating potential risk to human health.

AEFI page within the provincial government website. This web page (14) can serve as an avenue for disseminating AEFI-related information and resources in the face of what is perceived as prevailing poor communication among various provincial AEFI surveillance stakeholders.

Resources identified from the weaknesses-threats strategies

Periodic AEFI surveillance reports. These are seen as a way to mitigate a weakness with respect to feedback, or lack thereof, from the province to the regions on AEFI reports the latter submit, thereby addressing the perceived threat of health regions not being aware as to what reviews occur at the provincial level.

AEFI database printing function. This allows printing of individual database records in form view (as opposed to the line view printing function in Access, which is not very practicable) so that a fresh and clean copy of the AEFI report is generated directly from the provincial database and faxed to PHAC's Canadian AEFI Surveillance System (and others, such as MOHs, who require them), thereby circumventing the progressive degradation of paper reports with repeated printing and faxing as they move through the reporting process (reporter → MOH → MHHLS → PHAC).

AEFI standard operating procedure (SOP) and user guide. These rectify the need for guidance documents on the reporting process, the user guide focusing mainly on AEFI reporters and the SOP on surveillance staff at MHHLS. These are expected to help prevent or minimize inconsistent reporting.

The resources developed from the TOWS matrix are summarized in **Table 2**.

Table 2: Overview of the TOWS matrix for the MHHLS best practice model for vaccine safety

		INTERNAL	
		Strengths	**Weaknesses**
EXTERNAL	**Opportunities**	• Online AEFI education program	• AEFI surveillance roles and responsibilities document • Brighton assessment tool • Provincial AEFI causality assessment guide • AEFI signal detection methodology • Online AEFI tool linked directly to database • AEFI management aid
	Threats	• Improved AEFI reporting form • AEFI risk assessment tool • AEFI web page	• Periodic AEFI surveillance reports • AEFI database printing function • AEFI SOP and user guide

Discussion and conclusion

The TOWS matrix and SWOT analysis are tools developed originally for the business sector that, used together, can also provide a powerful approach to public health planning. MHHLS has benefitted from the insight gained from the application of these business techniques that paved the way for generating the tools and resources needed in building what is hoped will be a sound vaccine safety program that can meet prevailing as well as emerging challenges posed by the continuing expansion of its overall immunization program. Most of the foregoing strategies are either actively underway or completed and continuously being improved. The ones pertaining to tapping Panorama, developing a management aid and revising the reporting form are either on hold or yet to commence.

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Conflict of interest

None

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Canada's Vaccine Vigilance Working Group

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Abstract

The Vaccine Vigilance Working Group (VVWG) was created in 2004 as part of the National Immunization Strategy to strengthen vaccine safety in Canada. The Group has representation from all federal/provincial/territorial immunization programs across the country, as well as Health Canada regulators and the Immunization Monitoring Program ACTive (IMPACT) network. VVWG works to harmonize vaccine safety monitoring and adverse event reporting and management across Canada by developing and following national guidelines and seeking out best pharmacovigilance practices, including training. It also provides a national vaccine safety sentinel network that uses several mechanisms to rapidly share information on emerging safety issues to enable effective public health response. The "vigilance" in VVWG emphasizes the watchful, ever alert nature and activities of the Group's work. Increased public and health professional awareness of the VVWG's role and activities should help to allay concerns about vaccine safety that lead to vaccine hesitancy and in turn limit the effectiveness of immunization.

Introduction

Vaccine safety monitoring, from local to provincial/territorial and the national level, has always been part of Canada's commitment to immunization This was evident in 1999 when a multi-year collaborative federal/provincial/territorial (F/P/T) initiative known as the National Immunization Strategy (NIS) was initiated to strengthen immunization in Canada (1). Vaccine safety was one of five main components of the NIS. The 2003 NIS report described some key gaps/limitations in the safety system that included: a lack of national guidelines for reporting, verification, management and information sharing of adverse events following immunization (AEFIs); a need for more timely national AEFI data; and a stronger capacity to respond to urgent vaccine safety issues.

One strategy to improve vaccine safety monitoring and public health response was to set up a network of dedicated F/P/T vaccine safety contacts in all jurisdictions. Multiple roles were envisioned for the network including: AEFI surveillance and reporting; identification and addressing of potential vaccine safety issues; communication; and capacity to respond in a coordinated fashion given urgent national situations.

Such a network was created in 2004—the Vaccine Vigilance Working Group (VVWG). The name was carefully chosen; vigilance is derived from the Latin "vigilare" meaning "to be awake" or "to keep watch" (2). Vaccine pharmacovigilance is defined as the science and activities relating to the detection, assessment, understanding, communication, and prevention of AEFI, or of any other vaccine- or immunization-related issues (3). The purpose of this paper is to describe the VVWG structure, process and output, and show how it "keeps watch" on vaccine safety across Canada.

How VVWG works

The VVWG works to:

- Develop national guidelines and procedures for AEFI monitoring, reporting and management.
- Serve as a national forum to identify, share and promote best practices regarding vaccine safety including training in AEFI reporting and management.
- Provide a national network of safety sentinels that can rapidly detect and respond to emerging vaccine safety issues or signals.

The Working Group has two Co-Chairs, one federal and one provincial. Core members consist of one representative from each provincial and territorial jurisdiction, except Ontario which has two: one representing the Ministry of Health which oversees immunization, and one from Public Health Ontario which manages AEFI surveillance. Liaison members are non-voting representatives from the following departments/organizations: the Immunization Monitoring Program ACTive (IMPACT) network; two Health Canada vaccine regulators representing the Marketed Health Products Directorate (MHPD) and the Biologics and Genetic Therapies Directorate (BGTD); four from federal jurisdictions with immunization program responsibilities, including: Health Canada's First Nations and Inuit Health Branch (FNIHB); the Department of National Defence (DND); the Royal Canadian Mounted Police (RCMP); and Correctional Services Canada (CSC). Liaison members bring additional knowledge and expertise to the Working Group, expressing the views of and communicating back to their organizations, as permitted by the VVWG.

VVWG reports to the Canadian Immunization Committee (CIC), which was also formed in response to the recommendations of the National Immunization Strategy and has a mandate to facilitate the achievement of the NIS recommendations. The CIC in turn reports up to higher committees that are part of the Public Health Network Council, which reports to the Conference of F/P/T Deputy Ministers of Health.

What VVWG has done

In response to the challenges identified in the 2003 NIS report, the VVWG has done a number of things, including the development of national standard procedures and guidelines, the development of a secure web-based AEFI alerting communication tool and enhanced surveillance during the 2009 H1N1 pandemic (**Table 1**).

Table 1: Vaccine Vigilance Working Group activities and accomplishments

Vaccine safety challenges/gaps identified in 2003 NIS Final Report	Key activities	Specific accomplishments
Lack of national adverse event following immunization (AEFI) standard procedures and guidelines	Develop national guidelines and procedures for AEFI monitoring and management to harmonize vaccine safety surveillance activities across Canada	• National AEFI case definitions (4) • Revision of the national AEFI report form to facilitate standard quality AEFI reporting, including capture of key elements of AEFI case definitions • National user manual to guide AEFI reporting (4) • Ensure that the Public Health Agency of Canada website has up-to-date F/P/T contact information to facilitate reporting and communication on AEFI-related questions • Standard procedures for several aspects of AEFI reporting • Standard vaccine abbreviations
Need for more timely AEFI data	National forum to share and promote	• Creation and use of a secure web-based AEFI-alerting communication tool (via the Canadian

	best practices for vaccine safety	Network for Public Health Information) • Standard procedure for expedited reporting of serious and other high priority AEFIs • Draft AEFI technical annex for multi-lateral F/P/T information data-sharing agreements
Need to strengthen urgent response capacity	National safety sentinel network	• Enhanced surveillance and information sharing during 2009 H1N1 pandemic and subsequent seasonal influenza mass campaigns via weekly aggregate AEFI reporting and teleconferences • Draft AEFI signal response protocol

For example, the enhanced surveillance during the 2009 H1N1 pandemic was done through weekly VVWG teleconferences that enabled rapid communication regarding any emerging vaccine safety concerns. Each F/P/T jurisdiction participated in the calls followed by weekly aggregate AEFI counts sent to the Public Health Agency of Canada (PHAC) that included serious AEFIs as well as AEFIs of special concern, such as anaphylaxis, febrile seizures and Guillain-Barré syndrome. This enabled PHAC to report to stakeholders, including the public, in close to real time on the safety of the pandemic vaccine during and after the mass campaign.

Lessons learned in 2009 have been applied to subsequent mass immunization campaigns. Since 2010, the VVWG has set up weekly calls at the beginning of each seasonal influenza campaign to share vaccine safety data and review any potential vaccine safety issues in a timely manner.

On an ongoing basis, potential vaccine safety signals detected at local, provincial, federal, or international levels are rapidly communicated to all VVWG members using a secure public health web-based communication tool, the Canadian Network for Public Health Information (CNPHI). Vaccine safety issues that require immediate attention are shared via phone or e-mail and urgent conference calls are convened when needed.

More information on the VVWG and its members are available in its guide to AEFI reporting (4).

Future directions

Currently, VVWG is drafting an AEFI Signal Response Protocol, which describes the processes and required actions for timely management of any newly detected or emerging vaccine safety signal. This protocol will detail procedures from signal detection, validation, analysis and prioritization, to signal assessment, necessary communications and actions at each level of government, as well as final recommendations. At each step, roles and responsibilities of F/P/T health jurisdictions, the Public Health Agency of Canada, and the vaccine regulators at Health Canada will be clearly described, including an ongoing communication plan from start to finish when a recommendation is made or when the signal is considered a false signal. Protocol annexes will include general and AEFI specific templates and checklists to facilitate timely data collection.

Conclusion

Since its origin in 2004, VVWG has provided an essential F/P/T forum of front-line workers in vaccination and vaccine pharmacovigilance and developed the capacity for rapid communication of vaccine safety information. However, challenges remain. A key NIS priority was to have dedicated trained personnel focused on vaccine safety at local, P/T and federal levels. In an era of reduced spending and unexpected public health crises it is sometimes difficult to meet this priority; the impact of gaps was clearly demonstrated during the 2009 pandemic. Following that experience, pandemic pharmacovigilance planning shifted towards efforts to ensure key NIS priorities were operationalized for everyday practice. Elsewhere in this supplement, pilot projects started by VVWG to address remaining gaps are described (5,6).

Since VVWG's inception there have been many potential but few real vaccine safety concerns. Much of VVWG's work is invisible to the public, immunization providers and other health care professionals. However, it is important that they be aware that vaccine vigilance is on ongoing daily activity coordinated across Canada. As such, the absence of significant safety concerns is not because someone isn't watching and ready to act should something emerge.

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Conflict of interest

None

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The Canadian Immunization Monitoring Program, ACTive (IMPACT): Active surveillance for vaccine adverse events and vaccine-preventable diseases

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Abstract

For almost 25 years the Canadian Immunization Monitoring Program, ACTive (IMPACT) has been conducting active surveillance for severe adverse events following immunization (AEFIs) and vaccine-preventable diseases in children. The network, which consists of volunteer paediatric infectious diseases investigators at 12 tertiary care paediatric hospitals, is an important component of Canada's AEFI monitoring. The network employs nurses at each of the sites to search for and report possible AEFIs to local, provincial and national public health authorities. The active nature of the surveillance ensures a high level of vigilance for severe AEFIs in children.

Introduction

The Canadian Immunization Monitoring Program, ACTive (IMPACT) continues to be an innovative model for vaccine safety surveillance. 2014 marks its 23rd year of operation as a collaboration between the Canadian Paediatric Society and the Public Health Agency of Canada (PHAC). IMPACT active surveillance aims to detect unexpected or unusual occurrences that result in hospitalization after vaccination and to monitor vaccine-preventable diseases. It is well-positioned to detect and monitor changes in serious events, signals of concern, and emerging diseases in the paediatric inpatient population. This paper describes IMPACT's role in vaccine safety monitoring in Canada.

The original impetus for the project was increased public concern about vaccine safety, particularly around whole cell pertussis vaccines, and recognition of the need for enhanced vaccine safety surveillance in children after the passive surveillance system failed to identify an increased risk of aseptic meningitis from a new mumps combination vaccine in the mid-1980s (1,2). IMPACT has two key active surveillance components: adverse events following immunization (AEFIs) and vaccine-preventable diseases. IMPACT's AEFI reporting reflects temporal associations, which means events are reported if they occur after a vaccination, but these events may not be caused by the vaccine. This follows the international best practice for AEFI reporting as causality cannot be determined *a priori*. IMPACT's vaccine-preventable disease surveillance monitors vaccine effectiveness by tracking children who continue to experience vaccine-preventable diseases.

IMPACT started in 1991 as a two-year pilot project in five tertiary care paediatric hospitals, expanded to 10 centres in 1993, to 11 in 1994, with the 12th centre added in 1999. Selection was based on geographical distribution, local centralization of pediatric beds, and availability of a pediatric infectious disease specialist to serve as the local IMPACT investigator. The current network encompasses approximately 90% of the pediatric tertiary care beds in Canada with about 50% of Canadian children directly residing within an IMPACT centre's catchment area.

Because immunization history is not available at the time of admission for most hospitalized cases and because finding the immunization history for every hospital admission would be impractical, IMPACT uses predetermined targets as the first step to identify post-immunization adverse events (**Table 1**). These predetermined targets represent serious events for which either biologic plausibility exists that they could be caused by a vaccine or the severity of the event is such that immediate action would be warranted if a new signal were to be detected. The 12 IMPACT nurse monitors actively screen every hospital admission to determine whether or not it meets a predetermined target. All targets are then reviewed to determine whether or not there was a temporal association with previously administered vaccine(s). If an association is found (i.e., if a vaccine was administered within a specific time frame before the event) the event becomes an AEFI.

All AEFIs are reported within 15 days of being identified to PHAC for entry into the national pharmacovigilance database—Canadian Adverse Events Following Immunization Surveillance System (CAEFISS)—as well as to local or provincial public health officials to ensure appropriate follow-up at the individual level. Most target cases have no temporal association with a vaccine. Cases with an association, but with a confirmed non-vaccine cause, are not reported. However, if there is even a small doubt about the cause, the case is reported. In a typical year IMPACT monitors screen around 6,000 admissions to identify about 100 (less than 2%) that are reportable as AEFIs. As a specific example, among cases screened from October 2013 to March 2014, a total of 3,084 target cases were identified and of these only 56 (1.8% of all identified) met the temporal criteria and were reported as an AEFI.

Table 1: The Canadian Immunization Monitoring Program ACTive (IMPACT) adverse events following immunization surveillance targets and reporting intervals, 2014

Specific targets	IMPACT intervals for reporting
Neurologic Events	
Seizure	0−3 days after inactivated vaccine(s); 0−15 days after live vaccine(s) [1]
Guillain-Barré syndrome (GBS)	0−42 days after inactivated or live vaccine(s)
Other acute flaccid paralysis (AFP)	0−42 days after inactivated or live vaccine(s)
Encephalitis	0−42 days after inactivated or live vaccine(s)
Acute disseminated encephalomyelitis (ADEM)	0−42 days after inactivated or live vaccine(s)
Myelitis	0−42 days after inactivated or live vaccine(s)
Aseptic meningitis	0-42 days after inactivated or live vaccine(s)
Thrombocytopenia (<100 x 10^9/litre with clinical evidence of bleeding, including Idiopathic Thrombocytopenic Purpura (ITP) [2]	0−42 days after inactivated or live vaccine(s)
Intussusception in infants <1 year of age	Within 0−21 days after live attenuated rotavirus vaccine only
Vasculitides (Kawasaki disease, Henoch-Schonlein Purpura (HSP), etc.)	0-42 days after inactivated or live vaccine(s)
Complication of vaccination	
Anaphylactic shock	48 hours after any vaccine
Vaccination site cellulitis or abscess	No specific timeline but needs to be localized to the vaccination site.
Non-vaccination site infectious complication including sepsis or infection of a normally sterile body site	No specific timeline but needs clear evidence linking the infection to a prior vaccination.
Varicella vaccine reactivation illness (Varicelliform rash or Zosteriform rash)	>42 days after varicella vaccination
Other AEFIs: All *reportable* AEFIs that the monitor finds during searches for the above IMPACT targets.	Follow the CAEFISS user guide

[1] Note: This interval is for seizure alone—presentation with any other neurologic symptoms would require the 0−42 day interval

[2] Note: This <100 criteria for reporting is different than the national user guide as it is focused on a more severe criterion which is specific to IMPACT active surveillance.

An AEFI detected after BCG (bacille Calmette-Guerin) vaccine is a good example of IMPACT in action. IMPACT's identification of deaths following BCG vaccination (3) prompted a review of BCG complications that indicated the risk of severe complications in First Nations infants was high and led to changes in the routine use of BCG vaccine in First Nations populations (4). The first evidence of improved safety with acellular pertussis vaccines was demonstrated with IMPACT data, which found a 79% decrease in febrile seizures associated with the receipt of pertussis vaccine (5). The data have been used to quantify the risk of hypotonic-hyporesponsive episodes and post-vaccination seizures in children (6, 7). IMPACT also published the largest case series in the world on post-vaccination thrombocytopenia, showing that the condition is usually benign and resolves within one month in most children (8−10).

Discussion

IMPACT's focus on admitted paediatric cases means the most serious AEFI in children are actively sought and identified. Although less serious AEFI signals might not be identified through IMPACT, it fulfills a key role in Canada's vaccine safety surveillance and is an excellent complement to Canada's other AEFI reporting systems. Over the next three years the network will transition to electronic reporting, which will enable faster transmission and follow-up of information.

While IMPACT captures approximately 90% of pediatric tertiary care beds in Canada, it does not capture all paediatric admissions. With only two centres in Ontario, Canada's most populous province, the network does not adequately represent tertiary care admissions there. Solutions are being sought to address this. In spite of these limitations, IMPACT continues to be well suited to the Canadian context and provides a high level of vigilance for serious AEFIs among children.

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Conflict of interest

None

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