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# Annual Report on Vaccine Safety in Ontario, 2014

TECHNICAL REPORT

November 23, 2015

## Public Health Ontario

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# Annual Report on Vaccine Safety in Ontario, 2014

# Authors

**Tara Harris, RN, MHSc**
Nurse Consultant
Immunization and Vaccine-Preventable Diseases, Public Health Ontario

**Jill Fediurek, RN, MPH**
Manager
Immunization and Vaccine-Preventable Diseases, Public Health Ontario

**Kenny Wong, MPH**
Epidemiologist
Immunization and Vaccine-Preventable Diseases, Public Health Ontario

**Shelley L. Deeks, MD, MHSc, FRCPC, FAFPHM**
Medical Director
Immunization and Vaccine-Preventable Diseases, Public Health Ontario

**Tonya Campbell**
MPH practicum student
Immunization and Vaccine-Preventable Diseases, Public Health Ontario

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In addition, we would like to acknowledge the Vaccine Safety Surveillance Working Group (VSSWG) for their valuable input and advice on AEFI surveillance system improvements and knowledge services staff at Public Health Ontario including Aaron Furfaro, Kiran Gill, Steven Janovsky and Lina Trillis for their support with the production of this document as well as materials to support its public release.

November 2015

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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-B | meningococcal serogroup B |
| 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

Public health surveillance of adverse events following immunization (AEFIs) is essential for monitoring the safety of vaccines administered in Ontario and provides valuable information to support and inform immunization program planning and evaluation. With this third annual assessment of AEFIs reported in Ontario we aim to provide relevant and timely information about the safety of vaccines administered in the province to support health care professionals, reassure the public and build confidence in immunization.

AEFIs reported following vaccines administered between January 1 and December 31, 2014, were extracted from the integrated Public Health Information System (iPHIS). There were 568 reports of confirmed AEFIs representing an reporting rate of 4.2 per 100 000 population. This rate was slightly lower compared to the previous two years however an overall increasing trend since 2010 was observed. The AEFI reporting rate relative to population size in Ontario also continues to be lower than the national AEFI reporting rate, although some vaccine-specific rates are more comparable, such as those delivered primarily in school-based settings (e.g. 24.1 vs. 23.7 per 100 000 doses distributed of Men-C-ACWY in Ontario vs. Canada, respectively). The age-specific reporting rate varies by age with the highest reporting rate in infants less than one year of age (24.4 per 100,000 population). A female predominance in AEFI reports continues to be observed, particularly in adults 18 to 64 years of age where the female:male reporting rate ratio was 7.1. The highest vaccine-specific reporting rate was observed for Men-C-ACWY and HPV4, both of which are school-based vaccination programs (24.1 and 20.0 per 100 000 dose distributed, respectively). The most frequently reported events overall were pain, redness or swelling at the injection site; rash and allergic skin reactions (40.3%, 22.4% and 15.7% of reports, respectively). The majority of events (74.6%) were completely recovered at the time of reporting. There were 23 serious AEFIs, including 22 following publicly funded vaccines for a serious reporting rate of 2.6 per million doses distributed.

This report finds that vaccines administered in Ontario in 2014 resulted in a low rate of reported adverse events. Results were generally consistent with the previous two years with continued improvements in data quality. Most reported events were mild (e.g., injection site reactions) and resolved completely. No unexpected safety issues were identified. Under-reporting of AEFIs continues to be an important limitation of passive vaccine safety surveillance in Ontario. Further research is needed to evaluate health professionals' awareness and practices regarding reporting of AEFIs and inform strategies to increase AEFI reporting for a more robust provincial vaccine safety surveillance system.

# Background

Canada has long been recognized as having one of the best vaccine safety systems in the world.[1,2] Vaccines are rigorously tested and reviewed for safety and efficacy prior to being authorized for use and are also closely monitored after authorization to ensure their continued safe use in the population. The success of this system is made possible by communication and coordination across multiple stakeholders including government regulators, vaccine industry, public health officials, health care providers, and members of the public.

Public health surveillance of adverse events following immunization (AEFIs) is a cornerstone of the vaccine safety system in Canada. Individual case reports of AEFIs to public health authorities provide an important source of data which can identify previously unrecognized or rare AEFIs or an increase in frequency or severity of known AEFIs which can be further evaluated.[3] In addition, surveillance of AEFIs by public health provides valuable information to support and inform immunization program planning and evaluation.

**What is an AEFI?**
An AEFI is 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.[3]

AEFIs are generally reported to public health by either health care providers, vaccine recipients or their caregivers. In Ontario, health care provider reporting to the local public health unit (PHU) is mandated by provincial public health legislation. PHUs play a central role as the primary recipients of AEFI reports, who investigate and document for the purposes of provincial surveillance. They also provide information, support and advice to vaccine recipients or their parents and health care providers in their community. Public Health Ontario (PHO) conducts provincial AEFI surveillance and participates in the national AEFI surveillance system maintained by the Public Health Agency of Canada (PHAC).[4]

Ontario's AEFI surveillance objectives 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

Ontario has made great strides in strengthening provincial AEFI surveillance processes in the recent years. Several key initiatives have been implemented to support provincial surveillance objectives including: revised provincial case definitions for AEFIs[5], enhanced surveillance guidelines[6] and forms[7-9], improved training and resources for public health units (PHUs) and information for health care providers.[10] While these initiatives have contributed to a renewed focus on AEFI surveillance and

preliminary improvements in AEFI data quality, work is ongoing to monitor the impact of changes and plan new initiatives to further engage system stakeholders, particularly health care providers who administer immunizations.

As immunization issues continue to dominate public and media discourse -from high profile outbreaks of vaccine preventable diseases[11-13] to the ongoing debate about mandatory vaccination[14,15] - now more than ever, open and transparent information about vaccine safety is vitally important to ensuring the continued success of immunization programs. With this 3rd annual report on vaccine safety in Ontario we aim to provide relevant and timely information about the safety of vaccines administered in the province to support health care professionals, reassure the public and build confidence in immunization.

# Report objectives and scope

This report will summarize AEFIs reported in Ontario following vaccines administered in 2014. In addition, reporting trends will be assessed by comparison with AEFIs reported following vaccines administered between 2010 and 2013.

# Methods

Reports of AEFIs are investigated by PHUs and entered into the integrated Public Health Information System (iPHIS), the electronic reporting system for reportable diseases and events in Ontario. AEFI reports are required to be reported in iPHIS according to provincial protocols, bulletins and directives issued by the Ministry of Health & Long-Term Care (MOHLTC).[5,16] The minimum data elements for each AEFI report are specified in the iPHIS AEFI User Guide (2015).[6] In preparation for this report, PHUs participated in a formal data clean-up initiative between March 9 and April 17, 2015, to update missing or incomplete information for AEFIs reported following vaccines administered in 2014. For more detailed information about AEFI surveillance system roles and processes please see the Annual Report on Vaccine Safety in Ontario, 2012.

## Analysis of epidemiologic data

We extracted all reports of AEFIs with a vaccine administration date between January 1 and December 31, 2014, from iPHIS on May 1, 2015. AEFI reports were classified as "confirmed" or "does not meet definition" (DNM) case classification according to provincial surveillance case definitions.[5]

> **Confirmed**
> Any reported event (listed in section 5.0 - Clinical Evidence, of the provincial surveillance case definitions) 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.

Temporal trends were presented by year of vaccine administration and included reports between 2010 and 2013. AEFI data from 2010 and 2013 were extracted from iPHIS on the same day as the 2014 data. Case counts for historical data will differ slightly than presented in previous reports [17,18] due to delayed reporting and data entry of adverse events after these reports were completed.

Descriptive analyses were limited to "confirmed" reports following vaccines administered in 2014. Age categories for analysis were based on key age milestones within the provincial immunization schedule (<1 year, 1-3 years, 4-10 years, 11-17 years, 18-64 years, 65+).[19] The AEFI reporting source is the source of the initial AEFI report to the PHU and not necessarily the only source of information in the AEFI investigation. Reporting source categories presented were mutually exclusive (i.e., physicians are a separate category from other health professionals which includes nurses and pharmacists). Proportions are based on reports with completed data and therefore will vary by iPHIS field.

The term "vaccine" refers to a generic active immunizing agent and includes one or more vaccine products (e.g., "influenza vaccine" refers to all influenza vaccine products). Standard acronyms for vaccines are used in this report as per the Glossary (e.g., MMR for measles, mumps, and rubella vaccine). For a list of vaccine abbreviations and corresponding products and trade names see Appendix 1. Each AEFI report includes one or more adverse events temporally associated with receipt of one or more vaccines administered at the same time (i.e., during the same day). Adverse events have been presented both individually and by categories as per the provincial surveillance case definitions.[5] All rashes following live virus vaccines were reviewed to determine the proportion that occurred within the expected time to onset for rash associated with receipt of a live virus vaccine. For the purposes of this analysis, we have typically used a range of 5-42 days which is consistent with provincial surveillance definitions which include temporal criteria for reporting of rash following live vaccines.[5]

Serious AEFIs are defined based upon International Conference on Harmonisation (ICH) E2A and E2D guidelines[20,21] adapted for public health surveillance of AEFIs in Canada by PHAC.[22]

> **Serious AEFI**
> 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.

Of note, persistent or significant disability/incapacity, or congenital anomaly/birth defect were not systematically captured in provincial surveillance data due to the relatively brief follow-up period. Other important medical events that do not otherwise meet the above definition of serious are presented separately in the report and include the following: anaphylaxis, encephalitis, acute disseminated encephalomyelitis, myelitis, meningitis, Guillain-Barré syndrome (GBS), acute cerebellar ataxia, intussusception and thrombocytopenia. Events managed as anaphylaxis were assessed using the Brighton Collaboration case definition and diagnostic levels of certainty.[23]

We calculated population-based AEFI reporting rates using Ontario population estimates[24] and projections[25] for 2010-2013 and 2014, respectively. Vaccine-specific reporting rates for publicly funded universal vaccines (i.e., excluding travel and publicly funded high risk-only vaccines) were calculated based on vaccine distribution data provided by the Ontario Government Pharmaceutical and Medical Supply Service (OGPMSS). These estimates were adjusted for wasted or reusable vaccine returned to OGPMSS. Reporting rates by provider type were estimated using a combined vaccine-specific reporting rate for specific age categories and vaccines which are primarily delivered by one provider type (e.g., primary care providers – infant/toddler vaccines, PHUs – school-based vaccines). 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, 2015.

# Notes on interpretation

The adverse events we describe in this report were **temporally associated** and not necessarily **causally linked** to vaccines. Our assessment was based on iPHIS data only and not comprehensive chart review. We provided 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. Table 1 identifies program changes in recent years that may impact AEFI surveillance data presented in this report.[19,26]

**Table 1.** Changes to the publicly funded immunization programs in Ontario (2010-2014)

| Time period | Vaccine program changes |
|---|---|
| December 2014 | • Meningococcal B vaccine for high risk children aged 2 months to 17 years<br>• Meningococcal ACYW vaccine; for high risk individuals 9 months to 55 years of age; booster doses and expanded high risk criteria<br>• Pertussis (Tdap) vaccine for all adults ≥18 years of age, regardless of whether Tdap was received in adolescence<br>• Pneumococcal conjugate 13 for high risk individuals ≥50 years of age |
| September 2012 | 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. |
| April 2012 | Replacement of DTaP-IPV (Quadracel®) with Tdap-IPV (Adacel-IPV®, Boostrix®-Polio) for the 4- to 6-year-old booster dose |
| October 2011 | 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 |
| August 2011 | • Rotavirus vaccine (Rot-1/Rotarix®) for infants at ages two and four months<br>• 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)<br>• Second dose varicella vaccine catch-up program for children born on or after January 1, 2000, and at least four years of age<br>• 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 |
| November 2010 | Reduction from four to three doses of pneumococcal conjugate 13-valent (Pneu-C-13) vaccine for low-risk children |

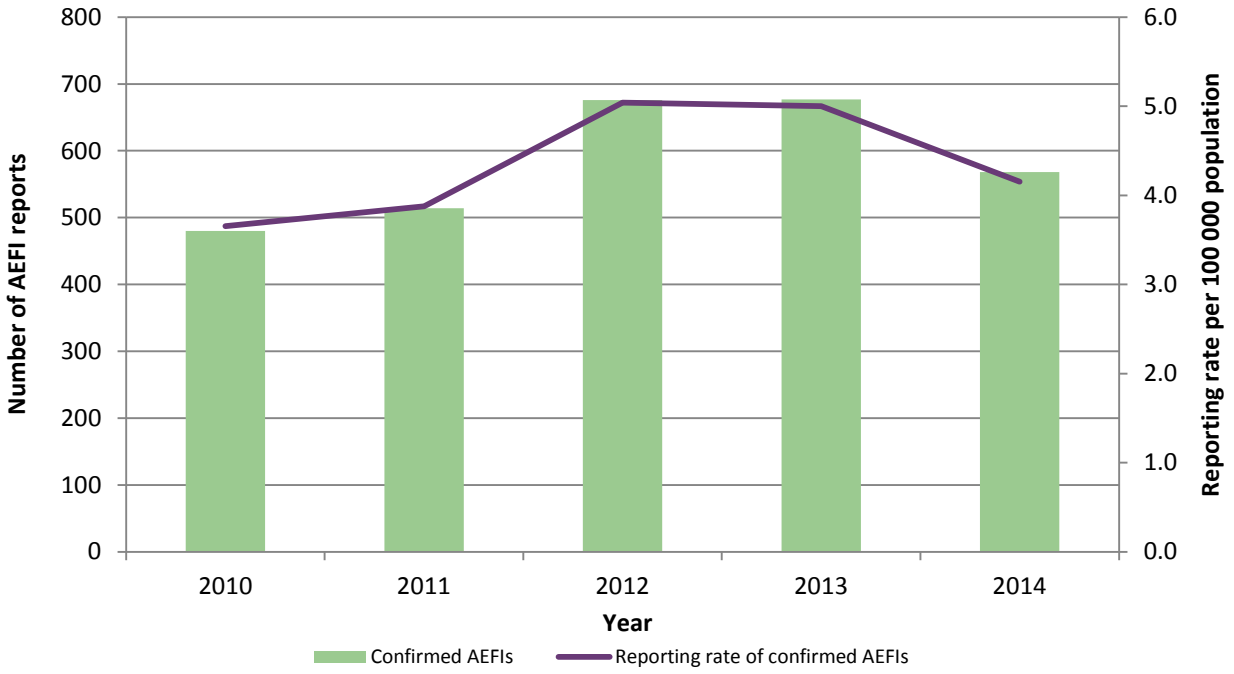
# Results

There were 645 AEFIs reported in iPHIS where the date of vaccination was between January 1 and December 31, 2014. Of these, 568 (88.1%) had a case classification of "confirmed" and 77 (11.9%) had a case classification of DNM.

## Reporting trends

The population-based reporting rate of "confirmed" AEFIs following vaccines administered in Ontario in 2014 was 4.2 per 100,000 population. This is lower relative to the 2012 and 2013 reporting rates (5.0 per 100,000 population in both years). However, reporting rates between 2012 and 2014 have increased (31.6% increase for 2012 and 2013, and 10.5% for 2014) compared to the average annual reporting rate of 3.8 per 100,000 population in 2010 and 2011 (3.7 and 3.9 per 100,000 population, respectively) (Figure 1). The increasing trend in reporting rate from 2010 to 2014 is statistically significant ($p<0.05$).

**Figure 1.** Number of AEFI reports and reporting rate in Ontario, by year, 2010–14



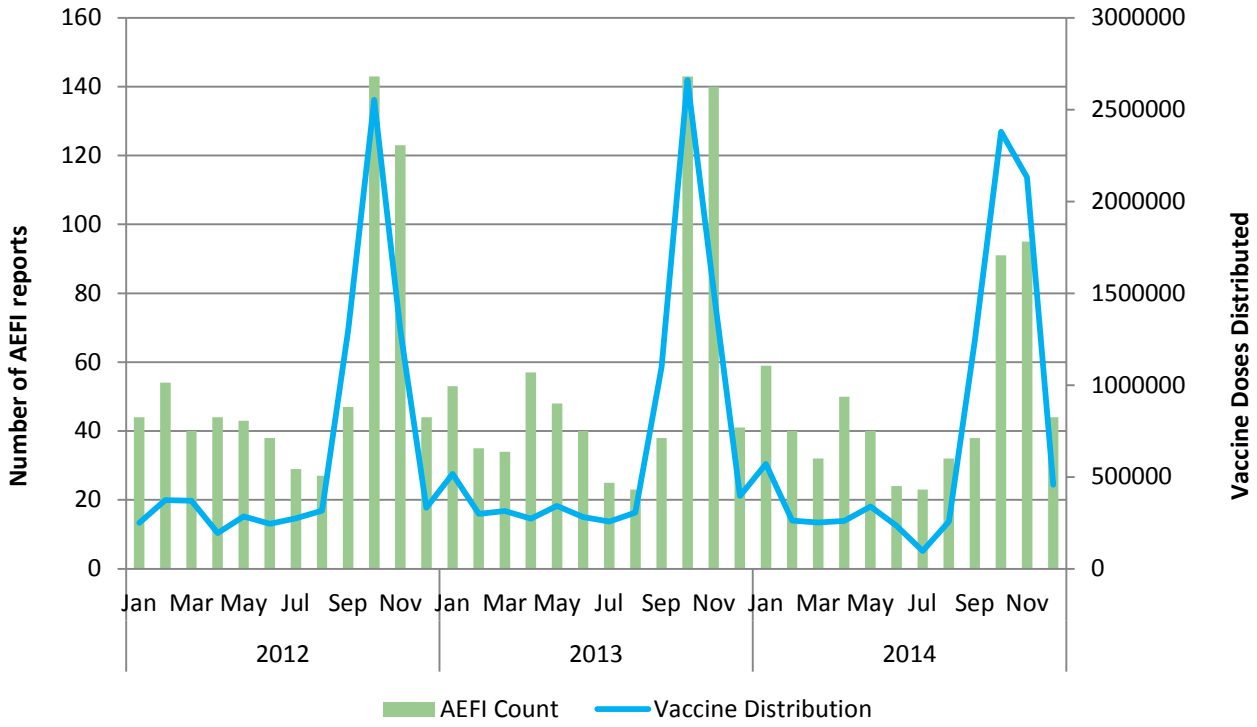

**Notes:**

1. AEFI counts are accurate as of May 1, 2015.
2. Delayed reports accounted for a 7.1% increase of the total number of confirmed AEFIs in 2012, and a 5.5% increase of the total number of confirmed AEFIs in 2013. Delayed reports accounted for a <1% increase of the total number of confirmed AEFIs in 2010 and 2011.

The proportion of all reports classified as "confirmed" (relative to all case classifications) has stabilized in 2014 (88.1%) following an increasing trend between 2010 and 2013 (78.7%, 77.6%, 84.9% and 88.8% respectively). The proportion of reports classified as "confirmed" by PHU in 2014 ranged from 55.2% to 100%. All subsequent analyses are limited to AEFI reports classified as "confirmed."

Reports of AEFIs by month of vaccine administration in 2014 ranged from a low of 23 reports in July to a peak of 91 and 95 reports in October and November, respectively. Smaller peaks in AEFI reporting were observed in January and April. This overall trend is similar to previous years and generally mirrors the monthly distribution of vaccine by OGPMSS; however the peak monthly volume of AEFI reports and vaccine distribution decreased in 2014 compared to previous years (Figure 2).

**Figure 2.** Number of AEFI reports and publicly funded vaccine distribution[1] in Ontario, by month, 2012-14



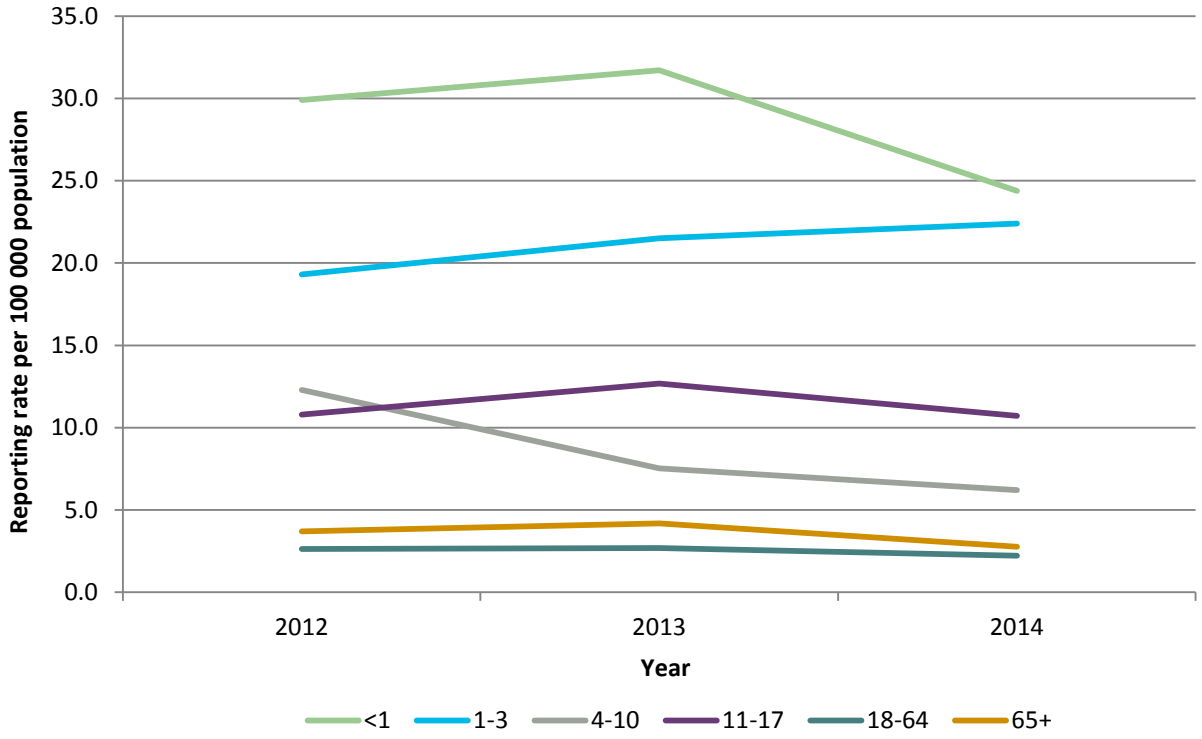

**Notes:**

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 2014.

# Age and sex distribution

The age of persons with AEFI reports in 2014 ranged from two months to 96 years of age (median of 14.3 years). The age-specific reporting rates were higher among younger age groups, with the highest reporting rate in infants less than one year. The age-specific reporting rates for infants under one and children 4- to 10-years old have decreased between 2012 and 2014 (from 29.9 to 24.4 and 12.3 to 6.2 per 100,000 population, respectively), while the rate for 1- to 3- year olds has increased over the same time period from 19.3 to 22.4 per 100,000 population (Figure 3).

**Figure 3.** AEFI reporting rate per 100,000 population in Ontario, by age group, 2012-14

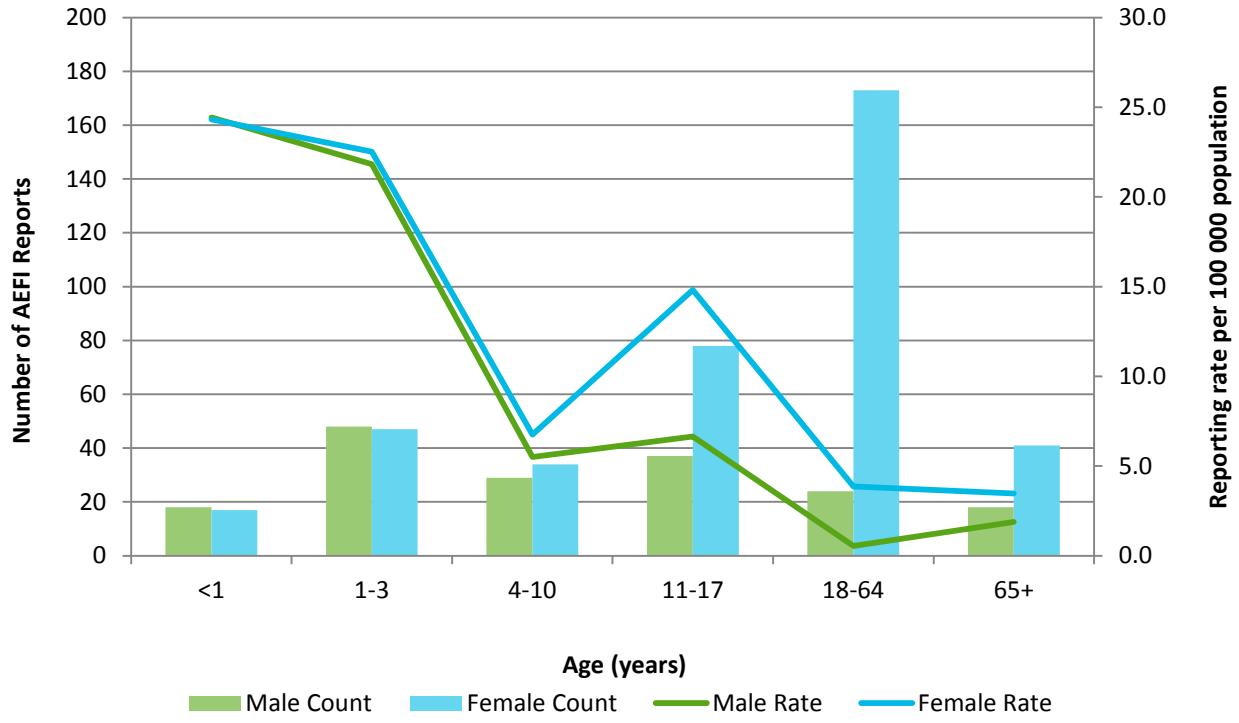



**Notes:**

1. One report was excluded from the figure due to missing age.

AEFI reports by sex continues to be weighted towards females (68.8% of all reports), with female predominance primarily among adults 18- to 64-years of age (reporting rate ratio: 7.1) followed by adolescents 11- to 17-years of age and those 65 years of age and older (reporting rate ratios: 2.2 and 1.8, respectively) (Figure 4). For the 11- to 17-year-olds, it should be noted that there is one publicly funded vaccination program that targets only female adolescents (HPV4 vaccine); therefore we would expect more AEFI reports among females in this age group.

**Figure 4.** Counts and reporting rates of AEFIs in Ontario by age group and sex, 2014



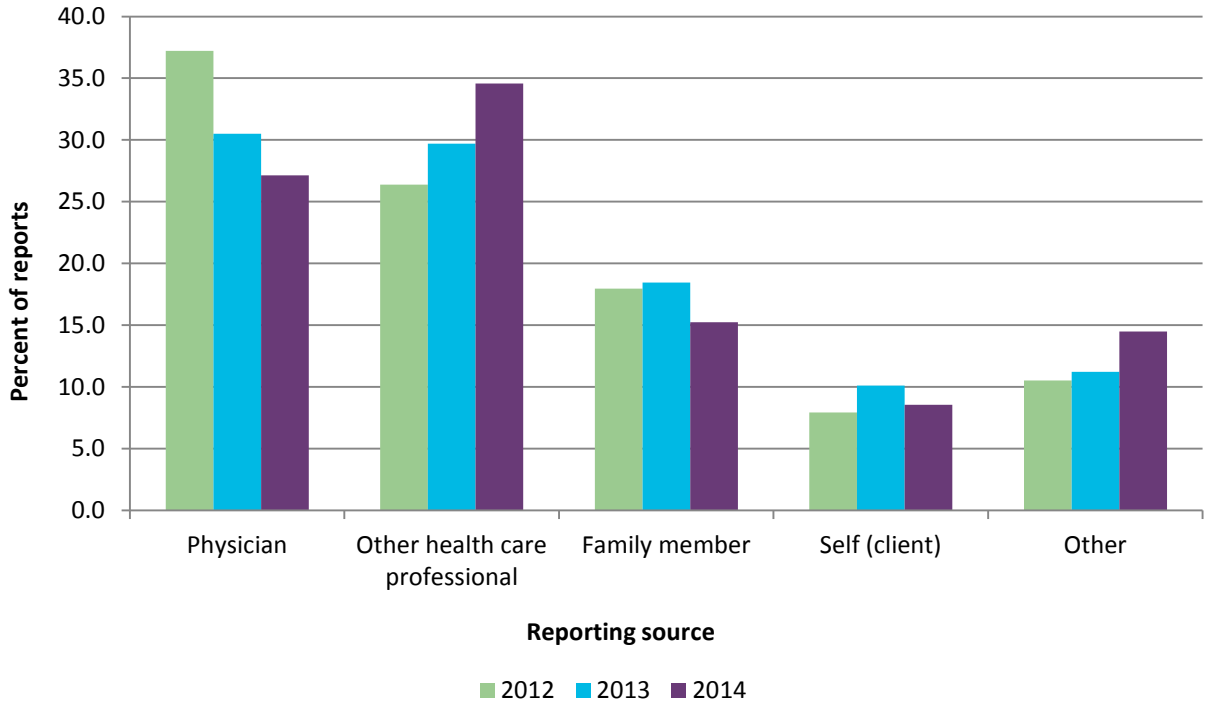

**Notes:**

1. Four reports are excluded from this figure due to missing information related to age and gender.

# Reporting source

Among AEFIs with reporting source completed (94.5%; n=537) the most frequent reporting sources were other healthcare professionals (e.g., nurses, pharmacists) who reported 34.5% of AEFIs, followed by physicians (27.2%), family members (15.3%), and self-reports (8.6%). The proportion of AEFIs reported by physicians has steadily decreased, while the proportion reported by other health care professionals has increased and replaced physicians as the most frequent reporting source (Figure 5).

**Figure 5.** Percent distribution of AEFIs by reporting source, 2012-14




**Notes:**

1. Reporting source 'Other' includes: Facility, other agency, workplace, personnel, lab, friend, detention centre and other (specify).

In 2014, the reporting rate for adolescent immunization programs primarily delivered by PHUs in school-based clinics (HB, Men-C-ACWY, HPV4 vaccines) was 15.1 per 100,000 doses distributed and the reporting rate for infant and toddler immunization programs primarily administered by primary care providers (DTaP-IPV-Hib, Rot-1, Pneu-C-13, MMR, Men-C-C, Var vaccines) was 5.6 per 100,000 doses distributed in 2014. Between 2012 and 2014, the reporting rate for programs primarily delivered by PHUs has decreased while the reporting rate for those delivered mainly by primary care has remained relatively stable (Table 2).

**Table 2.** Counts and reporting rates of AEFIs for school-administered and primary care-administered vaccines, 2012-14

| Reporting source | 2014 | | 2013 | | 2012 | |
|---|---|---|---|---|---|---|
| | Count | Reporting rate (per 100,000 doses[3] distributed) | Count | Reporting rate (per 100,000 doses[3] distributed) | Count | Reporting rate (per 100,000 doses[3] distributed) |
| **School-administered vaccines[1]** | 89 | 15.1 | 115 | 20.3 | 103 | 19.5 |
| **Primary care-administered vaccines[2]** | 110 | 5.6 | 122 | 6.0 | 101 | 4.9 |

**Notes:**

1. Includes AEFI reports occurring after the administration of Men-C-ACWY, HB, or HPV4 vaccines, in adolescents between 11 and 17 years of age, inclusive. See Appendix 1 for a list of all possible vaccines, corresponding vaccine products and agent abbreviations.
2. Includes AEFI reports occurring after the administration of DTaP-IPV-Hib, Pneu-C-13, Rot-1, Men-C-C, MMR, or Var vaccines, in children less than 4 years of age.
3. Doses distributed are obtained from Ontario Government Pharmacy and Medical Supply Service (OGPMSS) and are calculated for school- and primary care-administered agents.

# Vaccines

There were 568 AEFI reports temporally associated with 26 different vaccines in 2014. Most reports were associated with administration of a single vaccine (81.2%), while 10.7% of reports were associated with receipt of two vaccines and 8.1% were associated with the receipt of three or more vaccines. There were 514 AEFI reports associated with vaccines that are included within the publicly funded immunization program. As seen in Table 3, the highest overall vaccine-specific reporting rates in 2014 were observed with Men-C-ACWY and HPV4, both of which are school-based immunization programs. The lowest reporting rates were observed for Td and MMRV. There was some fluctuation in vaccine-specific reporting rates in 2014 compared to 2013, most notably was an increase in Tdap and decreases in MMRV and Tdap-IPV, both of which had relatively few reports in 2014.

**Table 3.** Number and reporting rate of AEFIs in Ontario, by vaccine, 2014

| Vaccine[1] | 2014 | | | | 2013 vaccine-specific reporting rate |
|---|---|---|---|---|---|
| | Number of AEFI reports by vaccine | Number of serious reports[2] | Doses distributed[3] | Vaccine-specific reporting rate[4] | |
| **Infant and childhood vaccines** | | | | | |
| DTaP-IPV-Hib | 53 | 5 | 564,520 | 9.4 | 11.7 |
| Pneu-C-13 | 54 | 9 | 432,470 | 12.5 | 11.6 |
| Rot-1 | 21 | 4 | 259,680 | 8.1 | 8.0 |
| Men-C-C | 26 | 6 | 160,485 | 16.2 | 14.8 |
| MMR | 50 | 4 | 272,320 | 18.4 | 15.5 |
| Var | 48 | 3 | 263,798 | 18.2 | 19.5 |
| MMRV | 1 | 0 | 99,310 | 1.0 | 14.1 |
| DTaP-IPV[5] | 13 | 0 | - | - | 340.4 |
| Tdap-IPV | 6 | 0 | 211,432 | 2.8 | 12.5 |
| **Adolescent vaccines** | | | | | |
| Men-C-ACWY | 39 | 1 | 161,864 | 24.1 | 35.2 |
| HB | 43 | 1 | 268,034 | 16.0 | 24.3 |
| HPV4 | 32 | 0 | 160,052 | 20.0 | 26.4 |
| Tdap | 76 | 2 | 631,905 | 12.0 | 8.1 |
| **Routine adult vaccines** | | | | | |
| Pneu-P-23 | 33 | 3 | 241,318 | 13.7 | 25.5 |
| Td | 5 | 0 | 267,105 | 1.9 | 4.7 |
| **Universal Influenza Immunization Program (UIIP)** | | | | | |
| Inf | 147 | 3 | 4,436,080 | 3.3 | 4.4 |
| **Other high-risk publicly funded, travel, and non-publicly funded vaccines** | | | | | |

| Vaccine[1] | 2014 | | | | 2013 vaccine-specific reporting rate |
|---|---|---|---|---|---|
| | Number of AEFI reports by vaccine | Number of serious reports[2] | Doses distributed[3] | Vaccine-specific reporting rate[4] | |
| | | | | | |
| Chol-Ecol-O | 2 | 0 | - | | - |
| Men-B | 3 | 0 | - | | - |
| HA | 3 | 1 | - | | - |
| HAHB | 17 | 0 | - | | - |
| IPV | 1 | 0 | - | | - |
| Typh-I | 4 | 1 | - | | - |
| Typh-O | 1 | 0 | - | | - |
| YF | 6 | 1 | - | | - |
| Zos | 40 | 0 | - | | - |
| Rab | 4 | 1 | - | | - |

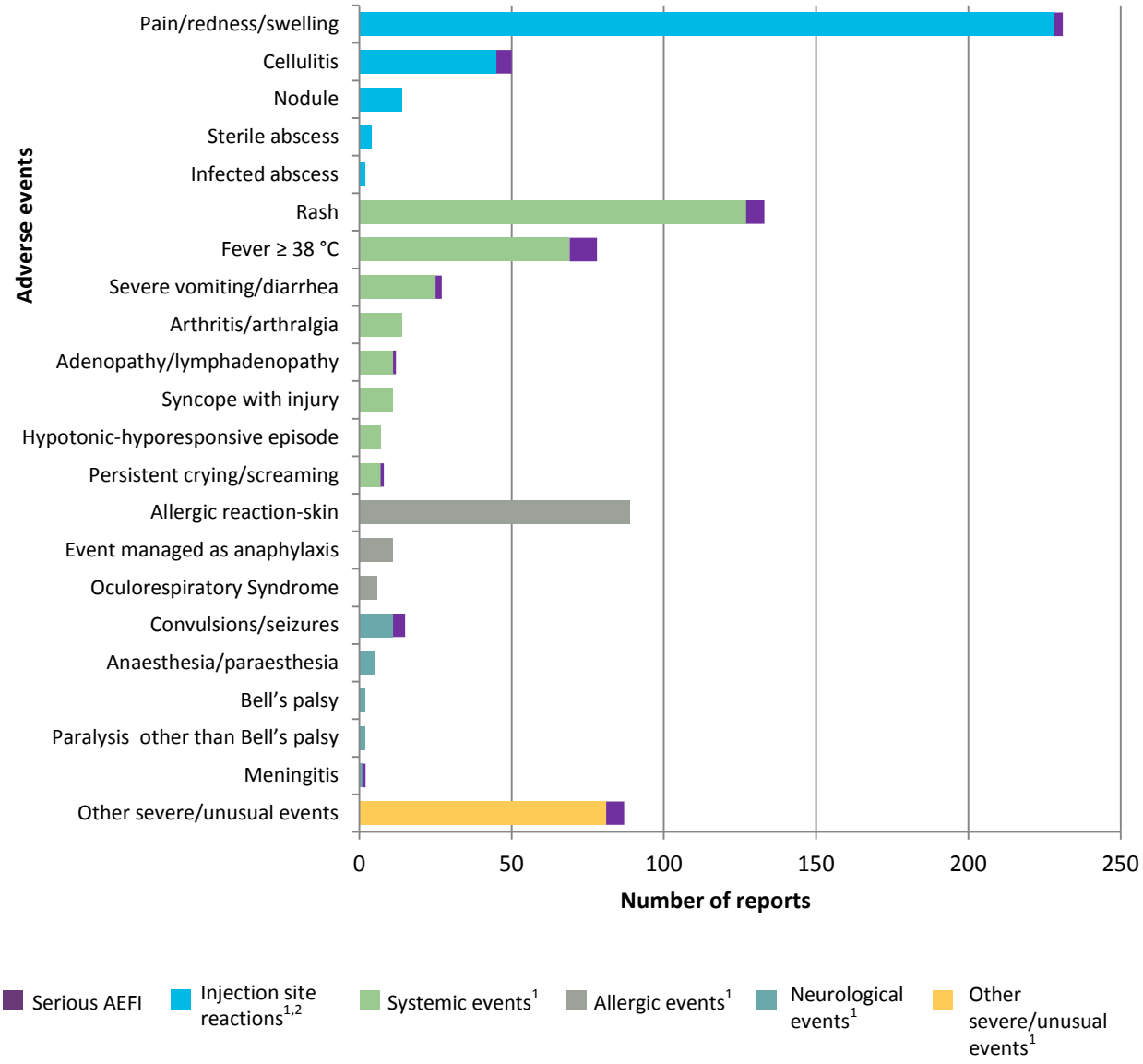
**Notes:**

1. Only those vaccines with AEFI reports are shown. See Appendix 1 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 immunization status of individuals and vaccine-specific indications.
2. Number of reports within each vaccine that are serious.
3. Doses distributed are obtained from Ontario Government Pharmacy and Medical Supply Service (OGPMSS) for publicly funded vaccines only
4. Vaccine-specific reporting rates per 100,000 doses distributed. As part of a program switch in the publicly funded immunization schedule, DTaP-IPV was replaced with Tdap-IPV for the 4-6 year old booster. Doses distributed for DTaP-IPV was omitted due to fluctuations vaccine distribution and wastage data caused by the program switch. As a result, a vaccine-specific reporting rate for DTaP-IPV could not be calculated.

# Adverse events

Adverse events were recorded in 99.6% (n=566) of reports. Of those reports with a recorded adverse event, most were associated with one event (70.1%), while 24.7% of reports were associated with two events and 5.1% were associated with three or more adverse events. The most frequently reported events were pain, redness or swelling at the injection site (40.3% of reports; n=228), followed by rash (22.4%; n=127), and allergic reactions of the skin in (15.7%; n=89) (Figure 6).

**Figure 6.** Number of non-serious and serious AEFI reports in Ontario, by adverse event and category, 2014




**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 4-10 days, ≥10 days and/or pain, redness or swelling at the injection site (of any duration) extending beyond the nearest joint.

Overall, injection site reactions were recorded in 44.7% of all reports (Table 4) and for the majority of these reports (75.5%; n=191)the injection site reaction was the only reported event. Routinely administered vaccines with the highest reporting rate for injection site reactions were Pneu-P-23, Var and Tdap (10.8, 9.1, 7.8 per 100,000 doses distributed, respectively).

The next most frequently reported event was rash which was present in 22.4% of reports (n=127). The highest rash reporting rate for routinely administered vaccines was MMR, Men-C-C and Var (12.5, 10.6, 5.7 per 100,000 vaccine-specific doses distributed, respectively). Nearly half of all rash reports (42.5%, n=54) were associated with live virus vaccines (MMR, Var and Zos). There were no rashes reported following MMRV. Rashes occurred within 5 to 42 days (i.e., the expected time to onset range for live virus vaccines) for 53.3% (n=8), 55.9% (n=19), 20.0% (n=1) for MMR, Var and Zos vaccines, respectively. There were 7 rashes reported following MMR vaccine where vaccine-strain measles virus was identified, as well as one lab-confirmed vaccine strain zoster infection following varicella vaccine.

**Table 4.** Number and distribution of AEFI reports in Ontario, by adverse event category, 2014

| Adverse event category[1] | Adverse event[2] | Number of AEFI reports[3] | Percent of all AEFI reports[4] | Number of serious reports |
|---|---|---|---|---|
| **Injection site reactions** | | **253** | **44.7** | **8** |
| | Cellulitis | 45 | 8.0 | 5 |
| | Infected abscess | 2 | 0.4 | 0 |
| | Nodule | 14 | 2.5 | 0 |
| | Pain/redness/swelling at the injection site[1] | 228 | 40.3 | 3 |
| | Pain/redness/swelling extending beyond nearest joint | 67 | 11.8 | 1 |
| | Pain/redness/swelling 4-10 days | 127 | 22.4 | 2 |
| | Pain/redness/swelling >10 days | 34 | 6.0 | 0 |
| | Sterile abscess | 4 | 0.7 | 0 |
| **Systemic reactions** | | **216** | **38.2** | **19** |
| | Adenopathy/lymphadenopathy | 11 | 1.9 | 1 |
| | Arthritis/arthralgia | 14 | 2.5 | 0 |
| | Fever ≥ 38 °C in conjunction with another reportable event | 69 | 12.2 | 9 |
| | Hypotonic-hypo-responsive episode (HHE) | 7 | 1.2 | 0 |
| | Persistent crying/screaming | 7 | 1.2 | 1 |
| | Rash | 127 | 22.4 | 6 |
| | Severe vomiting/diarrhea | 25 | 4.4 | 2 |
| | Syncope with injury | 11 | 1.9 | 0 |
| **Allergic events** | | **106** | **18.7** | **0** |
| | Allergic reaction – skin | 89 | 15.7 | 0 |
| | Event managed as anaphylaxis[5] | 11 | 1.9 | 0 |
| | Oculorespiratory syndrome (ORS) | 6 | 1.1 | 0 |

| Adverse event category[1] | Adverse event[2] | Number of AEFI reports[3] | Percent of all AEFI reports[4] | Number of serious reports |
|---|---|---|---|---|
| **Neurologic events** | | **20** | **3.5** | **5** |
| | Anaesthesia/paraesthesia | 5 | 0.9 | 0 |
| | Bell's palsy | 2 | 0.4 | 0 |
| | Convulsions/seizures | 11 | 1.9 | 4 |
| | Meningitis[5] | 1 | 0.2 | 1 |
| | Paralysis other than Bell's palsy | 2 | 0.4 | 0 |
| **Other severe/unusual events** | Other severe/unusual events | **81** | **14.3** | **6** |

**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.
4. 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 566 (two reports had missing adverse events and were therefore excluded).
5. Medically important events.

The frequency of reporting of specific events in 2014 was similar to 2012 and 2013 (See Appendix 3). Of note, the number of reported neurologic events declined in 2014 (3.5%, n=20) relative to 2013 (5.2%, n=35). The frequency of reporting of "Other severe/unusual events" remains decreased from 19.2% (n=130) in 2012 to 14.3% in both 2013 and 2014 (n=81, n=97 respectively).

There were 12 AEFIs reported which included "medically important events" representing 2.1% of all reports. One event (meningitis) also met the definition of a serious AEFI and is therefore described below. The remaining 11 were reported as "events managed as anaphylaxis" all of which were following publicly funded vaccines. The reporting rate using all publicly funded vaccine doses distributed in 2014 as the denominator was 1.3 per million doses distributed. Upon further assessment, six (54.5%) reports met the Brighton definition of anaphylaxis (four level II and two level III). Among the remaining reports, four were managed as anaphylaxis (i.e., epinephrine administered) but had insufficient documented evidence to meet the Brighton definition and one was clearly not anaphylaxis. The proportion of anaphylaxis reports that met Brighton definition increased in 2014 (54.5%) compared with 2012 and 2013 (33.3%, 31.3% respectively).

# Health care utilization and outcome

In reports with health care utilization information completed, out-patient medical consultation was sought in 72.4% (402/555), while 20.5% (116/565) had an emergency room visit and 3.9% (22/557) were admitted to hospital.

Outcome information was completed in 93.5% (n=531) of reports in 2014, which has steadily increased since 2012 (91.6% in 2013 and 88.2% in 2012). The majority (74.6%; n=396) were recovered at the time of reporting and 22.8% were not yet recovered but likely to recover, as per the outcome definitions in the iPHIS User Guide.[6] In a very small proportion of AEFI reports (2.4%; n=13) the outcome was reported as "residual effects" which refers to residual disability or sequelae related to the reported event. After case-level review of these reports, none met the definition of "residual effects" per the iPHIS User Guide 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 23 reports of AEFIs that were classified as serious, representing 4.0% (23/568) of all reports and a serious AEFI reporting rate of 0.17 per 100,000 population or 0.26 per 100,000 doses distributed[1]. The proportion of AEFIs defined as serious has remained stable since 2012 (4.1% and 4.6%, respectively). All but one of the serious reports in 2014 was admitted to hospital for a mean length of stay of 3.9 days. There was a report of a death following immunization which did not occur in the hospital (see below for further information). The majority of serious AEFIs (82.6%) were under 18 years of age, and 21.7% were less than one year of age. There were eight serious AEFIs that were documented as reported by IMPACT (Immunization Monitoring Program Active)[2], ranging in age from 4 months- to 3-years old. Two thirds (65.2%) of all serious AEFIs were 4 years of age or younger. Outcome information was available for all 23 serious reports. The majority (69.6%; n=16) were recovered, four were not yet recovered (defined as an event that is likely to resolve, but is not resolved at the time the AEFI report is closed), two were classified as having residual effects, and one was deceased (see below for further information). It should also be noted that there were no notable differences in the distribution of outcomes between serious and non-serious AEFIs.

The highest vaccine-specific serious reporting rates were for Men-C-C, Pneu-C-13 and Rot-1 (3.7, 2.3, 1.9 per 100,000 doses distributed, respectively). There were five publicly funded vaccines not associated

[1] The latter serious reporting rate is calculated using combined, net publicly funded doses distributed as the denominator. The numerator includes all serious AEFI following publicly funded vaccines (n=22). One serious AEFI following YF has been excluded from the serious rate calculation as it is a privately funded vaccine for which doses distributed is unavailable.

[2] 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

with any serious AEFIs in 2014. The most frequently reported events among serious AEFIs were fever (n=8) (which by definition is only reportable in conjunction with another reportable event) followed by "Other severe/unusual events" (n=6), rash (n=6) and cellulitis (n=5).

The following is a summary of all serious AEFI reports based on case-level review of all information entered in iPHIS, including case notes.

- Seven reports of fever/rash illness including three diagnosed as Kawasaki disease and one lab-confirmed vaccine-strain measles infection: age range 6- to 17-months of age
- Five reports of cellulitis, two following Pneu-P-23 vaccine, two Var and one Inf; age range 2- to 5-years old
- Four reports of seizures; two diagnosed seizure disorders, one diagnosed as infantile spasms, one febrile seizure : age range 2 months- to 3-years old
- Two severe injection site reactions in adults with concurrent conditions requiring hospitalization
- One report of aseptic meningitis in an infant
- One report of optic neuritis in an adolescent following HB and Men-ACWY
- One report of rhabdomyolysis (in the injected arm) in an adult following rabies vaccine
- One report of possible vaccine-associated encephalitis in an adult following yellow fever vaccine

In addition, there was one report of death in an infant four days after receipt of DTaP-IPV-Hib, Pneu-C-13 and Rot-1 vaccines. A coroner's investigation was completed which found the cause of death to be unascertained, with unsafe sleep environment as a contributing factor. No link with vaccine was reported.

# Risk factors

Among all reports, 14.6% (n=83) had risk factor information completed in iPHIS, which is slightly increased compared to 2013 when risk factors were completed in 13.6% of reports. Similar to previous years, the most frequently reported risk factor in 2014 was "Chronic illness/underlying medical condition" reported in 68.7% (n=57) of reports with risk factors completed, followed by "Immunization program error" (8.4%; n=7) and "Immunocompromised" (6.0%; n=5). Table 5 describes AEFIs in which an immunization program error was reported.

**Table 5.** Summary of AEFI reports in Ontario where "Immunization program error" was selected under "Risks" in iPHIS, 2014

| Age (years) | Agent | Error | Adverse event category | Additional case details |
|---|---|---|---|---|
| 1-3 | MMR (Priorix®) | Expired vaccine administered | Rash | MMR vaccine expired two months prior; onset of hive-like rash 2 days after receipt of vaccines; also received Men-C-C, Pneu-C-13 as per routine schedule |
| 1-3 | Var (Varivax® III) | Incorrect site | Nodule | Vaccine administered subcutaneously in the anterolateral thigh instead of triceps area of the arm which is the indicated site |
| 11-17 | Tdap (Adacel®) | Vaccine not indicated | Fever, other severe/unusual events | Client had already received the adolescent dose of Tdap two years prior therefore dose was not indicated; allergic-like symptoms with second dose, referral to an allergist recommended |
| 18-64 | Inf (Fluviral®) | Incorrect land-marking | Pain/redness/swelling (lasting greater than 10 days) | Incorrect land-marking with administration of the vaccine too high in the deltoid muscle; resulting in prolonged pain and immobility in injected arm |
| 18-64 | Inf (Fluviral®) | Incorrect land-marking | Pain/redness/swelling (lasting greater than 10 days), Pain/redness/swelling extending beyond nearest joint | Incorrect land-marking with administration of the vaccine too high in the deltoid muscle; resulting in prolonged pain and immobility in injected arm |
| 18-64 | Zos (Zostavax®) | Vaccine contraindicated | Pain/redness/swelling (lasting 4-10 days), allergic reaction - skin | Vaccine administered despite known allergy to neomycin which is present in the vaccine; vaccine therefore contraindicated |
| 18-64 | Zos (Zostavax®) | Incorrect route | Cellulitis, pain/redness/swelling (lasting 4-10 days) | Vaccine administered intramuscularly in the deltoid as opposed to subcutaneously, as indicated |

# Discussion

This assessment of adverse events reported following vaccines administered in 2014 is the third annual assessment of vaccine safety in Ontario. No unexpected safety issues were identified as a result of this analysis and findings were generally consistent with the previous two reports with continued improvements in data quality. The information presented contributes to the safety profile of vaccines administered in Ontario, and provides relevant and timely information about the safety of vaccines administered in the province to support health care professionals, reassure the public and build confidence in immunization.

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 iPHIS has not been completed. Reporting rate estimates should not be interpreted as incidence rates, but are used for comparison purposes and monitoring over time.

The provincial AEFI reporting rate was lower in 2014 following two years of increasing rates; however, the overall increasing trend in the annual AEFI reporting rate since 2010 remains statistically significant. Reasons for the decrease in 2014 are likely multifactorial, however there were notable decreases in AEFIs following vaccines which typically contribute a high proportion of reports overall (i.e., Inf and Pneu-P-23). In addition, changes to provincial AEFI surveillance definitions made on January 1, 2013 may be continuing to influence AEFI reporting in 2014 due to increasing awareness and incorporation of the changes into routine PHU reporting practice. Many of the revised AEFI definitions increased the specificity which could reduce the overall number of reports that meet provincial reporting criteria.

There were some continued improvements in the quality and completeness of AEFI surveillance data in 2014. For example, completeness of the reporting source field in iPHIS continued to increase from 91.4% and 92.0% in 2012 and 2013 respectively, to 94.6% in 2014. Other data fields which showed initial improvements in completeness between 2012 and 2013, levelled off in 2014. For example the proportion of reports classified as “confirmed” remained the same in 2014 (88.1%) after increasing from 84.9% to 88.4% between 2012 and 2013. The increase in 2013 is most likely the result of revised provincial surveillance definitions which clarified that a “confirmed” AEFI requires only a temporal and not causal association between a vaccine and an adverse event and excludes only reports with a clear, alternative diagnosis . In addition, for the past three years, PHO has reviewed all AEFIs on a weekly basis to ensure that they are classified appropriately and requested revisions from PHUs where indicated. Continued monitoring and follow-up over the next few years will confirm whether the proportion of reports classified as “confirmed” has stabilized or if further increases are possible.

The provincial AEFI reporting rate in 2014 continues to be lower in comparison to the national reporting rate. A higher overall reporting rate is an indicator of a robust passive vaccine safety surveillance system, where the quantity of AEFI reports establish a clear historical baseline to help identify future vaccine safety signals. The most recently published population-based AEFI reporting rate for Canada from 2012 is 10.1 per 100,000 population[22], which is more than double Ontario’s 2014 rate of 4.2 per

100,000 population. The disparity between the national and provincial reporting rates is even more pronounced for serious AEFIs where the national population-based reporting rate is over three times the provincial population-based rate (0.60 vs. 0.17 per 100,000 population, respectively). While publicly funded immunization schedules [27]and administration practices [28] are relatively similar across the country, immunization program delivery models as well as other health system factors which have the potential to influence AEFI reporting rates can vary widely between jursidictions. For example, in Ontario, one factor that may be influencing the AEFI reporting rate is under-reporting by health care professionals.[18] Our analysis further explores this finding, showing that the rate of AEFI reporting within primary care-delivered (infant & toddler) immunization programs is much lower compared to PHU-delivered (school-based) programs. Looking at school-based programs only, which are primarily delivered by PHUs, Ontario's reporting rates are much more comparable or higher than the national reporting rates[22] (e.g., 24.1 vs. 23.7 per 100 000 doses distributed of Men-C-ACWY in Ontario vs. Canada, respectively). Additionally, comparison of reporting source and health care utilization data suggests that for at least some AEFI reports, medical consultation was sought, yet the event was not reported by a health care professional (74.2% sought medical consultation; 61.6% reported by a physician or other health care professional). The reasons for under-reporting of AEFIs, particularly by health care professionals are not yet fully understood in Ontario. However, surveys from other jurisdictions have identified barriers to health care professional reporting, which include lack of familiarity with the AEFI reporting process (i.e., paper form), uncertainty with who is responsible for reporting and unclear definitions of a reportable AEFI.[29,30]

Age-specific population-based reporting rates of AEFI were as expected, with the highest rates among the youngest age groups who receive the highest number of recommended vaccine doses (i.e. nine dose of vaccine by one year of age).[19]This is consistent with national AEFI data which shows a similar trend[22].

AEFI reporting by vaccine in 2014 was generally consistent with previous years with some fluctuations. The highest reporting rates were for vaccines delivered by PHUs within the school-based program, which is consistent with related findings of higher reporting rates within PHU-delivered immunization programs. There were marked decreases in the 2014 reporting rate, compared to 2013 for some vaccines including: Pneu-P-23, Td, Tdap-IPV and MMRV. For Pneu-P-23, this decrease in reporting is mainly attributable to much lower reporting of injection site reactions following this vaccine in 2014 (n=26) compared to 2013 (n=60). For Td, Tdap-IPV and MMRV, the reasons for the decrease are not clear although these rates are prone to fluctuations due to a low volume of reports. Though not as dramatic in terms of magnitude, the influenza AEFI reporting rate has steadily decreased each year since 2012 (5.4, 4.4 and 3.3 per 100 000 in 2012, 2013 and 2014 respectively) but continues to have the highest volume of reports of any vaccine. The low rate of reporting for AEFIs following influenza vaccine is consistently observed within other AEFI surveillance systems[31,32] including nationally where influenza vaccine has the lowest vaccine-specific AEFI reporting rate (8.5 per 100 000 doses distributed).

Injection site reactions were again, as expected, the most frequently reported events, present in 45% of all AEFI reports. However, for the first time in 2014, both the volume and rate of reporting of injections site reactions have decreased slightly (1.85 vs. 2.02 per 100 000 population in 2014 and 2013, respectively). This may suggest early impact of revised AEFI surveillance definitions which were in part

designed to reduce the reporting burden of these typically mild events that do not require any public health action. However, further monitoring of the trend over the next few years will be required to fully assess the impact of this change. In terms of other commonly reported events, rash was assessed in more detail for the first time in this report. As expected, a substantial proportion of rashes were reported following receipt of live virus vaccines which are known to produce virus-like rashes, particularly after the first dose (5-10% and 3-5% for MMR and varicella vaccines, respectively).[33,34] Case level review found that up to half of all reported rashes following live virus vaccines (depending on the vaccine) occurred within the expected time to onset (5 to 42 days) while others occurred outside this timeframe and therefore may have been coincidental or related to other causes.

Events managed as anaphylaxis were rarely reported in 2014, with a reporting rate slightly less than in 2013 (1.3 vs. 1.8 per million doses distributed) but still within the range of expected rates which is between one and ten episodes per million vaccine doses administered.[35] The proportion of anaphylaxis reports with adequate information to assess using the Brighton case definition and diagnostic levels of certainty[23] has steadily increased since 2012 (50.0%, 56.3% and 63.6% for 2012, 2012 and 2014, respectively). This is likely the result of improved data entry guidelines, data quality initiatives and most recently, the implementation of an anaphylaxis reporting form in September of 2014.[8] This form addressed a recommendation made in the 2012 vaccine safety report [17] for improved quality and completeness of anaphylaxis reporting in order to conduct systematic assessment using the Brighton case definitions.

Serious AEFIs were rarely reported in 2014, at a reporting rate of 2.6 serious AEFIs per million doses of vaccine distributed and the proportion of AEFI reports that were serious was consistent with previous years. The most frequently reported serious events were febrile/rash illness and cellulitis requiring hospital admission for treatment with intravenous antibiotics – all recovered at the time of reporting. Other serious reports were rare events which have been assessed by the Institute of Medicine (IOM) and have not been causally linked to vaccines (E.g. infantile spasms,optic neuritis).[36] There was one report of possible vaccine-associated encephalitis in a hospitalized adult following yellow fever vaccine in which the individual recovered fully. Yellow fever vaccine-associated neurotropic disease (YEL-AND) is a known but rare reaction which has been estimated to occur at a rate of between 0.4 and 0.8 per 100,000 doses distributed, although it is higher for individuals ≥60 years of age.[37] YEL-AND is a group of clinical syndromes that includes meningoencephalitis (neurotropic disease), acute disseminated encephalomyelitis, Guillain Barré syndrome, and acute bulbar palsy.[38]

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 cause of death to be unascertained and the manner of death undetermined[3], with unsafe sleep environment as a contributing factor. This event is included in this

[3] 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" [54]
http://www.mcscs.jus.gov.on.ca/stellent/groups/public/@mcscs/@www/@com/documents/webasset/ec167691.pdf

report as it meets 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.[5] As noted previously, events described in this report are temporally and are not necessarily causally linked to vaccines. 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.[39-41] While rare, these reports have been observed in previously in Ontario and other passive AEFI surveillance systems[31,32,42,43] however no association has been found between vaccines and sudden infant deaths.[43-52]

# Limitations

One important limitation of this analysis is the lack of a population-based provincial immunization registry to estimate the number of individuals who were immunized or doses administered. This would enable estimation of AEFI incidence rates by vaccine or event type. In lieu of this, AEFI reporting rates are estimated using either the entire population irrespective of immunization status or doses distributed as the denominator. Doses distributed are widely used in analyses of passive AEFI surveillance systems [22,53] and can be a reasonable proxy for doses administered for established programs with known vaccine wastage. When the amount of wastage is unknown and underestimated, this can result in underestimates of reporting rates. When doses distributed are unknown (i.e. privately purchased vaccine is not included), this can result in an overestimation of reporting rates. Additionally, in the context of new or discontinued vaccines/programs, the AEFI reporting rate using doses distributed as the denominator can be temporarily rendered invalid due to fluctuations in vaccine distribution caused by stockpiling or large returns of unused/expired doses.

Other general limitations are shared with other passive AEFI surveillance systems such as data quality, completeness and reporting bias including under-reporting, particularly for mild or common reportable events as well as stimulated (elevated) reporting which can occur in response to media coverage and subsequently increased public awareness.[53] Additionally, the provincial AEFI surveillance system does not include an unimmunized group for comparison, therefore determining whether immunization is associated with an increased risk of a specific adverse event is not possible.[53]

# Conclusions

The Annual Report on Vaccine Safety in Ontario is now in its third year, and has established a valuable mechanism to communicate the safety of vaccines administered in the province to support health care professionals, reassure the public and build confidence in immunization. This report finds that vaccines administered in Ontario in 2014 resulted in a low rate of reported adverse events. Most reported events were mild (i.e., injection site reactions) and resolved completely. No unexpected safety issues were identified.

Under-reporting of AEFIs continues to be an important limitation of AEFI surveillance in Ontario. Further research to evaluate health professionals' awareness and practices regarding reporting of AEFIs is needed to inform strategies to increase AEFI reporting in order to contribute to a more robust provincial vaccine safety surveillance system.

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# Appendices

## Appendix 1: 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-B | Men-B | Bexsero® |
| Men-C-ACWY | Men-C-ACWY - Meningococcal - Conjugate ACWY | Menactra®, Menveo®, Nimenrix® |
| Men-C-C | Men-C-C - Meningococcal - Conjugate C | NeisVac-C®, Menjugate®, |

| Vaccine abbreviations used in the report | "Agent" values in iPHIS (as of April 1, 2013) | Product/trade name |
|---|---|---|
| | | Meningitec® |
| MMR | MMR - Measles, Mumps, Rubella | MMR I , MMRII®, Priorix |
| MMRV | MMRV - Measles, Mumps, Rubella, Varicella | Priorix-Tetra™ |
| 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 2: 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 3: Number and distribution of confirmed AEFI reports, by adverse event category, 2012-14

| Adverse event category[2] | Adverse event[2] | 2014 n (%)[6] | 2013 n (%)[6] | 2012 n (%)[6] |
|---|---|---|---|---|
| **Allergic events** | | **106 (18.7)** | **139 (20.6)** | **174 (25.7)** |
| | Allergic reaction – other[3] | N/A | N/A | 27 (4.0) |
| | Allergic reaction - skin | 89 (15.7) | 126 (18.6) | 133 (19.7) |
| | Event managed as anaphylaxis[5] | 11 (1.9) | 17 (2.5) | 20 (3.0) |
| | Oculorespiratory Syndrome (ORS) | 6 (1.1) | 1 (0.1) | 5 (0.7) |
| **Injection site reactions** | | **253 (44.7)** | **274 (40.5)** | **274 (40.5)** |
| | Cellulitis | 45 (8.0) | 62 (9.2) | 60 (8.9) |
| | Infected abscess | 2 (0.4) | 6 (0.9) | 4 (0.6) |
| | Nodule | 14 (2.5) | 10 (1.5) | 23 (3.4) |
| | Pain / redness / swelling (extending beyond nearest joint) | 67 (11.8) | 56 (8.3) | 16 (2.4) |
| | Pain/redness/swelling <4 days[3] | N/A | N/A | 57 (8.4) |
| | Pain/redness/swelling >4 days[3] | N/A | N/A | 58 (8.6) |
| | Pain/redness/swelling 4-10 days[4] | 127 (22.4) | 152 (22.5) | 59 (8.7) |
| | Pain/redness/swelling >10 days[4] | 34 (6.0) | 37 (5.5) | 21 (3.1) |
| | Sterile abscess | 4 (0.7) | 0 (0) | 7 (1.0) |
| **Neurologic events** | | **20 (3.5)** | **35 (5.2)** | **31 (4.6)** |
| | Acute disseminated encephalomyelitis (ADEM)[5] | 0 (0) | 1 (0.1) | 0 (0) |
| | Anaesthesia / paraesthesia[4] | 5 (0.9) | 15 (2.2) | 7 (1.0) |
| | Bell's palsy | 2 (0.4) | 2 (0.3) | 3 (0.4) |
| | Convulsions/seizures | 11 (1.9) | 14 (2.1) | 14 (2.1) |
| | Encephalopathy/encephalitis[5] | 0 (0) | 1 (0.1) | 2 (0.3) |
| | Guillian-Barre syndrome (GBS)[5] | 0 (0) | 1 (0.1) | 2 (0.3) |
| | Meningitis[5] | 1 (0.2) | 1 (0.1) | 0 (0) |
| | Paralysis other than Bell's palsy | 2 (0.4) | 1 (0.1) | 3 (0.4) |

| Adverse event category[2] | Adverse event[2] | 2014 n (%)[6] | 2013 n (%)[6] | 2012 n (%)[6] |
|---|---|---|---|---|
| **Other events of interest** | | **104 (18.4)** | **118 (17.5)** | **141 (20.9)** |
| | Arthritis / arthralgia | 14 (2.5) | 14 (2.1) | 11 (1.6) |
| | Intussusception[5] | 0 (0) | 1 (0.1) | 0 (0) |
| | Other severe / unusual events | 81 (14.3) | 97 (14.3) | 130 (19.2) |
| | Syncope with injury[4] | 11 (1.9) | 6 (0.9) | 0 (0) |
| | Thrombocytopenia[5] | 0 (0) | 2 (0.3) | 0 (0) |
| **Systemic reactions** | | **194 (34.3)** | **234 (34.6)** | **194 (28.7)** |
| | Adenopathy/lymphadenopathy | 11 (1.9) | 10 (1.5) | 5 (0.7) |
| | Fever ≥ 38 °C | 69 (12.2) | 58 (8.6) | 54 (8.0) |
| | Hypotonic-hyporesponsive episode (HHE) | 7 (1.2) | 3 (0.4) | 5 (0.7) |
| | Parotitis | 0 (0) | 1 (0.1) | 2 (0.3) |
| | Persistent crying/screaming | 7 (1.2) | 6 (0.9) | 6 (0.9) |
| | Rash | 127 (22.4) | 155 (22.9) | 146 (21.6) |
| | Severe vomiting/diarrhea[4] | 25 (4.4) | 35 (5.2) | 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. Data extracted from iPHIS on May 1, 2015. 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 566 (two reports had missing adverse events and were therefore excluded), 676 (one report had missing adverse events and was therefore excluded), and 676 for 2014, 2013 and 2012 respectively.

**Public Health Ontario**
480 University Avenue, Suite 300
Toronto, Ontario
M5G 1V2

647.260.7100
communications@oahpp.ca
**www.publichealthontario.ca**