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Annual Report on Vaccine Safety in Ontario, 2013

TECHNICAL REPORT

January 2015

Public Health Ontario

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Annual Report on Vaccine Safety in Ontario, 2013

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January 2015

Important Notice

This document was developed by Public Health Ontario (PHO). PHO provides scientific and technical advice to Ontario's government, public health organizations and health care providers. PHO's work is guided by the current best available evidence.

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Glossary of Active Immunizing Agent (Vaccine) Acronyms Used in This Report

BCG	bacille Calmette-Guérin
Chol-O	cholera (oral)
Chol-Ecol-O	cholera, *E. coli* (oral)
DTaP-IPV	diphtheria, tetanus, acellular pertussis, inactivated polio
DTaP-IPV-Hib	diphtheria, tetanus, acellular pertussis, inactivated polio, *Haemophilus influenzae* type b
HA	hepatitis A
HAHB	hepatitis A and B
HA-Typh-I	hepatitis A and typhoid (injectable)
HB	hepatitis B
Hib	*Haemophilus influenzae* type b
HPV2	human papillomavirus bivalent
HPV4	human papillomavirus quadrivalent
Inf	influenza (trivalent inactivated; adjuvanted and non-adjuvanted and live attenuated vaccines)
JE	Japanese encephalitis
Men-C-ACWY	meningococcal conjugate serogroups A, C, W, Y
Men-C-C	meningococcal conjugate serogroup C
MMR	measles, mumps, rubella
MMRV	measles, mumps, rubella, varicella
Pneu-C-13	pneumococcal conjugate 13- valent
Pneu-P-23	pneumococcal polysaccharide 23- valent
Rab	rabies
Rot-1	rotavirus monovalent
Td	tetanus, diphtheria,
Tdap	tetanus, diphtheria, acellular pertussis
Tdap-IPV	tetanus, diphtheria, acellular pertussis, inactivated polio
Td-IPV	tetanus, diphtheria, inactivated polio
Typh-I	typhoid (injectable)
Typh-O	typhoid (oral)
Var	varicella
YF	yellow fever
Zos	herpes zoster

Executive Summary

This report summarizes adverse events following immunization (AEFIs) reported in Ontario following vaccines administered in 2013. This second comprehensive annual assessment of vaccine safety builds upon last year's report, which was the first of its kind to be undertaken in Ontario. The information presented in this report contributes to the development and maintenance of a robust provincial vaccine safety surveillance system and provides relevant and timely information to support health professionals to communicate effectively about vaccine safety.

AEFIs reported following vaccines administered between January 1 and December 31, 2013, were extracted from the integrated Public Health Information System (iPHIS). There were 642 reports of confirmed AEFIs representing an overall reporting rate of 4.7 per 100 000 population, which is comparable to 2012. However, the annual rate of reporting relative to population size in Ontario continues to be lower compared to other jurisdictions.The highest age-specific reporting rates were in infants less than one year of age and young children one to three years of age (29.5 and 19.6 per 100 000 population, respectively). A female predominance was notable in adults 18 to 64 years of age (85.7% of reports). The most frequently reported events were pain, redness or swelling at the injection site lasting >4 days, systemic rash and allergic skin reactions (33.7%, 22.8% and 18.7% of reports, respectively). The majority of events (74.9%) were completely recovered at the time of reporting. There were 27 serious AEFIs (4.2%). Vaccine-specific reporting rates ranged from 4.3 to 340.4 per 100 000 doses distributed for influenza and DTaP-IPV (diphtheria, tetanus, acellular pertussis, inactivated poliovirus) vaccines, respectively.

Overall, this report finds that vaccines administered in Ontario in 2013 resulted in a low rate of reporting of adverse events. Most reported events were mild (i.e., injection site reactions) and resolved completely. Serious reports were rarely reported and were most often related to known but rare events following vaccine. A number of limitations are described, including under-reporting, which is a known limitation inherent to many passive AEFI surveillance systems but appears more pronounced in Ontario relative to other jurisdictions. Other limitations specific to Ontario include the lack of a population-based immunization registry required to calculate incidence rates of AEFIs and limited analysis of trends over time. While some key improvements in AEFI data quality were observed, specific ongoing challenges with data completeness and validity have been noted. It is expected that recently implemented updates to AEFI surveillance guidelines will contribute towards improved data quality.

The following actions will continue or be undertaken to further strengthen the provincial AEFI surveillance system:

- Continue efforts to address the quality and completeness of AEFI data in iPHIS through maintaining up-to-date guidance documents on AEFI iPHIS data entry; regular education and training for PHUs; follow-up of specific data quality issues through weekly review of AEFI reports; and annual AEFI data clean-up initiatives

- Implement targeted provincial strategies to increase AEFI reporting among health care providers, in particular within the Universal Influenza Immunization Program (UIIP) in collaboration with health professional associations, PHUs and the Ministry of Health & Long-Term Care in addition to enhanced support for PHUs to promote AEFI reporting with local immunization providers.
- Explore new methods to promote the use of current AEFI surveillance forms and guidance documents to PHU staff using new or existing communication channels including the PHO website, PHO education events, conferences and workshops, email distribution lists, and monthly provincial manager's teleconferences in collaboration with the MOHLTC and PHUs.

Background

Confidence in vaccines is essential to the success of immunization programs. In recent years, perception of vaccines as unsafe or unnecessary has contributed to a growing number of individuals who are hesitant about vaccines.[1] While reasons for vaccine hesitancy are multifactorial, specific concerns about safety may be addressed through effective communication with health professionals and the public about the vaccine safety surveillance system and the safety of specific vaccines.[1-3]

In Canada, vaccines are thoroughly reviewed for efficacy and safety prior to being approved for use by Health Canada. Once approved, vaccines continue to be monitored closely in the context of increased production and use in the population. Post-marketing surveillance has the potential to identify previously unrecognized or rare adverse events following immunization (AEFIs) or an increase in frequency or severity of known AEFIs which can be further evaluated.[4] Within the context of post-marketing surveillance, AEFIs are defined as any untoward medical occurrence that follows immunization and does not necessarily have a causal relationship with the vaccine. The adverse event may be any unfavourable or unintended sign, laboratory finding, symptom, or disease.[4]

In Canada, post-marketing surveillance is a shared responsibility between Health Canada, the vaccine manufacturers, the Public Health Agency of Canada (PHAC), provinces and territories, as well as local public health authorities. PHAC and Health Canada coordinate post-marketing vaccine safety surveillance nationally while provinces and territories coordinate surveillance of AEFIs occurring within their jurisdiction in collaboration with their local partners.

In October 2013, PHO released the Annual Report on Vaccine Safety in Ontario, 2012, to all PHUs in the province.[5] The findings of this report represented the first comprehensive annual assessment of vaccine safety in the province. It was initiated to facilitate ongoing assessment of AEFIs and contribute to the provision of relevant and timely information for health professionals and the public about the safety of vaccines administered in Ontario. To this end, an abridged version of the 2012 report was released publicly on the PHO website in February 2014 along with an immunizer overview, which included data from the report as well as key vaccine safety messages for health professionals.[6] The public release of the report resulted in substantial print, broadcast, and online media coverage from national and local media sources including a widely reprinted article “Study finds low rate of adverse events related to vaccinations in Ontario.”[7]

This second vaccine safety report builds upon the first and represents continued commitment to developing and maintaining a robust provincial vaccine safety surveillance system and regularly communicating surveillance findings to local PHU stakeholders, health professionals and members of the public.

Adverse event following immunization surveillance in Ontario

The objectives of AEFI surveillance in Ontario are to:

- Identify and investigate serious or unexpected occurrences of AEFIs, particularly for new vaccines
- Detect and investigate safety signals (e.g., lot-specific problems)
- Estimate provincial rates of reported AEFIs by vaccine
- Report to stakeholders on the safety of publicly funded vaccines in Ontario
- Maintain public confidence in vaccine programs.

The *Health Protection and Promotion Act (HPPA)* requires that specified health professionals report AEFIs to their local medical officer of health (MOH).[8] The Ontario Public Health Standards (OPHS) describe the role of PHUs in the monitoring, investigation, and documentation of AEFIs, subsequent provincial reporting via the integrated Public Health Information System (iPHIS), as well as promotion of AEFI reporting by health care providers in their jurisdiction.[9,10] For more detailed descriptions of the legislative mandate, policy framework and process of AEFI reporting in Ontario, please refer to the Annual Report on Vaccine Safety in Ontario, 2012.[6]

On January 1, 2012, PHO assumed responsibility for provincial AEFI surveillance and case management from the MOHLTC. Following a period of assessment and consultation, a number of changes were implemented on January 1, 2013, with the goal of improving data quality and strengthening the provincial AEFI surveillance system. These changes included:

- **Revised provincial AEFI case definitions** [10] to address identified gaps and align with national/international definitions where available
- **Updates to the iPHIS application and iPHIS User Guide for AEFIs** [11] to align with provincial case definitions and improve support for valid, complete and timely data entry
- **A new Ontario AEFI reporting form** [12] to support health professional reporting and local AEFI case management and reporting processes, replacing the PHAC AEFI form previously in use
- **Continuation of the provincial Vaccine Safety Surveillance Working Group (VSSWG)** with representation from PHUs, MOHLTC, PHAC, and PHO to oversee the renewal and enhancement of AEFI surveillance in Ontario (originally initiated in June 2012).

Objectives and scope

This report will summarize AEFIs reported in Ontario following vaccines administered in 2013. In addition, reporting trends will be assessed by comparison with AEFIs reported following vaccines administered between 2010 and 2012. Recommendations for improved AEFI data/surveillance processes are also included based on the findings of this report.

Methods

Provincial surveillance systems to monitor AEFIs in Ontario

AEFI reports are entered by PHUs into iPHIS, an electronic reporting system for reportable diseases and reportable events in Ontario. AEFIs should be reported in iPHIS within five business days of the PHU receiving initial notification.[13] The minimum data elements for each AEFI report are specified in the iPHIS AEFI User Guide (2013) and associated bulletins and directives issued by the MOHLTC.[11,13] Starting on January 1, 2013, AEFI reports were classified in iPHIS according to the Infectious Diseases Protocol, Provincial Case Definitions for AEFI, 2013.[10] AEFIs reported between 2010 and 2012 (included in this analysis for comparison of temporal trends) were classified according to the Infectious Diseases Protocol, Appendix B: Provincial Case Definitions for AEFI, 2009.[11,15] Appendix 1 provides a detailed summary of the iPHIS revisions made as a result of the updated case definitions, however it is important to note that as of January 1, 2013 pain, redness orswelling at the injection site lasting less than 4 days was no longer reportable. The rationale for this change was to reduce the reporting burden of this common event which is mild and does not require any public health action.

PHO reviews all AEFIs reported by PHUs on a weekly basis for data quality and completeness, with an emphasis on serious AEFIs (defined below). PHUs are contacted directly if required information is missing or incomplete. In addition to monitoring ongoing data quality throughout the year, a formal data clean-up initiative occurred between February 24 and March 31, 2014, whereby PHUs were requested to review AEFI reports following vaccines administered in 2013 and update missing or incomplete information for selected data fields.[15]

Analysis of epidemiologic data

We extracted all reports of AEFIs with a vaccine administration date between January 1 and December 31, 2013, from iPHIS on April 28, 2014. In addition, all AEFI reports following vaccines administered between 2010 and 2012 were extracted at the same time for assessment of temporal trends only. For in-depth assessment of AEFIs following vaccines administered in 2012, please see the Annual Report on

Vaccine Safety in Ontario, 2012. AEFI data from 2012 included in this report may different from data presented in the 2012 annual report due to late reporting and data entry of adverse events occurring in 2012.

Excluded from this analysis are reports of adverse events associated with passive immunizing agents (e.g., immune globulin) or diagnostic agents (e.g., tuberculin skin test) only (i.e., when no active immunizing agents were administered at the same time).

As of January 1, 2013, AEFI reports are classified as "Confirmed" or "Does not meet definition" (DNM) case classification according to provincial surveillance case definitions.[10] As per the iPHIS User Guide, the "Person under investigation" (PUI) case classification is for use in the investigation stage only. When the investigation is complete, the case classification should be updated to "Confirmed" or "DNM."[11] Other case classifications such as "Suspect" or "Probable" are not applicable to AEFI and are not recommended. The case definitions are:

- **Confirmed**

  Any reported event listed in sections 5.0 (Clinical Evidence) in a vaccine recipient which follows immunization which cannot be clearly attributed to other causes. A causal relationship with the administration of the vaccine does not need to be proven.

- **Does not meet definition (DNM)**

  Any reported event in a vaccine recipient which follows immunization which has been clearly attributed to other causes. [10]

As of the data extraction date, there was a single case under active investigation, and classified as a PUI. We included this case under its ultimate classification ("confirmed") for the purposes of this analysis. This classification occurred on July 23, 2014.

For this report, all case classifications by year between 2010 and 2013 were included in the assessment of overall trends in AEFI reporting only. Temporal trends are presented by date of vaccine administration. Descriptive analyses are limited to "Confirmed" reports following vaccines administered in 2013 with some comparison to 2012. Age categories for analysis (<1 year, 1-3 years, 4-10 years, 11-17 years, 18-64 years, 65+) are based on key age milestones within the provincial immunization schedule.[16] The AEFI reporting source is the source of the initial AEFI report and not necessarily the only source of information in the AEFI investigation. Reporting source categories presented are mutually exclusive (i.e., physicians are a separate category from other health professionals which includes nurses and pharmacists). While it is not possible to directly estimate an AEFI reporting rate by reporting source without comprehensive immunization registry data, reporting rates are estimated for agents that are primarily administered by one category of provider (i.e., physicians, PHUs). Proportions are based on AEFI reports with completed data. As such, denominators will vary by iPHIS field.

The term "vaccine" is used to refer to a generic active immunizing agent and may include more than one vaccine product (e.g., "influenza vaccine" refers to all influenza vaccine products). Active immunizing

agents are referred to throughout this report using standard acronyms as per the Glossary (e.g., MMR for measles, mumps, rubella). For a complete list of vaccine abbreviations, corresponding products and trade names and available "Agent" values in iPHIS see Appendix 2.

Each AEFI report represents one individual vaccine recipient and describes one or more adverse events that have been temporally associated with receipt of one or more vaccines administered at the same time. Adverse events have been presented both individually and by categories as per the Infectious Diseases Protocol, Provincial Case Definitions for AEFI, 2013.[10] Of note, provincial case definitions include events that are potentially overlapping. For example the case definition of "Rash" refers to a systemic reaction of skin or mucosal changes (either new or an exacerbation of a previous condition); however, there are some important caveats. Urticaria (hives), a specific form of rash, is captured under the case definition of "Allergic reaction – skin" which includes specific dermatologic/mucosal signs and symptoms of an allergic reaction. In addition, redness or swelling occurring at the site of injection only (i.e., in the absence of systemic presentation or urticaria) is captured under the case definition of "Pain, redness or swelling at the injection site."

Serious AEFIs were defined according to public health AEFI reporting guidelines from PHAC (See Appendix 3) which were most recently updated in 2014.[17] The definition is consistent with the International Conference on Harmonisation (ICH) E2A and E2D definitions[18,19], which defines an AEFI as serious if it 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. In the context of passive AEFI surveillance in Ontario, serious AEFIs are those that result in death or hospital admission. Persistent or significant disabilities and congenital anomalies are not systematically captured in iPHIS due to the relatively brief follow-up period, however AEFI reports with "Residual effects" selected as the outcome in iPHIS are reviewed to identify any additional serious reports. Additionally, "medically important events" are presented separately per revised PHAC guidelines, which define these events as "adverse events of special importance" rather than as "serious events"; in the 2012 report, these events would have been captured under the serious category. These events include anaphylaxis, encephalitis, acute disseminated encephalomyelitis, myelitis, meningitis, Guillain-Barré syndrome (GBS), acute cerebellar ataxia, intussusception and thrombocytopenia.[17] Where the above listed events also meet the definition of serious (e.g., hospitalization), they are also included within the serious category. Events managed as anaphylaxis are assessed using the Brighton Collaboration case definition and diagnostic levels of certainty for anaphylaxis.[20]

We calculated AEFI reporting rates using the 2010 to 2012 Ontario population estimates and population projections for 2013[21] (overall reporting rate per 100 000 population) and doses distributed within the publicly funded immunization program (vaccine-specific reporting rate per 100 000 doses distributed) using net vaccine distribution data provided by the Ontario Government Pharmaceutical and Medical Supply Service (OGPMSS). Net vaccine distribution data estimates are adjusted for vaccine wasted or reusable vaccine returned to OGPMSS. Reporting rates using doses distributed as the denominator were not calculated for vaccines that were exclusively privately purchased (i.e., not publicly funded) in Ontario. We performed statistical analyses using SAS version 9.3 and Microsoft Excel 2010.

This project was reviewed on behalf of the PHO Ethics Review Board (ERB) through the administrative review process and was granted approval for a period of one year commencing May 16, 2014.

Notes on interpretation

The adverse events we describe in this report are **temporally associated** and are not necessarily **causally linked** to vaccines. Our assessment is based on iPHIS data only and not comprehensive chart review. We provide reporting rate estimates for comparison to other passive surveillance systems and monitoring reporting trends over time; they should not be interpreted as incidence rates.

Trends in reported AEFIs are influenced by changes to the publicly funded program. Program changes within the last few years that may impact on AEFI surveillance data presented in this report include:

- Implementation of a new/revised publicly funded programs in August 2011, including: [22]
    - Rotavirus vaccine (Rot-1/Rotarix®) for infants at ages two and four months
    - Reduction from four to three doses of pneumococcal conjugate 13-valent (Pneu-C-13) vaccine for low-risk children
    - Routine second dose of varicella vaccine administered as the combined agent MMRV at four to six years of age (previously second dose of MMR vaccine was administered at 18 months of age)
    - Second dose varicella vaccine catch-up program for children born on or after January 1, 2000, and at least four years of age
    - Pertussis vaccine for all adults 19 to 64 years of age who have not received an adolescent booster at 14 to 16 years of age.
- Replacement of DTaP-IPV (Quadracel®) with Tdap-IPV (Adacel-IPV®, Boostrix®-Polio) for the 4- to 6-year-old booster dose in April 2012.
- New influenza vaccine products implemented for the 2011–12 influenza season including Fluad® (for high-risk persons 65 years of age and older) and Agriflu® for all those aged six months and older, as well as a full dose of trivalent influenza vaccine (TIV) for infants and children 6 to 35 months of age and removal of egg allergy as a contraindication to TIV.
- Extended HPV4 vaccine eligibility until the end of grade 12 for girls who didn't receive or complete the three-dose HPV immunization series in Grade 8, starting in September 2012.[23]

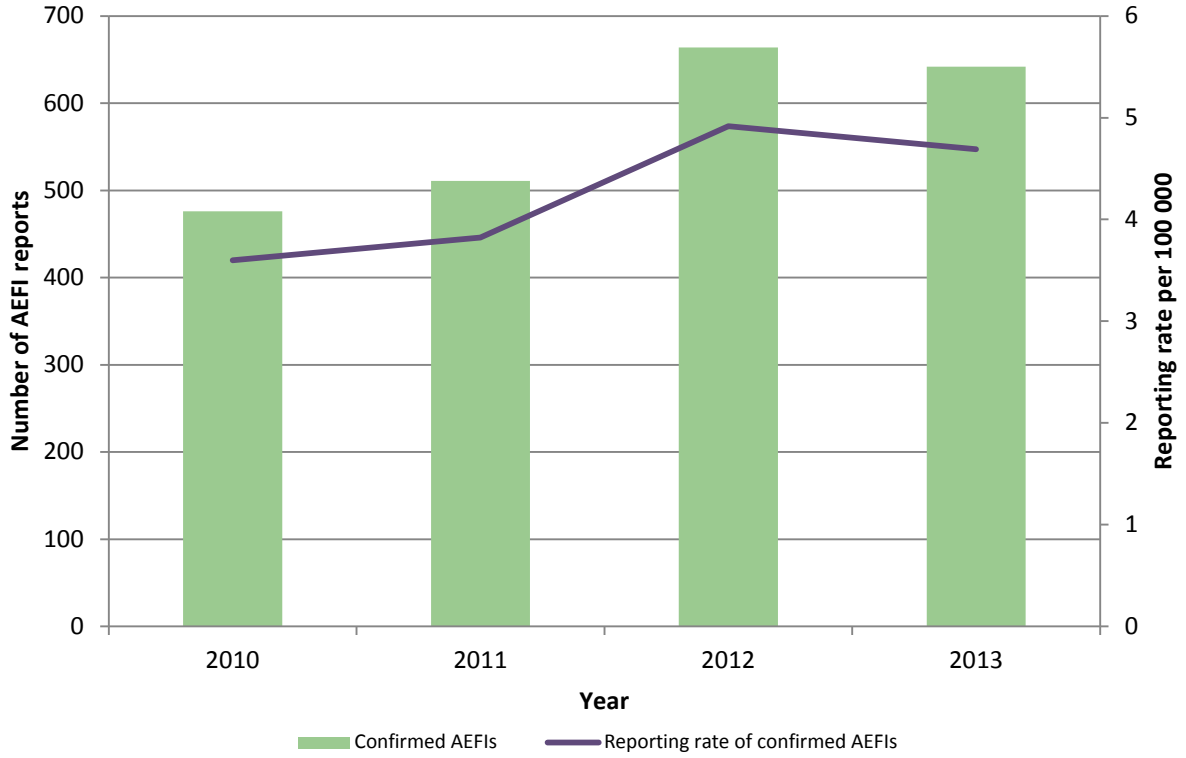
Results

There were 726 AEFIs reported in iPHIS where the date of vaccination was between January 1 and December 31, 2013. Of these, 642 (88.4%) had a case classification of "Confirmed" and 84 (11.6%) had a case classification of "Does not meet definition." There were no reports with other case classifications (i.e., "PUI") in 2013. All subsequent analyses are limited to AEFI reports classified as "Confirmed."

Reporting trends

The population-based reporting rate of "Confirmed" AEFIs following vaccines administered in Ontario in 2013 was 4.7 per 100 000 population. This is slightly lower compared with the 2012 reporting rate (4.9 per 100 000 population); however, both years have increased (32.4% increase for 2012 and 27.0% for 2013) compared with the average annual reporting rate of 3.7 per 100 000 population in 2010 and 2011 (3.6 and 3.8 per 100 000 population, respectively) (Figure 1).

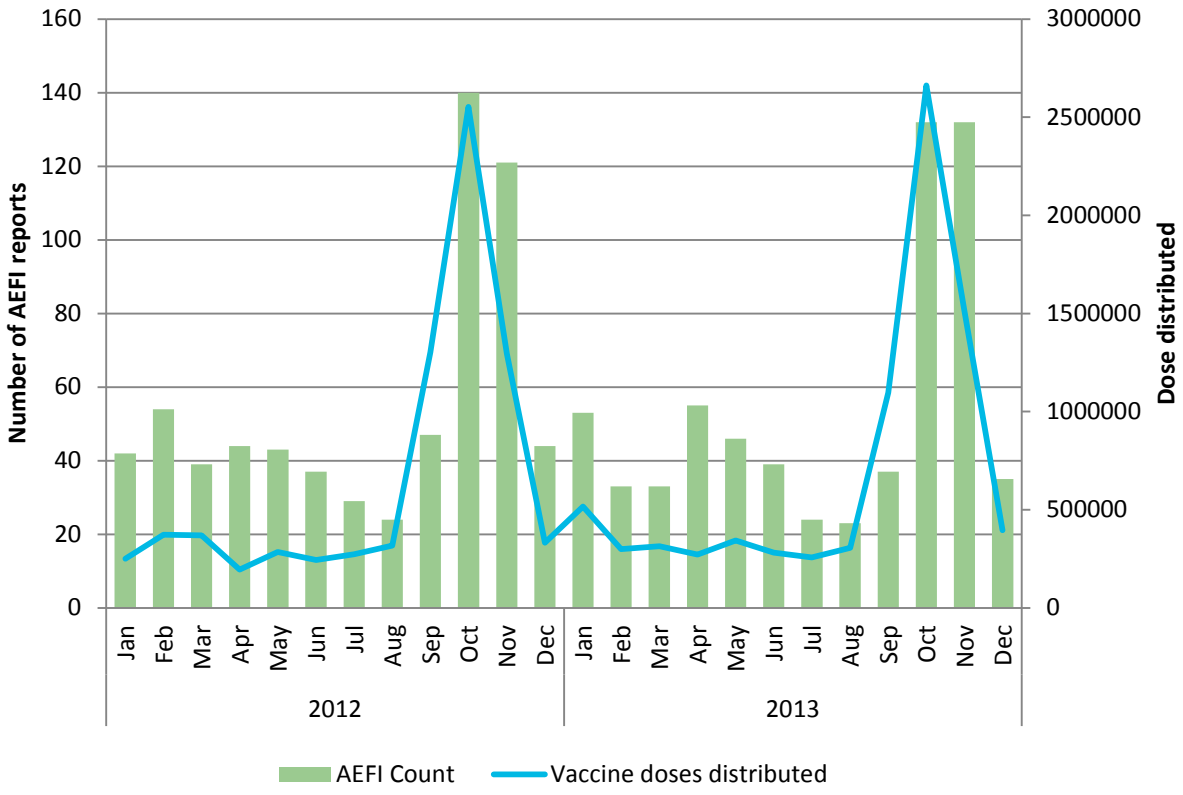
Figure 1. Number of "Confirmed" AEFI reports and reporting rate per 100 000 population in Ontario, by year, 2010–13



Reports of AEFI by month of vaccine administration in 2013 ranged from a low of 23 reports in August to a peak of 132 reports in both October and November, followed by small peaks observed in January and April. AEFI reports by month of administration generally mirror the monthly distribution of vaccine by OGPMSS with the exception of November, which likely reflects continued vaccine use following bulk

distribution of influenza vaccine in October. For both AEFI reports by month and vaccine distribution, the overall trend by month in 2013 is consistent with 2012 (Figure 2).

Figure 2. Number of AEFI reports and publicly funded vaccine distribution[1] by month in Ontario, 2012-13



Notes:

1. Includes net vaccine distribution from Ontario Government Pharmacy & Medical Supply Service (OGPMSS) (i.e., publicly funded vaccine doses) only. Counts include all confirmed AEFIs reported 2012 to 2013.

Age and sex distribution

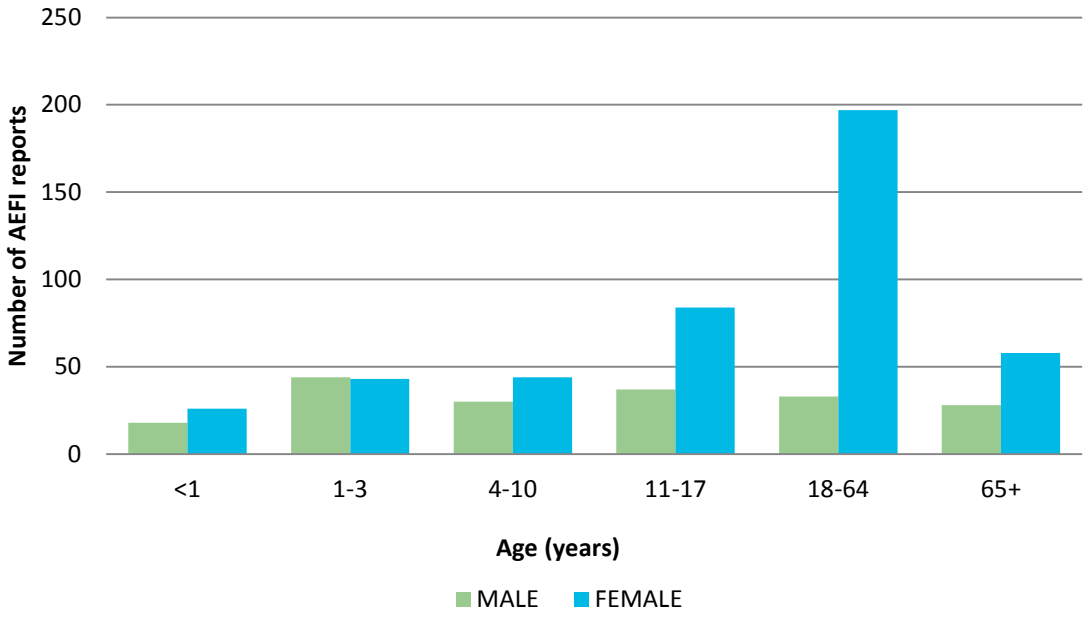
The age-specific reporting rates in 2013 were higher among the younger age groups, with the highest reporting rate in infants less than one year of age and the lowest among adults 18 to 64 years of age. Age-specific reporting rates were consistent between 2012 and 2013 with the exception of 4- to 10-year-olds, where the rate decreased in 2013 (Table 1).

Table 1. Number of AEFI reports and reporting rate per 100 000 population in Ontario, by age group, 2012-13

Age Group (Years)	2013		2012	
	Count	Reporting rate (per 100 000 population)	Count	Reporting rate (per 100 000 population)
<1	44	29.5	41	29.0
1-3	87	19.6	81	18.9
4-10	74	7.1	125	12.2
11-17	121	11.1	119	10.8
18-64	230	2.6	225	2.5
65+	86	4.2	73	3.7
Total	**642**	**4.7**	**664**	**4.9**

The distribution of AEFI reports in 2013 by sex is weighted towards females, who comprised 70.4% (n=452) of all AEFI reports. The distribution of AEFI reports by sex also varies with age, where female predominance is seen mostly in adults 18 to 64 years of age (85.7%), followed by adolescents 11 to 17 years of age (69.4%) and those 65 years of age and older (67.4%). This is consistent with the age–sex distribution in 2012. For the adolescent age group, it should be noted that there is one publicly funded vaccination program that targets only female adolescents (HPV4), therefore we would expect more AEFI reports among females in the 11 to 17 year age category. Only a slight female predominance is observed in children less than 11 years of age where 55.1% of reports are female (Figure 3).

Figure 3. Age and sex distribution of AEFI reports in Ontario, 2013



Reporting source

Among AEFIs with reporting source completed (91.6%; n=588) the most frequent reporting sources were physicians who reported 31.0% of AEFIs, followed by other health care professionals (29.1%), family members (17.9%), other (11.6%) and self-reports (10.5%). Although the proportion of all AEFI reported by physicians decreased in 2013 (31.0%) compared to 2012 (37.5%); the distribution of AEFIs by reporting source in 2013 was otherwise similar to 2012 (data not shown).

For school-based programs primarily administered by PHUs (HB, Men-C-ACWY, HPV4 vaccines), the reporting rate was 20.0 per 100 000 doses distributed. For infant and preschool immunization programs primarily administered by physicians (DTaP-IPV-Hib, DTaP-IPV, Tdap-IPV, Rot-1, Pneu-C-13, MMR, MMRV, Men-C-C vaccines), the reporting rate was 7.7 per 100 000 doses distributed.

Vaccines

There were 642 AEFI reports associated with 28 different vaccines in 2013. Most reports were associated with administration of a single vaccine (79.1%) while 14.6% of reports were associated with receipt of two vaccines and 6.2% were associated with three (the highest number of vaccines in a single report). There were 590 AEFI reports associated with vaccines that are included within the publicly funded immunization program. As seen in Table 2, the highest overall vaccine-specific reporting rates in 2013 were observed with DTaP-IPV, rabies and monovalent Hib, although no serious AEFIs were reported in association with any of these vaccines. The lowest vaccine-specific reporting rates were observed for influenza and Td. In terms of serious AEFIs, Rot-1 and Pneu-C-13 vaccine had the highest rates, whereas 7 publicly funded vaccines were not associated with any serious AEFIs in 2013. Although influenza vaccines account for 50.9% of all publicly funded vaccine distributed in the province, they were associated with 30.5% of all confirmed AEFI reports.

Table 2. Number, percent and reporting rate of AEFI reports in Ontario, 2013

Vaccine[1]	Number of AEFI reports by vaccine	Percent serious[2]	Publicly funded vaccines only				
			Doses[3] distributed	Vaccine-specific reporting rate[4]	Vaccine-specific serious reporting rate[4]	Percent[5] of all confirmed AEFI reports	Percent of all vaccine distributed[3]
Infant and childhood vaccines							
DTaP-IPV-Hib	63	15.9	564,840	11.2	1.8	10.7	6.9
Pneu-C-13	52	17.3	438,650	11.9	2.1	8.8	5.3
Rot-1	21	33.3	263,809	8.0	2.7	3.6	3.2
Men-C-C	23	13.0	148,660	15.5	2.0	3.9	1.8
MMR	45	6.7	302,720	14.9	1.0	7.6	3.7
Var	58	8.6	303,144	19.1	1.6	9.8	3.7
MMRV	4	0.0	28,320	14.1	0.0	0.7	0.3
DTaP-IPV	8	0.0	2,350	340.4	0.0	1.4	<0.1
Tdap-IPV	26	0.0	207,240	12.5	0.0	4.4	2.5
Adolescent vaccines							
Men-C-ACWY	37	0.0	119,352	31.0	0.0	6.3	1.5
HB	56	0.0	267,934	20.9	0.0	9.5	3.3
HPV4	40	0.0	177,999	22.5	0.0	6.8	2.2
Tdap	51	2.0	675,070	7.6	0.1	8.6	8.2

Vaccine[1]	Number of AEFI reports by vaccine	Percent serious[2]	Publicly funded vaccines only				
			Doses[3] distributed	Vaccine-specific reporting rate[4]	Vaccine-specific serious reporting rate[4]	Percent[5] of all confirmed AEFI reports	Percent of all vaccine distributed[3]
Routine adult vaccines							
Pneu-P-23	59	5.1	235,330	25.1	1.3	10.0	2.9
Td	13	0.0	278,805	4.7	0.0	2.2	3.4
Universal Influenza Immunization Program (UIIP)							
Inf	180	3.9	4,186,390	4.3	0.2	30.5	50.9
Other high-risk publicly funded, travel and non-publicly funded vaccines							
Chol-Ecol-O	1	0.0	-	-	-	-	-
Chol-O	1	0.0	-	-	-	-	-
HA	3	0.0	9,950	30.2	0.0	0.5	0.1
HAHB	7	0.0	-	-	-	-	-
HA-Typh-I	4	0.0	-	-	-	-	-
Hib	3	0.0	3,105	96.6	0.0	0.5	<0.1
HPV2	1	100.0	-	-	-	-	-
Typh-I	1	0.0	-	-	-	-	-
Typh-O	1	0.0	-	-	-	-	-
YF	7	0.0	-	-	-	-	-
Zos	42	0.0	-	-	-	-	-
Rab	9	0.0	8,672	103.8	0.0	1.5	0.1

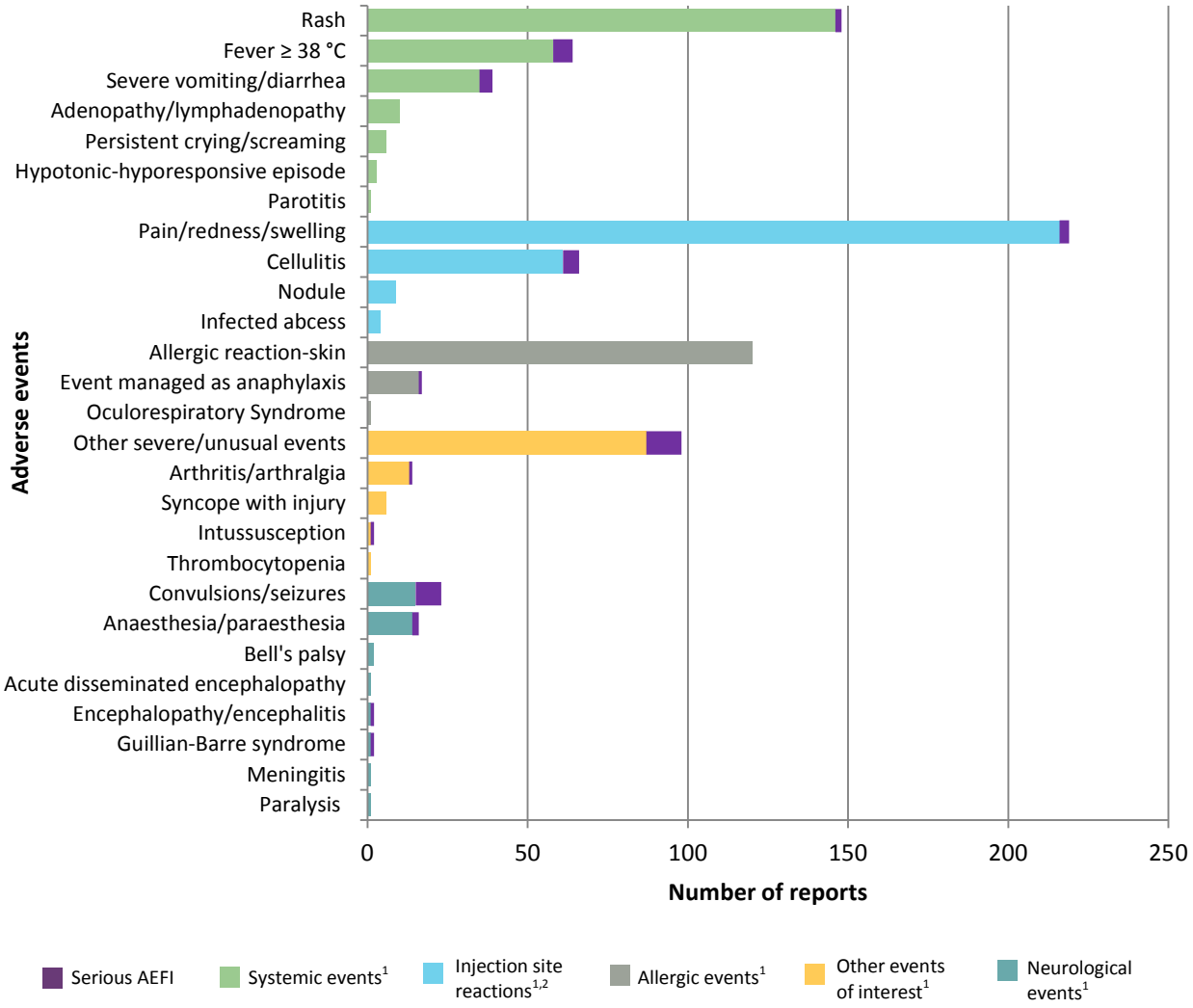
Notes:

1. Only those vaccines with AEFI reports are shown. See Appendix 2 for a list of all possible vaccines, corresponding vaccine products and agent abbreviations. Vaccines are grouped by recommended age of receipt as per the Publicly Funded Immunization Schedules for Ontario.[16] Age of receipt of some vaccines may vary according to age and immunization status of individuals and vaccine-specific indications.
2. Proportion of reports within each vaccine that are serious (denominator is the total number of vaccine-specific AEFIs).
3. Doses distributed are obtained from Ontario Government Pharmacy and Medical Supply Service (OGPMSS) for publicly funded vaccines only (n=8,222,340).
4. Vaccine-specific reporting rates per 100 000 doses distributed.
5. Each AEFI report may include one or more agents. Percentages will not sum to 100%. The denominator is 590 (total number of confirmed AEFI reports following publicly funded vaccines).

Adverse events

The majority of reports were associated with one adverse event (73.6%) while 20.9% of reports were associated with two events and 5.5% were associated with three or more adverse events (the highest number of adverse events in a single report was four). The most frequently reported events were pain/redness or swelling at the injection site (33.7%; n=216), followed by rash (22.8%; n=146), and allergic reactions of the skin in 18.7%; (n=120) of all AEFI reports (Figure 5).

Figure 5. Number of serious and non-serious AEFI reports in Ontario, by adverse event and category, 2013



Notes:

1. Non-serious AEFIs within each event category. All serious AEFIs within each event are shaded purple.
2. Pain, redness or swelling at the injection site includes: pain, redness or swelling at the injection site lasting four days or more and/or pain, redness or swelling at the injection site (of any duration) extending beyond the nearest joint

The frequency of reporting of specific events is very similar to 2012 (See Appendix 4). Of note, the frequency of reporting of "Other severe/unusual events" decreased in 2013 (13.6%; n=87) compared with 2012 (19.0%; n=126). The most frequently reported category of events in 2013 was injection site reactions which were present in a large proportion of reports (41.0%; n=263) including 198 reports (30.9%) in which an injection site reaction was the only reported event (Table 3). Reports that included any injection site reaction in 2013 were about the same compared with 2012 despite 2012 data including reports less than four days duration (41.0% and 40.5% respectively).

Among all injection site reactions, the most frequently reported vaccines were influenza (26.2%; n=69), Pneu-P-23 (18.3%; n=48) and Tdap (14.4%; n=38). For rash, another frequently reported event, the most commonly reported vaccines included influenza (18.5%; n=27), MMR (17.8%; n=26), Pneu-C-13 (16.4%; n=24) and varicella (16.4%; n=24). Among all allergic skin reactions, influenza was again the most common vaccine reported (32.5%; n=39), followed by HB (15.0%; n=18) and Men-C-ACWY (12.5%; n=15).

Table 3. Number and distribution of AEFI reports in Ontario, by adverse event category, 2013

Adverse event category[1]	Adverse event[2]	All AEFI reports n[3] (%)	Serious AEFI n (%)[5]
Allergic events		**133 (20.7)**	**1 (0.8)**
	Allergic reaction – skin	120 (18.7)	0 (0)
	Event managed as anaphylaxis[4]	16 (2.5)	1 (6.3)
	Oculorespiratory syndrome (ORS)	1 (0.2)	0 (0)
Injection site reactions		**263 (41.0)**	**6 (2.3)**
	Cellulitis	61 (9.5)	5 (8.2)
	Nodule	9 (1.4)	0 (0)
	Infected abscess	4 (0.6)	0 (0)
	Sterile abscess	0 (0)	0 (0)
	Pain/redness/swelling at the injection site[1]	216 (33.7)	3 (0.01)
	Pain/redness/swelling extending beyond nearest joint	54 (8.4)	2 (3.7)
	Pain/redness/swelling 4-10 days	144 (22.5)	1 (0.7)
	Pain/redness/swelling >10 days	36 (5.6)	0 (0)
Neurologic events		**35 (5.5)**	**11 (31.4)**
	Acute disseminated encephalomyelitis (ADEM)[4]	1 (0.2)	0 (0)
	Anaesthesia/paraesthesia	14 (2.2)	2 (14.3)
	Bell's palsy	2 (0.3)	0 (0)
	Convulsions/seizures	15 (2.3)	8 (53.3)
	Encephalopathy/encephalitis[4]	1 (0.2)	1 (100)
	Guillain-Barré syndrome (GBS)[4]	1 (0.2)	1 (100)
	Meningitis[4]	1 (0.2)	0 (0)
	Paralysis other than Bell's palsy	1 (0.2)	0 (0)

Adverse event category[1]	Adverse event[2]	All AEFI reports n[3] (%)	Serious AEFI n (%)[5]
Other events of interest		**106 (16.5)**	**12 (11.3)**
	Arthritis/arthralgia	13 (2.0)	1 (7.7)
	Intussusception[4]	1 (0.2)	1 (100)
	Other severe/unusual events	87 (13.6)	11 (12.6)
	Syncope with injury	6 (0.9)	0 (0)
	Thrombocytopenia[4]	1 (0.2)	0 (0)
Systemic reactions		**224 (34.9)**	**10 (4.5)**
	Adenopathy/lymphadenopathy	10 (1.6)	0 (0)
	Fever ≥ 38 °C	58 (9.0)	6 (10.3)
	Hypotonic-hyporesponsive episode	3 (0.5)	0 (0)
	Parotitis	1 (0.2)	0 (0)
	Persistent crying/screaming	6 (0.9)	0 (0)
	Rash	146 (22.8)	2 (1.4)
	Severe vomiting/diarrhea	35 (5.5)	4 (11.4)

Notes:

1. Adverse event categories represent groupings of specific types of adverse events and are not mutually exclusive. For category totals, reports with more than one specific event within a category are counted only once. Thus category totals will not sum to the total specific adverse events overall or within a category.
2. Includes only those adverse events where the count was at least one. For a complete list of possible values in iPHIS and corresponding definitions, please refer to Appendix 1.
3. Each AEFI report may contain one or more specific adverse events which are not mutually exclusive. Percentages will not sum to 100%. The denominator is the total number of confirmed AEFI reports with at least one adverse event reported. The total number of confirmed AEFI reports was 641 (one report had missing adverse events and was therefore excluded).
4. Medically important events.
5. Percent of reports that were serious *within* each event.

There were 22 AEFIs reported which included "medically important events" representing 3.4% of all reports. Four (18.2%) of these events also met the definition of a serious AEFI (i.e., hospital admission); one each of anaphylaxis, encephalopathy/encephalitis, GBS, and intussusception. See below for further description of these serious AEFIs. The remaining 18 events did not meet the serious definition and included 15 additional reports of anaphylaxis, as well as one each of acute disseminated encephalomyelitis (ADEM), meningitis, and thrombocytopenia. The ADEM and meningitis reports were in individuals 65 years of age and older, following receipt of zoster vaccine (19 days and one day respectively). The ADEM and meningitis reports were in individuals 65 years of age and older, 19 days and one day, respectively, following receipt of zoster vaccine. The report of ADEM was in an adult subsequently diagnosed with new onset multiple sclerosis while the meningitis report had varicella zoster virus detected by lumbar puncture, however genotyping was not done to differentiate between wild-type and vaccine virus. The report of thrombocytopenia was in an adult, 11 days following receipt of influenza vaccine.

Among 16 reports of anaphylaxis, half were following influenza vaccine, three following HB and Men-C-ACWY administered concomitantly, two following Tdap (one Tdap alone and one where varicella was administered concomitantly), and one each following HPV4, HA-Typh-I administered concomitantly with YF, and DTaP-IPV administered concomitantly with Pneu-C-13. Five reports (31.3%) met the Brighton case definition of anaphylaxis (one level one and four level two). Among the remaining reports, four did not meet the Brighton case definition based on the information in the report and seven reports did not contain enough information to complete an assessment.

Health care utilization and outcome

In reports with health care utilization information completed, out-patient medical consultation was sought in 72.6% (453/624) while 22.4% (143/637) had an emergency room visit and 4.2% (26/613) were admitted to hospital.

Outcome information was completed in 91.1% (n=585) of 2013 reports, a slight increase in completeness compared to 2012 (88.1%; n=585). The majority (74.9%; 438) were recovered at the time of reporting, followed by 23.1% who were not yet recovered but likely to recover, as per the outcome definitions in the iPHIS User Guide.[11] In a very small proportion of AEFI reports (1.9%; n=11) the outcome was reported as "residual effects" which refers to residual disability or sequelae related to the reported event. Among those with residual effects, most (63.6%; n=7) were injection site reactions while the remaining reports were other mild or moderate reactions such as fever/rash (27.3%; n=3) and one "Other severe/unusual events" (subsequently determined to be brachial neuritis). Upon case-level review of these events, none met the definition of "residual effects" per the iPHIS User Guide[11] or the "persistent/significant disability/incapacity" criterion as part of the definition of serious AEFI (See Methods). In addition, there was one report of death, which is described below (See Serious AEFI).

Serious AEFI

There were 27 reports of AEFIs that were classified as serious, representing 4.2% (27/642) of all reports. The proportion of AEFIs defined as serious was comparable to 2012 (3.9%; 26/664). All but one of the serious reports in 2013 were admitted to hospital for a mean length of stay of 6.2 days, while one was a report of a death which did not occur in the hospital (see below for further information). The majority of serious AEFIs were under 18 years of age (74.1%) including 12 that were documented as reported by IMPACT (Immunization Monitoring Program Active)[1], ranging in age from two months to 13 years of age. Over half of all serious AEFIs were 18 months of age or younger (59.3%). Among serious AEFI reports with outcome information entered in iPHIS (n=23), the majority (82.6%; n=19) were recovered, three

[1] IMPACT is Canada's Immunization Monitoring Program ACTive, is a paediatric hospital-based national active surveillance network for adverse events following immunization, vaccine failures and selected infectious diseases that are, or will be, vaccine preventable. IMPACT is administered by the Canadian Paediatric Society with funding from the Centre for Immunization and Respiratory Infectious Diseases at the Public Health Agency of Canada and has sites in Ontario at the Hospital for Sick Children in Toronto and the Children's Hospital of Eastern Ontario in Ottawa. http://www.cps.ca/en/impact

were not yet recovered (defined as an event that while likely to resolve, but is not resolved at the time the AEFI report is closed) and one was deceased (see below for further information).

The most common vaccine associated with serious AEFIs was DTaP-IPV-Hib with ten reports including seven where Pneu-C-13 and Rot-1 were administered concomitantly, one where varicella was administered concomitantly and two following DTaP-IPV-Hib administered alone; followed by influenza with seven reports including two where Pneu-C-13 and Pneu-P-23 respectively were co-administered.

The most frequent type of event among serious AEFIs was "Other severe/unusual events" (n=11), including seven reports with other concurrent events reported (described later in this section) and four reports where this was the only event reported. Among these four reports, one was a report of abnormal muscle movement following DTaP-IPV-Hib which completely resolved within one month of onset, one report of post-infectious cerebellar ataxia with concurrent urinary tract infection following varicella vaccine, one report of possible conversion disorder following HPV2 and one report of a death in an infant two days following receipt of DTaP-IPV-Hib, Pneu-C-13 and Rot-1 vaccines. No direct link between vaccination and the death was reported. A coroner's investigation found the cause of death to be unascertained and the manner of death was undetermined. No direct link with vaccine was reported.

The next most frequent event type among serious AEFIs was febrile seizures (n=5), which resulted in admission to hospital for further investigations. Most of these events (80%;n=4) were in toddlers between 12 and 18 months of age, two following MMR administered concomitantly with Men-C-C, one following varicella vaccine and one following DTaP-IPV-Hib. The remaining report was in a four-month-old following administration of DTaP-IPV-Hib, Pneu-C-13 and Rot-1.

There were also five serious reports that all required hospitalization for treatment of cellulitis with intravenous (IV) antibiotics, two following both Pneu-P-23 and influenza vaccine and one DTaP-IPV. The other 13 serious AEFI reports were:

- One report of intussusception, as well as two other reports of "Severe diarrhea/vomiting" where intussusception was investigated and ruled out, all following Rot-1 administered concomitantly with DTaP-IPV-Hib and Pneu-C-13; one additional report of "Severe diarrhea/vomiting" following varicella vaccine
- One report of "Convulsions/seizure" (afebrile) following DTaP-IPV-Hib, Pneu-C-13 and Rot-1, possibly related to behavioural response from excessive crying as a result of gastroesophageal reflux
- One report of fever and rash following MMR administered concomitantly with Men-C-C
- One report of encephalopathy/encephalitis following DTaP-IPV-Hib, Pneu-C-13 and Rot-1, which was subsequently diagnosed as cerebral hypoxic ischemic encephalopathy
- One "Event managed as anaphylaxis" following concomitant administration of Tdap and varicella vaccine requiring hospital admission, thus meeting the criteria for a serious AEFI
- Two reports of "Anaesthesia/paraesthesia" following influenza vaccine
- One report of GBS following influenza vaccine

- One report of “Arthritis/arthralgia” following influenza vaccine which was subsequently diagnosed as bilateral purulent panuveitis
- One report of “injection site reaction” with subsequent hospital admission for pneumonia following Pneu-P-23.

Risk factors

Among all reports, 12.5% (n=80) had risk factor information completed in iPHIS, less than in 2012 when risk factors were completed in 16.1% of reports. The most frequently reported risk factor in 2013 was “Chronic illness/underlying medical condition” reported in 91.3% (n=73) of reports with risk factor completed, followed by “Immunization program error” (10.0%; n=8) and “Immunocompromised” (10.0%; n=8). Distribution of type of risk factor has shifted from 2012 to 2013 with the recommendation to discontinue use of specific risk factors options (i.e., “Pregnant,” “Other”) starting in 2013. Table 4 describes AEFIs in which an immunization program error was reported; two of these reports were serious.

Table 4. Summary of AEFI reports in Ontario where “Immunization program error” was selected under “Risks” in iPHIS, 2013

Age (years)	Agent	Error	Adverse event category	Additional case details
18-49	Tdap (Adacel®)	Partial dose	Allergic reaction – skin	Partial dose administered by primary health care provider due to concern about previous history of reaction following Td vaccine. Referral for further assessment by allergist recommended.
1-7	DTaP-IPV-Hib (Pediacel®)	Incorrect route	Abscess at the injection site (infected)	Incorrect administration by sub-cutaneous route
65+	Inf (Fluviral®)	Incorrect site	Pain/redness/swelling lasting 4-10 days	Incorrect land-marking resulting in administration of the vaccine too high in the deltoid muscle
18-49	Inf (Vaxigrip®)	Incorrect site	Pain/redness/swelling lasting greater than 10 days	Incorrect land-marking resulting in administration of the vaccine too high in the deltoid muscle
65+	Inf (Vaxigrip®)	Incorrect needle length	Cellulitis, convulsions/seizure	5/8 inch needle used when 1 to 1 1/2 inch needle was indicated. B12 injection administered at the same time at the same site. Case was admitted to hospital for treatment with IV antibiotics.
50-64	Inf (Agriflu*)	Incorrect site	Pain/redness/swelling lasting greater than 10 days	Incorrect land-marking resulting in administration of the vaccine too high in the deltoid muscle.

Age (years)	Agent	Error	Adverse event category	Additional case details
65+	Pneu-P-23 (Pneumovax® 23)	Expired vaccine	Pain/redness/swelling extending beyond nearest joint	Vaccine also administered subcutaneously due to emaciation. Case was admitted to hospital for treatment of concurrent pneumonia.
7-17	Pneu-P-23 (Pneumovax® 23), Td	Vaccine not indicated	Other severe/unusual events	Previous dose of Pneu-P-23 administered, booster dose not indicated. Minor local reaction, followed by onset of headache, abdominal pain, diaphoresis one week after vaccine. Spontaneously resolved.

Notes on 2012 data

Reports following vaccines administered in 2012 are included in this report for analysis of temporal trends. It is important to note that these data were extracted from iPHIS on April 28, 2014 whereas data presented in the Annual Report on Vaccine Safety, 2012 were extracted from iPHIS approximately a year earlier, on May 6, 2013. As a result, a slight increase in case counts is expected with the most recent data extraction due to reporting delay. These revisions are summarized in Table 6.

Table 6. Revisions to the number adverse events reported following vaccines administered in 2012 between iPHIS data extracts from May 6, 2013, and April 28, 2014

iPHIS data extraction date	Total number of AEFI reports	Confirmed AEFI reports n (%)	Serious reports (criteria revised in 2013 report)[1] n (%)	Serious reports (criteria used in 2012 report)[1] n (%)
May 6, 2013[2]	765	631 (82.5)	24 (3.8)	56 (8.9)
April 28, 2014[3]	795	664 (83.5)	26 (3.9)	62 (9.3)

Notes:

1. Serious AEFI criteria were revised in 2013 per AEFI reporting guidelines from the Public Health Agency of Canada (PHAC). See Methods for additional information about changes in serious AEFI criteria over time.
2. Data resulting from the iPHIS extraction date of May 6, 2013, are presented in the Annual Report on Vaccine Safety, 2012.
3. Data resulting from the iPHIS extraction date of April 28, 2014, are presented in this report.

Discussion

This assessment of adverse events reported in Ontario following vaccines administered in 2013 represents the second annual report on vaccine safety and builds upon the 2012 report, which was the first of its kind to be undertaken in Ontario. No unexpected safety issues were identified as a result of this analysis and findings were consistent with 2012 with some notable improvements in data quality. The information presented in this report contributes to the safety profile of vaccines administered in Ontario and provides relevant and timely information to support health professionals to communicate effectively about vaccine safety.

The following discussion is based upon analysis of AEFI information entered into iPHIS that were temporally associated with vaccines. A causality assessment or assessment of case information beyond what is available within the iPHIS application has not been completed. Reporting rate estimates are for comparison purposes and monitoring over time and should not be interpreted as incidence rates.

The provincial AEFI reporting rate in 2013 shows little change from 2012 (4.7 and 4.9 per 100 000 population, respectively). Comparison of 2012 and 2013 reporting rates may be affected by two key factors. The first is that the 2012 reporting rate has been updated in this report to reflect late reporting that occurred between May 6, 2013 and April 28, 2014, the data extraction dates for the 2012 and 2013 reports respectively. The second is the implementation of updated surveillance case definitions on January 1, 2013, including discontinued reporting of injection site reactions lasting less than four days. Using the original 2012 report dataset with injection site reactions lasting less than 4 days excluded, the 2013 reporting rate is slightly increased compared with 2012 (4.7 vs. 4.5 per 100 000 population respectively).

The provincial reporting rate was substantially lower than the most recently available national AEFI reporting rate from 2012 which was 10.1 per 100 000 population[24]; this was also observed in Ontario in 2012.[6] Given the similarity in vaccines used and immunization program practices across the country, this suggests that under-reporting of AEFIs may be a key factor contributing to Ontario's lower reporting rate. It is important to note that a higher overall reporting rate of AEFIs (across all vaccines) does not necessarily suggest a vaccine safety concern; rather, it is an indicator of a robust passive vaccine safety surveillance system. The quantity of AEFI reports to a passive vaccine safety surveillance system contributes to establishing a clear historical baseline that can be used to identify future vaccine safety signals.

Population-based age-specific reporting rates are presented for the first time in this report. The distribution of the reporting rate by age category is as expected with the highest reporting rates in the age groups with the highest number of recommended doses according to the provincial immunization schedule. Infants under one year of age have the highest age-specific reporting rate and also the highest number of recommended doses (nine in total).[16] One notable temporal trend is that the reporting rate for four- to ten-year-olds has decreased markedly from 12.2 to 7.1 per 100 000 population in 2012 and 2013 respectively whereas all other age-specific reporting rates remain relatively stable. This age

category has only two recommended doses of vaccine (Tdap-IPV and MMRV) and the timing coincides with the switch from DTaP-IPV to Tdap-IPV for the preschool (four- to six-year-old) booster dose in May 2012.[25] This program change has been associated with an overall decline in AEFI reporting rate for the preschool (four- to six-year-old) booster.[26]

The sex distribution is again weighted towards females, specifically in the adolescent and adult age groups. This observation was noted in the 2012 report and was consistent with observations from other passive safety surveillance systems.[6,27-29] It was noted that possible factors that may influence sex-related differences include higher uptake of vaccine among adult females, higher proportion of females among health care workers for which specific vaccines are targeted and possible differences in health care-seeking behaviours between males and females.[30-33] In addition, there are data to suggest that sex-specific biologic differences affect both the immune response and frequency and severity of adverse events following immunization.[34,35] Further analysis of gender by other report attributes would assist with further characterization of this phenomenon including whether AEFI reports among females are higher for specific vaccines or if females are more likely to self-report. For example, among 2013 AEFI reports 18 years of age and older who self-reported, the vast majority (84.2%) were female.

AEFI reporting rates vary widely by vaccine. The vaccine with the highest reporting rate was DTaP-IPV. This relatively high reporting rate was also observed in 2012; however the rate in 2013 is more than three times the magnitude (103.9 and 340.4 per 100 000 doses distributed respectively). In general, a relatively high frequency of AEFI reports is consistent with the safety profile of this vaccine, which is known to produce large local reactions[36-38]; none of the reports were serious. However, the increase between 2012 and 2013 is very likely an artefact arising from the replacement of DTaP-IPV with Tdap-IPV for the preschool booster, which was announced in May 2012. While the distribution of DTaP-IPV was reduced drastically after this point, it is very likely that many health care providers continued to use DTaP-IPV for the preschool booster until their existing stock was depleted. The result is that vaccine distribution for DTaP-IPV is an underestimate of the number of doses of this vaccine actually administered. This demonstrates that the use of doses distributed as an approximation of doses administered for the purposes of calculating an AEFI reporting rate should be interpreted with caution in the context of significant immunization program changes. A recent analysis of the switch from DTaP-IPV to Tdap-IPV in Ontario, estimated the DTaP-IPV AEFI reporting rate to be 33.1 per 100 000 doses distributed when a longer distribution period was examined (i.e., AEFIs reported between 2009 and 2013) and reports were limited to children four to six years of age.[26] Replacement of DTaP–IPV with Tdap–IPV vaccine appears to have resulted in an improved safety profile of the pre-school booster.

Other high vaccine-specific reporting rates observed in 2013 (103.8 per 100 000 doses distributed for rabies vaccine and 96.6 per 100 000 doses distributed for Hib vaccine) may be unstable due to a low number of reports (nine and three AEFI reports, respectively). In addition, the AEFI reporting rate for rabies vaccine may be an overestimate because the total distribution of this vaccine in Ontario is likely underestimated by not capturing privately purchased vaccines (i.e., travel vaccines). Notwithstanding these caveats, rabies vaccine is associated with a relatively frequent occurrence of injection site and mild systemic reactions, particularly the human diploid cell vaccine relative to other rabies vaccines (e.g., purified chick embryo).[39,40] The human diploid vaccine is the most commonly distributed type of

rabies vaccine (66.5% of all doses) within the publicly funded program (July 2014 email from T.Scott, Ministry of Health and Long-Term Care; unreferenced). Of note, the lowest vaccine-specific reporting rate is for influenza vaccine (4.3 per 100 000 doses distributed), which also has the highest distribution of all of the publicly funded vaccines. This low reporting rate relative to high volume of vaccine distribution has also been observed in other passive AEFI surveillance systems.[41,42] Under-reporting is one possible factor which may affect the influenza AEFI reporting rate. Influenza vaccine is administered by health professionals in a wide variety of community-based and institutional settings that do not provide other routine immunizations and thus have varying levels of familiarity with reporting requirements. In addition, these immunization providers do not necessarily have an ongoing primary health care relationship with vaccine recipients so they may be less likely to be aware or consulted if an adverse event occurs.

Injection site reactions were the most frequently reported events which is consistently observed in passive AEFI surveillance data.[6,41,42] There was no change in overall injection site reaction reporting between 2012 and 2013 despite discontinued reporting of injection site reactions lasting less than four days as a result of revised AEFI case definitions implemented in 2013. This change was made to reduce the reporting burden of these very mild, expected events which resolve on their own and do not require public health action. While it was expected that the overall frequency of reporting of injection site reactions would decrease as a result of this change, it appears that any reduction in 2013 may have been offset by other changes to the injection site reaction case definitions implemented at the same time (e.g., addition of the term “redness” in addition to “pain” and “swelling”). Continued assessment of the frequency of specific injection site reactions will help establish reporting burden of these events and inform any further revisions to provincial surveillance case definitions.

The relatively frequent reporting of rash and allergic skin reactions is a consistent finding both within Ontario’s passive AEFI surveillance data as well as in reports from other passive AEFI surveillance systems.[6,41-43] Fever is one event that is less frequently reported in Ontario (9.0% of all reports) compared with the US and Australia (25.8% and 23.6% of all reports respectively).[41,42] Ontario’s case definition of fever within AEFI surveillance is very specific, whereby fever is only reportable if it occurred in conjunction with another reportable event, which may explain the less frequent reporting. Reporting of “Other severe/unusual events” was decreased from 19.0% of reports in 2012 to 13.6% in 2013. This likely reflects targeted efforts in 2013 to reduce the use of this event in AEFI reports as it is challenging to interpret given its lack of specificity.

Reports of events managed as anaphylaxis were infrequent, representing 2.5% of all AEFI reports. All reports except one (n=15) involved administration of publicly funded vaccines therefore using a denominator of publicly funded dose distributed, the estimated reporting rate of anaphylaxis is 1.8 per 1 million doses distributed. This is consistent with the estimated range of occurrence of anaphylaxis following vaccines of between one and ten episodes per million doses of vaccine administered.[44] Further assessment of anaphylaxis reports using Brighton criteria are limited by missing/incomplete information. It is anticipated that the newly implemented anaphylaxis-specific AEFI reporting form will assist PHUs with improved data collection and entry into iPHIS.

Serious AEFIs were again reported at low frequency in 2013. One important change for 2013 was in the definition of a serious AEFI. The reason for this change was to align with recently updated national AEFI surveillance standards. As a result, the "Medically important events" are no longer included unless they otherwise meet the definition of serious. This results in the proportion of serious AEFI reports in 2013 (4.2%) appearing reduced compared with 2012 (8.9%); however, if the new definition is retrospectively applied to 2012 reports, the serious proportion (3.9%) is comparable to 2013. Of note, the majority of serious AEFIs were recovered at the time of reporting.

The reported death of an infant following receipt of routine vaccines was subject to a Coroner's investigation and review by the Pediatric Deaths Under Five Committee of the Office of the Chief Coroner of Ontario which found the that cause of death was unascertained with the manner of death undetermined. Unascertained cause of death refers to the absence of any anatomic or toxiologic cause of death, while undetermined manner of death indicates that "a full investigation has shown no evidence for any specific classification or there is equal evidence or a significant contest among two or more manners of death".[45] This event is included in this report per the provincial AEFI definition of a confirmed case, which includes events that are temporally associated with receipt of vaccine which cannot be clearly attributed to other causes.[10] As noted previously, events described in this report are temporally and are not necessarily causally linked to vaccines. While tragic, temporal association of unexplained infant death with vaccines is not unexpected given that infant primary immunization schedules temporally coincide with the peak age (two to four months) for the incidence of unexplained infant death.[46-48]

Physicians were the most frequent reporters of AEFIs (31.0% of all reports) followed closely by other health care professionals (29.1%), for a total of 60.1% of AEFIs reported by all health care providers in 2013. Compared to health care utilization data which indicated that 72.1% of AEFIs had been assessed by a health care professional (either as an outpatient medical consultation, ER visit or hospital admission) there appears to be some degree of under-reporting by health care professionals. Further differentiation is seen when comparing the reporting rate from primarily PHU-administered, school based programs, which is substantially higher than the reporting rate from primarily physician-administered infant/childhood immunization programs. Health professionals' under-reporting of AEFIs has also been shown in other passive AEFI surveillance systems. In the United States, results of a survey of office-based health care providers determined that of the 37% who reported that they had identified at least one AEFI, only 17% of these indicated that they had ever reported to the Vaccine Associated Adverse Event Reporting System (VAERS).[49] Barriers identified to AEFI reporting by health professionals include lack of awareness of reporting requirements, confusion about what types of AEFIs to report, lack of familiarity with the paper form, and the amount of time required to complete a report.[50,51]

With respect to data quality and completeness, some key improvements have been noted between 2012 and 2013 suggesting that the AEFI surveillance changes implemented on January 1, 2013, (See Background) including a new reporting form, revised case definitions, and guidelines for data entry in iPHIS have had an early positive impact on data quality. While improvements in data quality are promising, there are some continuing challenges including low completion of risk factors, invalid use of "residual effects" as the outcome and incomplete documentation of events managed as anaphylaxis.

Limitations

This analysis is limited in its assessment of temporal trends with only one previous year's data for comparison as well as some restricted data prior to this time. However, this situation will continue to improve with each annual report, as subsequent years of data are added to the analysis. It is also important to note that changes to the provincial surveillance system over time, in particular significant revisions to case definitions and reporting guidelines on January 1, 2013, have an impact on the interpretation of temporal trends.

At this time, it is not possible to calculate incidence rates of AEFIs by vaccine or event type due to the lack of a comprehensive population-based provincial immunization registry to estimate the number of individuals who were immunized. Therefore, AEFI reporting rates are calculated using the entire population irrespective of immunization status or doses distributed as the denominator. The use of doses distributed within the publicly funded immunization program in Ontario has previously been shown to be a good approximation of doses administered.[5] Additionally, some general limitations which are shared with other passive AEFI surveillance systems include under-reporting, reporting bias, missing/incomplete data, temporal and not causal association of reported events with vaccine, and lack of comparison to baseline rates.[51]

Conclusions and recommendations

Surveillance of AEFIs in Ontario is an essential component of the provincial immunization program. A robust AEFI surveillance system provides vital information about the safety of publicly funded vaccines and supports effective health professional communication about vaccine safety, an important determinant of public confidence in vaccines. This second annual report on vaccine safety finds that vaccines administered in Ontario in 2013 resulted in a low rate of reporting of adverse events. Most reported events were mild (i.e., injection site reactions) and resolved completely. Serious reports were rarely reported and were most often related to known but rare events following vaccine.

While some key improvements in AEFI data quality are observed, specific ongoing challenges with data completeness and validity are noted. Under-reporting is identified as a limitation which is inherent to many passive AEFI surveillance systems but appears more pronounced in Ontario relative to other jurisdictions. The following actions are recommended to further strengthen the provincial AEFI surveillance system:

1. Continue efforts to address the quality and completeness of AEFI data in iPHIS through maintaining up-to-date guidance documents on AEFI data iPHIS entry, regular education and training for PHUs, and follow-up of specific data quality issues through weekly review of AEFI reports and the annual AEFI data clean-up initiative.

2. Implement targeted provincial strategies to increase AEFI reporting among health care providers, in particular within the Universal Influenza Immunization Program (UIIP) in collaboration with health professional associations, PHUs and the Ministry of Health & Long-Term Care, in addition to enhanced support for PHUs to promote AEFI reporting with local immunization providers.

3. Explore new methods of promoting the use of current AEFI surveillance forms and guidance documents to PHU staff using new or existing communication channels including the PHO website, PHO education events, conferences and workshops, email distribution lists, and monthly provincial manager's teleconferences in collaboration with the MOHLTC and PHUs.

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Appendices

Appendix 1: Adverse event reaction(s) values in iPHIS pre- and post-January 1, 2013

The following table maps adverse event reaction(s) values in iPHIS pre- and post-January 1, 2013, and adverse event categories for analysis.

Adverse event presented for analysis	**"Adverse event reaction(s)" values available in iPHIS starting January 1, 2013**	**"Adverse event reaction(s)" values available in iPHIS January 1–December 31, 2012**
Acute disseminated encephalomyelitis (ADEM)	Acute disseminated encephalomyelitis (ADEM)	Acute disseminated encephalomyelitis
Adenopathy/ lymphadenopathy	Adenopathy/lymphadenopathy	Lymphadenitis
Allergic reaction - skin	Allergic reaction - skin	Allergic reaction – dermatologic/mucosa
Allergic reaction – other	N/A[1]	Allergic reaction – gastrointestinal Allergic reaction – respiratory Allergic reaction – cardiovascular
Anaesthesia/paraesthesia	Anaesthesia/paraesthesia	N/A[2] N/A[2]
Anaphylaxis	Event managed as anaphylaxis	Anaphylaxis – cardiovascular Anaphylaxis – dermatologic/mucosal Anaphylaxis – gastrointestinal Anaphylaxis – respiratory
Arthritis/arthralgia	Arthritis/arthralgia	Arthritis – joint redness Arthritis – joint swelling Arthritis – sensation of warmth over joint
Bell's palsy	Bell's palsy	Bell's palsy
Cellulitis	Cellulitis	Cellulitis

Adverse event presented for analysis	"Adverse event reaction(s)" values available in iPHIS starting January 1, 2013	"Adverse event reaction(s)" values available in iPHIS January 1–December 31, 2012
Convulsions/seizure	Convulsions/seizure	Seizure – associated with fever Seizure – history of afebrile seizures before immunization Seizure – history of febrile seizures before immunization Seizure – sudden loss of consciousness by report only Seizure – sudden loss of consciousness witnessed by healthcare professional Seizure – history of seizures before immunization unknown
Encephalopathy/ Encephalitis	Encephalopathy/Encephalitis	Encephalopathy/encephalitis - neuroimaging consistent with encephalitis Encephalopathy/encephalitis – brain pathology consistent with encephalitis Encephalopathy/encephalitis – CSFpleocytosis >5 WBC/mm3 Encephalopathy/encephalitis - depressed/altered level of consciousness Encephalopathy/encephalitis – EEG consistent with encephalitis Encephalopathy/encephalitis – fever 38.0C Encephalopathy/encephalitis – focal or multifocal neurologic sign(s) Encephalopathy/encephalitis – lethargy Encephalopathy/encephalitis - personality change lasting for >=24hrs Encephalopathy/encephalitis – seizures (if present, provide details in seizure section)
Fever ≥ 38c	Fever in conjunction with another reportable event	Fever ≥38c
Guillian-Barré syndrome (GBS)	Guillian-Barré syndrome (GBS)	Guillian-Barré syndrome (GBS)

Adverse event presented for analysis	"Adverse event reaction(s)" values available in iPHIS starting January 1, 2013	"Adverse event reaction(s)" values available in iPHIS January 1–December 31, 2012
Hypotonic-hyporesponsive episode (HHE)	Hypotonic-hyporesponsive episode (HHE)	Hypotonic-hyporesponsive episode – limpness Hypotonic-hyporesponsive episode – pallor/cyanosis Hypotonic-hyporesponsive episode – reduced responsiveness/unresponsiveness
Infected abscess	Abscess at the injection site (infected)	Infective abscess – erythema Infective abscess – positive gram stain or culture Infective abscess – purulent discharge Infective abscess – resolution on antimicrobial therapy
Intussusception	Intussusception	Intussusception
Meningitis	Meningitis	Meningitis
Myelitis	Myelitis	Myelitis
Nodule	Nodule	Nodule (discrete, well-demarcated, firm soft tissue mass or lump)
Oculorespiratory syndrome (ORS)	Oculorespiratory syndrome (ORS)	ORS – bilateral red eyes ORS – facial oedema ORS – respiratory symptoms
Other severe/unusual events	Other severe/unusual events N/A[1] N/A[1] N/A[1]	Other severe/unusual events Optic neuritis Autoimmune hepatitis Acute transverse myelitis

Adverse event presented for analysis	"Adverse event reaction(s)" values available in iPHIS starting January 1, 2013	"Adverse event reaction(s)" values available in iPHIS January 1–December 31, 2012
Pain/redness/swelling lasting less than 4 days	N/A[1]	Severe pain – lasting fewer than 4 days Severe swelling – lasting fewer than 4 days
Pain/redness/swelling lasting 4 days or longer	Pain/redness/swelling (lasting 4-10 days) Pain/redness/swelling (lasting greater than 10 days)	Severe swelling – lasting 4 days or more Severe pain – lasting 4 days or more
Pain/redness/swelling (extending beyond nearest joint)	Pain/redness/swelling (extending beyond nearest joint)	Severe swelling – extending past nearest joint(s)
Paralysis	Paralysis	Paralysis other than Bell's palsy
Parotitis	Parotitis	Parotitis
Persistent crying/screaming	Persistent crying/screaming	Screaming episode/persistent crying
Rash	Rash	Rash – generalized Rash – localized at injection site Rash – localized at non-injection site
Severe vomiting/diarrhea	Severe vomiting/diarrhea	N/A[2]
Sterile abscess	Abscess at the injection site (sterile)	Sterile abscess – non-purulent fluid
Syncope with injury	Syncope with injury	N/A[2]
Thrombocytopenia	Thrombocytopenia	Thrombocytopenia

Notes:

1. This value was discontinued in iPHIS as of January 1, 2013.
2. This is a new value available in iPHIS as of January 1, 2013.

Appendix 2: Vaccine abbreviations and corresponding product/trade names and iPHIS values

Vaccine abbreviations used in the report	"Agent" values in iPHIS (as of April 1, 2013)	Product/trade name
BCG	BCG - Bacillus Calmette Guerin	BCG vaccine
Chol-Ecol-O	Chol-Ecol-O - Cholera - E.Coli (Oral)	Dukoral™
DTaP-IPV	Dtap-IPV - Diphtheria, Tetanus, Acellular Pertussis, Polio	Infanrix™ IPV, Quadracel
DTaP-IPV-Hib	Dtap-IPV-Hib - Diphtheria, Tetanus, Acellular Pertussis, Inactivated Poliomyelitis, Haemophilus B (Pediatric)	Pediacel®, Infanrix™- IPV/Hib, Pentacel®
HA	HA - Hepatitis A (Adult), Ha - Hepatitis A (Pediatric)	Avaxim®, Havrix®, Vaqta® Avaxim® - Pediatric
HAHB	HAHB - Hepatitis A And B	Twinrix®, Twinrix® Junior
HA-Typh-I	HA-Typh-I - Hepatitis A and Typhoid (Injection)	ViVaxim™
HB	HB - Hepatitis B	Engerix®-B, Recombivax HB®
HPV2	HPV2 - Human Papilloma Virus	Cervarix®
HPV4	HPV4 - Human Papilloma Virus	Gardasil®
Inf	Inf - Influenza	Fluviral®, Vaxigrip®, Agriflu®, Intanza®, Flumist®, Fluad®, Fluzone®, Influvac®
IPV	IPV - Inactivated Poliomyelitis (Vero Cell)	Imovax® Polio, Inactivated poliomyelitis vaccine - IPV
JE	JE - Japanese Encephalitis	JE-VAX®
Men-C-ACWY	Men-C-ACWY - Meningococcal - Conjugate ACWY	Menactra®, Menveo®
Men-C-C	Men-C-C - Meningococcal - Conjugate C	NeisVac-C®, Menjugate®, Meningitec®
MMR	MMR - Measles, Mumps, Rubella	MMR I , MMRII®, Priorix
MMRV	MMRV - Measles, Mumps, Rubella, Varicella	Priorix-Tetra™

Vaccine abbreviations used in the report	"Agent" values in iPHIS (as of April 1, 2013)	Product/trade name
Pneu-C-13	Pneu-C-13 - Pneumococcal Conjugate 13 Valent	Prevnar® 13
PNEU-P -23	Pneu-P -23 - Pneumococcal - Polysaccharide 23 Valent	Pneumo® 23, Pneumovax® 23
Rab	Rab - Rabies (Purified Chick Embryo Cell)	RabAvert®
Rab	Rab - Rabies Vaccine Inactivated (Diploid Cell)	Imovax® Rabies
Rot-1	Rot-1 - Rotavirus	Rotarix™
Td	Td - Diphtheria, Tetanus (Adult)	Td Adsorbed
Tdap	Tdap - Tetanus, Diphtheria, Acelluar Pertussis	Adacel®, Boostrix®
Tdap-IPV	Tdap-Polio - Tetanus, Diphtheria, Acelluar Pertussis, Polio	Adacel-Polio®, Boostrix Polio®
Td-IPV	Td-IPV - Tetanus, Diphtheria, Inactivated Poliomyelitis (Adult)	Td Polio Adsorbed
Typh-I	Typh-I - Typhoid (Injection)	Typherix®, Typhim Vi®, Vivotif®
Typh-O	Typh-O - Typhoid (Oral)	Vivotif® L
Var	Var - VARICELLA	Varivax®, Varilrix®, Varivax III®
YF	Yf - Yellow Fever	YF-VAX®
Zos	Zos - ZOSTAVAX	Zostavax®

Appendix 3: Expedited Reporting of High Priority AEFI to the Canadian Adverse Events Following Immunization Surveillance System (CAEFISS), June 2014

Serious AEFI

Seriousness is a concept defined by ICH (International Conference on Harmonization) in the ICH E2A and E2D definitions and is based on patient/event outcome or action criteria that define regulatory reporting obligations.

For public health AEFI reporting in Canada, the definition of "serious" undertakes to be consistent with the ICH internationally accepted, regulatory definition, while interpreting 'hospitalization' in terms of Canadian realities. Thus an AEFI is considered "serious" when it:

- results in death,
- is life-threatening , defined as:
    - An event/reaction in which the patient was at real, rather than hypothetical, risk of death at the time of the event/reaction (includes: status epilepticus, status asthmaticus, cardiac arrest or respiratory arrest),
- requires inpatient hospitalization, defined as meeting at least one of the following criteria:
    - hospital stay lasting ≥24 hours based on known date/time of admission and discharge
    - hospital stay involving all or part of two consecutive days (i.e., admission and discharge date are at least 1 day apart but specific time of admission is not specified)results in prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity (if known at the time of reporting),
- is a congenital anomaly/birth defect.

Adverse Events of Special Importance (AESI)

The ICH E2A and E2D guidelines also state that other situations, such as other important medical events that may jeopardize the patient or may require intervention to prevent one of the outcomes above, should also be considered serious after applying medical and scientific judgment. Those "other situations" are open to interpretation and could vary from jurisdiction to jurisdiction. For Canada, in an effort to promote uniformity in reporting practices across the country, a list of high priority AESI is recommended based on both the impact of the event on the individual as well as public concern. This list may be amended periodically based on emerging issues or generation of evidence that enables rejection of the hypothesis that vaccine and event are causally related. (e.g., autism, SIDS, and most recently Bell's Palsy).

The designated Adverse Events of Special Importance are:

- Anaphylaxis (Brighton Collaboration Case Definition (BCCD) level 1-4)
- Encephalitis (including SSPE) (BCCD level 1-4)
- Acute disseminated encephalomyelitis (BCCD level 1-4)
- Myelitis (BCCD level 1-4)
- Aseptic meningitis/other meningitis (physician diagnosis) (BCCD level 1-4)
- Guillain Barre syndrome (BCCD level 1-4)
- Acute cerebellar Ataxia[iii]
- Intussusception (BCCD level 1-4)
- Thrombocytopenia (BCCD level 1: platelet count <150 AND clinical signs/symptoms of spontaneous bleeding)
- Emerging signal event based on group consensus.

Appendix 4: Number and distribution of confirmed AEFI reports, by adverse event category, 2012-2013

Adverse event category[2]	Adverse event[2]	2013 n (%)[6]	2012 n (%)[6]
Allergic events		**133 (20.8)**	**174 (26.2)**
	Allergic reaction – other[3]	N/A	25 (3.8)
	Allergic reaction - skin	120 (18.7)	135 (20.3)
	Event managed as anaphylaxis[5]	16 (2.5)	19 (2.9)
	Oculorespiratory Syndrome (ORS)	1 (0.2)	4 (0.6)
Injection site reactions		**263 (41.0)**	**269 (40.5)**
	Cellulitis	61 (9.5)	59 (8.9)
	Infected abscess	4 (0.6)	4 (0.6)
	Nodule	9 (1.4)	22 (3.3)
	Pain/redness/swelling (extending beyond nearest joint)	54 (8.4)	15 (2.3)
	Pain/redness/swelling <4 days[3]	N/A	56 (8.4)
	Pain/redness/swelling >4 days[3]	N/A	59 (8.9)
	Pain/redness/swelling 4-10 days[4]	144 (22.5)	59 (8.9)
	Pain/redness/swelling >10 days[4]	36 (5.6)	19 (2.9)
	Sterile abscess	0 (0)	7 (1.1)
Neurologic events		**35 (5.5)**	**31 (4.7)**
	Acute disseminated encephalomyelitis (ADEM)[5]	1 (0.2)	0 (0)
	Anaesthesia/paraesthesia[4]	14 (2.2)	7 (1.1)
	Bell's palsy	2 (0.3)	3 (0.5)
	Convulsions/seizures	15 (2.3)	14 (2.1)
	Encephalopathy/encephalitis[5]	1 (0.2)	2 (0.3)
	Guillian-Barré syndrome syndrome (GBS)[5]	1 (0.2)	2 (0.3)
	Meningitis[5]	1 (0.2)	0 (0)
	Paralysis other than Bell's palsy	1 (0.2)	3 (0.5)
Other events of interest		**105 (16.5)**	**138 (20.8)**
	Arthritis/arthralgia	13 (2.0)	12 (1.8)
	Intussusception[5]	1 (0.2)	0 (0)
	Other severe/unusual events	87 (13.6)	126 (19.0)
	Syncope with injury[4]	6 (0.9)	0 (0)
	Thrombocytopenia[5]	1 (0.2)	0 (0)
Systemic reactions		**224 (34.9)**	**190 (28.6)**
	Adenopathy/lymphadenopathy	10 (1.6)	5 (0.8)
	Fever ≥ 38 °c	58 (9.1)	52 (7.8)
	Hypotonic-hyporesponsive episode (HHE)	3 (0.5)	5 (0.8)
	Parotitis	1 (0.2)	2 (0.3)
	Persistent crying/screaming	6 (0.9)	6 (0.9)

Adverse event category[2]	Adverse event[2]	2013 n (%)[6]	2012 n (%)[6]
	Rash	146 (22.8)	144 (21.7)
	Severe vomiting/diarrhea[4]	35 (5.5)	6 (0.9)

Notes:

1. Adverse event categories represent groupings of specific types of adverse events and are not mutually exclusive. For category totals, reports with more than one specific event within a category are counted only once. Thus category totals will not be the sum to the total of specific adverse events overall or within a category.
2. Includes only those adverse events where the count was ≥1. For a complete list of possible values in iPHIS and corresponding definitions, please refer to Appendix 1.
3. These adverse event values were discontinued in iPHIS as of January 1, 2013.
4. These adverse event values were added in iPHIS as of January 1, 2013.
5. Medically important events
6. Each AEFI report may contain one or more specific adverse events which are not mutually exclusive. Percentages will not sum to 100%. The denominator is the total number of confirmed AEFI reports with at least one adverse event reported. The total number of confirmed AEFI reports was 641 (one report had missing adverse events and was therefore excluded) and 664 for 2013 and 2012 respectively.

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