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Annual Report on Vaccine Safety in Ontario, 2012

TECHNICAL REPORT
January 2014

Public Health Ontario

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How to cite this document:
Ontario Agency for Health Protection and Promotion (Public Health Ontario). Annual report on vaccine safety in Ontario, 2012. Toronto, ON: Queen's Printer for Ontario; 2014.

ISBN 978-1-4606-3256-7 [PDF]

Public Health Ontario acknowledges the financial support of the Ontario Government.

Annual Report on Vaccine Safety in Ontario, 2012

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Acknowledgements

We would like to extend our sincere thanks to public health unit staff across the province for their dedication and efforts in the investigation and reporting of adverse events following immunization which are essential to the assessment of vaccine safety in Ontario.

In addition, we would like to acknowledge Natasha Crowcroft, Dawn Williams, and the communications staff at Public Health Ontario including Keisha Mair, Steven Janovsky, Nicole Helsberg, and Cathy Mallove for their careful review and production of this document as well as materials to support its public release.

January 2014

Disclaimer

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Contents

Glossary of Active Immunizing Agent Acronyms Used in This Report

BCG	bacille Calmette-Guérin
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
HPV2	human papillomavirus bivalent
HPV4	human papillomavirus quadrivalent
Inf	influenza (both trivalent inactivated 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 2012. It represents the first comprehensive annual assessment of vaccine safety in the province and fulfils a previous recommendation to report Ontario AEFI data on an annual basis. The report aims to encourage ongoing assessment of vaccine safety and provide relevant and timely information for health professionals and the public about the safety of vaccines administered in Ontario.

AEFIs reported following vaccines administered between January 1and December 31, 2012, were extracted from the integrated Public Health Information System (iPHIS). There were 631 reports of confirmed AEFIs representing an overall reporting rate of 4.7 per 100 000 population. The number of reports increased in 2012 compared to the previous two years; however, the rate of reporting in 2012 relative to population size in Ontario is lower than some other jurisdictions. The distribution of AEFI reports by age was weighted toward younger ages with over half of all reports for individuals 18 years of age and under, and the distribution of reports by sex varied by age with a predominance of AEFI reports among adult females. AEFI reports by specific agent are primarily driven by the volume of vaccine distributed. Reported events were consistent with the safety profile of many vaccines in which injection-site reactions are most frequent.

A number of limitations are described, many of which are inherent to passive AEFI surveillance systems. 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. Recently implemented updates to AEFI surveillance guidelines will contribute towards improved quality and completeness of data.

Finally, the following actions are recommended to support dissemination of the report findings and contribute to continuous improvement of AEFI surveillance data in the province.

1. Continue to produce a report that assesses AEFIs on an annual basis, using an iPHIS data extraction date of May 1 for all AEFIs reported following vaccines administered in the previous calendar year and after an annual data-cleaning process to ensure consistency and comparability of data over time.
2. Develop and implement a knowledge translation plan for the annual report which includes distribution of an annual vaccine safety report to public health units (PHUs), health professionals and members of the public to contribute to openness and transparency of the vaccine safety surveillance system in Ontario.

3. Implement an anaphylaxis reporting tool to improve the quality and completeness of reporting of events managed as anaphylaxis and aid in provincial assessment and classification of these events using standard, internationally accepted criteria.
4. Further explore possible explanations for under-reporting of AEFIs and recommend strategies to improve reporting rates in Ontario.

Background

Vaccines are widely considered to be one of the most successful and cost-effective public health interventions.[1, 2] With this success and the declining incidence of many vaccine-preventable diseases, public focus has shifted to the safety of vaccines. Tolerance for adverse events is low because vaccines are administered to large cohorts of healthy people, particularly children.[3] In recent years, reports have shown that the public is more concerned about vaccine safety and less confident in vaccines.[4, 5] Improved communication about vaccine safety will contribute to restoring confidence and building trust in the vaccine system and continued success of immunization programs.[3, 5-8]

In Canada, vaccines are highly regulated and monitored to ensure they are as safe as possible.[6] They are thoroughly reviewed for efficacy and safety prior to being approved for use. Vaccine manufacturers are required to adhere to internationally accepted standards of manufacturing to ensure quality and consistency. In addition, all lots of vaccine are subject to Health Canada's lot release program which specifies standards for the production of each lot that must be met before sale in Canada.[3] The National Advisory Committee on Immunization (NACI) independently reviews the available evidence on safety and efficacy. It also makes recommendations for the use of currently or newly approved vaccines, including identification of groups at risk for vaccine-preventable disease for whom vaccine programs should be targeted.[9]

Following approval of a new vaccine, post-marketing surveillance is initiated to ensure the ongoing monitoring of safety in the context of "scaled up" vaccine production and expansion of the population receiving the vaccine. Individual AEFI case reports represent an important source of data because they have the potential to generate safety signals not previously recognized or an increase in frequency or severity of a previously recognized AEFI which can be further evaluated.[10] This is particularly important for rare adverse events, which may not have been evident in clinical trials due to their limited sample size. 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.[10]

Post-marketing surveillance is a shared responsibility between Health Canada, the vaccine manufacturers, the Public Health Agency of Canada (PHAC) and provincial/territorial (P/T) public health authorities. Reports of AEFIs made directly to vaccine manufacturers are sent to Health Canada, while AEFIs reported to P/T public health authorities are reported to the Canadian Adverse Event Surveillance System (CAEFISS), maintained by PHAC. PHAC and Health Canada coordinate post-marketing vaccine safety surveillance nationally.

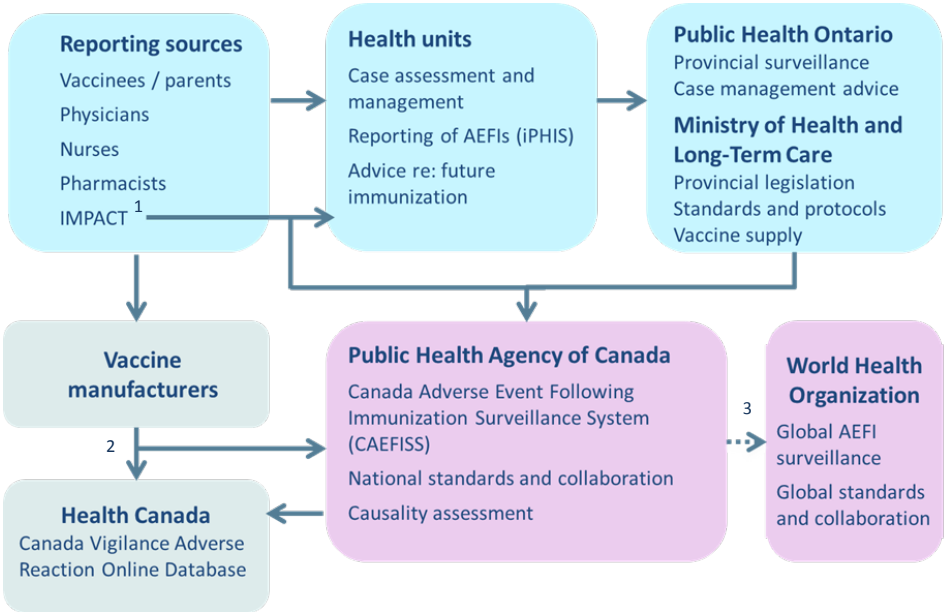
Adverse event following immunization surveillance in Ontario

The objectives of adverse event following immunization (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

Reports of AEFIs generally originate from a health professional or a vaccine recipient reporting to their local public health unit (PHU) (Figure 1). While this passive reporting mechanism represents the majority of AEFI surveillance, Ontario does receive reports from two hospitals in the province that participate in the Immunization Monitoring Program ACTive (IMPACT), a paediatric hospital-based sentinel surveillance system of selected vaccine preventable diseases and AEFIs in Canada. The two sites are in Toronto (The Hospital for Sick Children) and Ottawa (Children's Hospital of Eastern Ontario).

Figure 1. Overview of the adverse event following immunization (AEFI) surveillance process in Ontario



Notes:

1. IMPACT = Immunization Monitoring Program ACTive.
2. AEFIs reported to the vaccine manufacturer directly are reported to the Canada Vigilance Adverse Reaction database, maintained by Health Canada. For reports made via this route only, there is no public health follow-up or validation of information.
3. Dotted line indicates proposed reporting process.

Reporting of AEFIs by specific health professionals is mandated under Section 38 of the *Health Protection and Promotion Act (HPPA)* which specifies that:

> *"A physician, a member of the College of Nurses of Ontario or a member of the Ontario College of Pharmacists who, while providing professional services to a person, recognizes the presence of a reportable event and forms the opinion that it may be related to the administration of an immunizing agent shall, within seven days after recognizing the reportable event, report thereon to the medical officer of health of the health unit where the professional services are provided".*[11]

The HPPA also outlines adverse events and immunizing agents that are specifically reportable. Although some vaccines are not specifically listed in the HPPA as immunizing agents, the Ministry of Health and Long-Term Care (MOHLTC) has requested that PHUs voluntarily report adverse events following all vaccines (March 27, 2009, memorandum to medical officers of health from the chief medical officer of health, MOHLTC; unreferenced). In addition to mandated reporting by some health professionals, AEFIs are also voluntarily reported by vaccine recipients or their parents/guardians. Reports may be made by telephone or by completing an AEFI reporting form and sending it by mail or fax to the PHU.

PHUs monitor, investigate, and document all suspected cases of AEFIs that meet the provincial reporting criteria and promptly report these cases to PHO as required by the Ontario Public Health Standards (OPHS).[12] The OPHS also requires that PHUs promote the reporting of AEFIs by health care providers in their jurisdiction in accordance with the HPPA. The medical officer of health (MOH) may also provide recommendations with respect to additional follow-up and receipt of further doses of vaccine to vaccine recipients who experience an AEFI.

On January 1, 2012, PHO assumed responsibility for provincial AEFI surveillance and case management from the MOHLTC. In early 2012, PHO completed an assessment of the current status of vaccine safety surveillance in Ontario with respect to the overall surveillance objectives. It also hosted a vaccine safety meeting at which Canadian and international experts were invited to share best practices and models of AEFI surveillance. The findings of this assessment and consultation process identified a number of strengths and challenges in the current passive AEFI surveillance system. There was consensus that enhancements were both necessary and feasible within the existing framework. Building on this work, an HPV safety assessment completed in the fall of 2012 included a detailed description of the limitations of provincial AEFI surveillance data.[13] Based on the HPV safety assessment, the following five recommendations were made to improve overall data quality:

1. Revise the Infectious Diseases Protocol (2009), Appendix B, Case Definitions for AEFIs [14] to clarify the AEFI confirmed-case definition and criteria for specific events of interest to reflect national case definitions and incorporate best practices from other Canadian jurisdictions and Brighton Collaboration case definitions, where available.
2. Update the iPHIS application with adverse-event values that are consistent with provincial case definitions for AEFIs.

3. Revise the iPHIS AEFI User Guide[15] with specific, detailed instructions and rationale to support valid, complete and timely data entry with emphasis on case and adverse-event classifications.
4. Implement an Ontario-specific AEFI reporting form for use by health care providers to reduce the barriers identified with PHAC's current AEFI reporting form.
5. Produce an annual report of Ontario AEFI data.

The first four recommendations were implemented on January 1, 2013. The implementation of these recommendations was guided by the Vaccine Safety Surveillance Working Group (VSSWG), a provincial working group with representation from PHUs, MOHLTC, PHAC, and PHO, formed in June 2012.

In 2012, PHO transmitted data on all AEFIs reported in Ontario to PHAC on a monthly basis for inclusion in the Canadian Adverse Events Following Immunization Surveillance System (CAEFISS), a national database containing AEFIs reported from all provinces and territories in Canada.

Objectives and scope of the AEFI annual report

The purpose of this report is to summarize AEFIs reported in Ontario following vaccines administered in 2012. This report represents the first comprehensive annual vaccine safety assessment in Ontario. PHUs and vaccine providers are the primary intended audience of this report.

Given that this is the first report of its kind in Ontario, it includes a complete description of the provincial AEFI surveillance system and a discussion of its limitations. In addition, the report includes recommendations for improved AEFI data/surveillance processes.

Methods

Provincial surveillance systems to monitor AEFIs in Ontario

AEFI information is reported by PHUs via the integrated Public Health Information System (iPHIS), an electronic reporting system for reportable diseases and reportable events, including AEFIs, in Ontario. AEFIs must be reported using iPHIS within five business days of receipt of initial notification to a PHU.[16] AEFI reports are classified in iPHIS according to the Infectious Diseases Protocol, Appendix B (AEFI), 2009[14] with the exception of AEFIs reported after January 1, 2013, which were classified according to the Infectious Diseases Protocol, Appendix B (AEFI), 2013.[17] Appendix 1 provides a detailed summary of the revisions to the iPHIS field affected by this update. The minimum data elements to be reported for each AEFI are specified in the iPHIS AEFI User Guide (2009) and associated bulletins and directives issued by the MOHLTC.[15, 16] On January 1, 2013, a revised iPHIS User Guide for AEFIs was issued. It is aligned with the revised Appendix B (AEFI) 2013 document and provides direction for data entry of AEFIs reported on or after January 1, 2013.[18]

From January 2012 onward, PHO reviewed all AEFIs reported by PHUs on a weekly basis for data quality and completeness, with an emphasis on serious AEFIs (defined on page 9). PHUs were contacted directly to request an amendment of a report if key information was missing/incomplete (e.g., agent, reaction, case notes). In addition to monitoring ongoing data quality, PHO led a formal data clean-up initiative between February 15 and March 31, 2013. PHO requested via the Weekly iPHIS Bulletin that PHUs review AEFI reports following vaccines administered in 2012 and update missing/incomplete information for selected data fields.[19]

Analysis of epidemiologic data

We extracted all reports of AEFIs with a vaccine administration date from January 1 to December 31, 2012, from iPHIS as of May 6, 2013. 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., no active immunizing agent administered at the same time).

Reports of AEFIs are classified as “Confirmed,” “Persons under investigation (PUI),” or “Does not meet” (DNM) case definition according to the iPHIS User Guide for AEFI. [15, 18] As per these guidelines, the “PUI” case classification is for use in the investigation stage only. When the case is closed, it should be updated to “Confirmed” or “Does not meet.” Other case classifications such as “Suspect” or “Probable” are not applicable to AEFI and are not used. As of January 1, 2013, when updated provincial case definitions were published, [17] the “Confirmed” and “Does not meet” 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

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

Prior to January 1, 2013, there was no explicit definition of a confirmed AEFI report separate from criteria for specific types of events.[14] For this report, we limited descriptive analyses of demographic, temporal, agent/event-specific and geographical trends to "Confirmed" AEFI reports. 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 active immunizing agents administered at the same time. For each AEFI report, one or more specific adverse events are selected from the "Adverse event reaction(s)" field in iPHIS based on criteria for specific AEFIs described in Appendix B (AEFI).[14, 17] We grouped these values into categories of adverse events for this analysis. See Appendix 1 for a complete description of adverse event reaction(s) values available in iPHIS (both before and after changes implemented on January 1, 2013) as well as corresponding adverse-event categories for analysis.

For each AEFI report there is also one or more active immunizing agents selected from the "Agent" field in iPHIS. We refer to these agent values throughout this report using standard acronyms (e.g., MMR for measles, mumps, rubella). See Appendix 3 for a complete list of agent abbreviations, corresponding product/trade names and available "Agent" values in iPHIS.

We defined reports of AEFIs as "serious" using the International Conference on Harmonisation (ICH) definition which defines a serious AEFI as an event that resulted in death, was life threatening, required in-patient hospitalization of 24 hours or more or prolongation of existing hospitalization, resulted in persistent or significant disability/incapacity, causes congenital anomaly/birth defect, or, any other important medical event that may have jeopardized the patient or may have required intervention to prevent one of the outcomesabove.[10] We designated specific medically important events as serious based on the Vaccine Vigilance Working Group (VVWG), a Federal-Provincial-Territorial working group led by PHAC, for the purpose of AEFI surveillance in Canada. For AEFI surveillance in Ontario, medically important events include anaphylaxis, Guillain Barré syndrome (GBS), Bell's palsy, paralysis (other than Bell's palsy), seizure, meningitis, encephalopathy/encephalitis, intussusception and thrombocytopenia (See Appendix 2).

We calculated AEFI reporting rates using the 2010 and 2011 Ontario population estimates and 2012 projected population of Ontario[20] (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 include vaccine

wastage/reusable vaccine returned to OGPMSS. Reporting rates using doses distributed as the denominator were not calculated for vaccines that were exclusively privately purchased in Ontario in 2012 (i.e., not publicly funded). We performed statistical analyses using commercially available software, including SAS version 9.3 (SAS Institute, Cary, NC, USA), IBM SPSS version 19.0 (IBM, Armonk, NY, USA) and Microsoft Excel 2010 (Microsoft, Redmond, WA, USA).

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, 2013.

Notes on interpretation

The adverse events we describe in this report are **temporally associated** and are not necessarily **causally linked** to vaccine. 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 and they should not be interpreted as incidence rates.

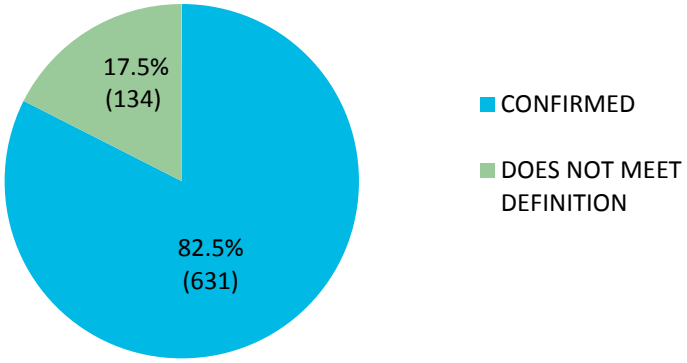
Trends in reported AEFIs are influenced by changes to the publicly funded program. Recent changes that may impact on AEFI surveillance data presented in this report include:[21]

- Implementation of a new/revised publicly funded programs in August 2011, including:
  - Rotavirus vaccine (Rot-1/Rotarix®) for infants at ages 2 and 4 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 (Var) administered as the combined agent MMRV at four to six years of age (previously second dose of MMR was administered at 18 months of age)
  - Second dose Var vaccine catch-up program for children born on or after January 1, 2000, and who are at least 4 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®) for the 4- to 6-year-old booster dose in April 2012.
- New influenza vaccine products implemented for the 2011-2012 influenza season including Fluad® (for high- risk persons 65 years of age and older) and Agriflu® for all those aged 6 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.

Results

In total, 765 AEFIs were reported in Ontario following vaccines administered between January 1 and December 31, 2012. Of these, 631 had a case classification of "Confirmed" and 134 had a case classification of "Does not meet" definition (Figure 2). There were no AEFIs with a case classification of "Persons under investigation."

Figure 2. Adverse events following immunization reports following vaccines administered in 2012, by classification status

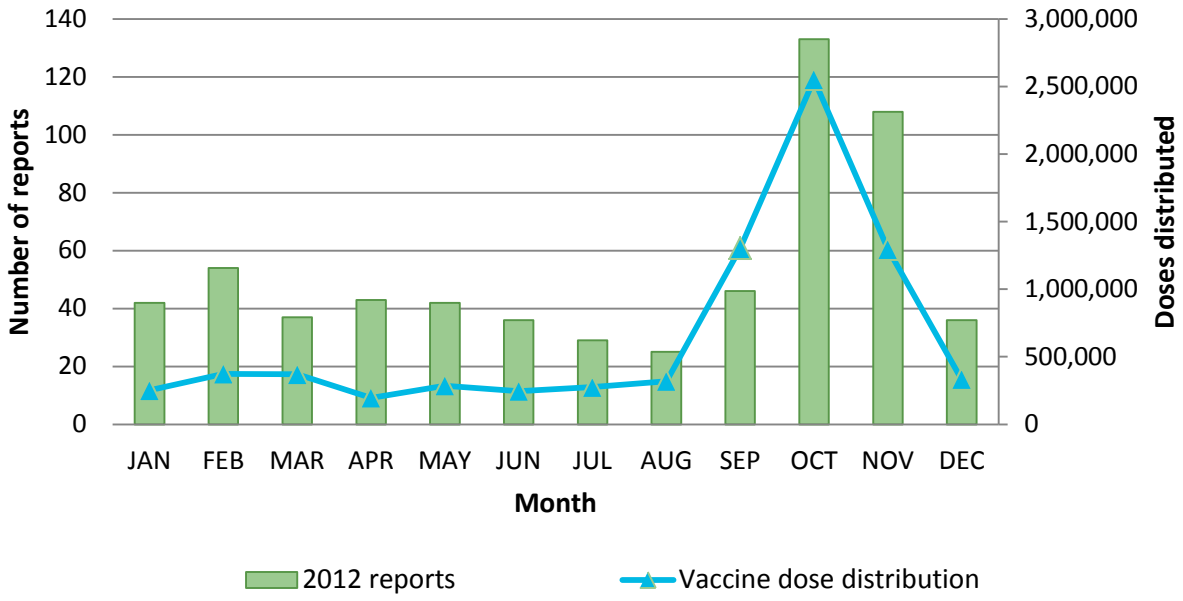


Among the 631 confirmed AEFIs, 56 (8.9%) were classified as serious (described below). From all confirmed AEFI reports where the reporting source was completed (n=583), the most frequent reporting source was physicians representing (38%). Health care professionals (21%) and family members (17%) were the second and third most common reporting sources.

The overall reporting rate of "Confirmed" AEFIs following vaccines administered in Ontario in 2012 was 4.7 per 100 000 population. The annual reporting rate increased 30.6% in 2012 from an average reporting rate of 3.6 per 100 000 population in 2010 and 2011 (3.5 and 3.7 per 100 000 population in 2010 and 2011 respectively). In addition, the proportion of reports classified as "Confirmed" (relative to other case classifications, e.g., DNM, PUI) increased from 2010 (72.4%; 466/644) and 2011 (73.4%; 500/681) to 2012 (82.5%; 631/765).

Reports of AEFIs by month of vaccine administration in 2012, range from a low of 25 reports in August to a peak of 133 reports in October, followed by 108 in November and a small peak in February (n=54). This general trend by month of administration in 2012 is consistent with the average number of AEFI reports by vaccine administration month in 2010 and 2011 (not shown) and mirrors the monthly distribution of vaccine by OGPMSS (Figure 3).

Figure 3. Total confirmed AEFI reports following vaccines administered and publicly funded vaccine distribution[1] by month in Ontario, 2012



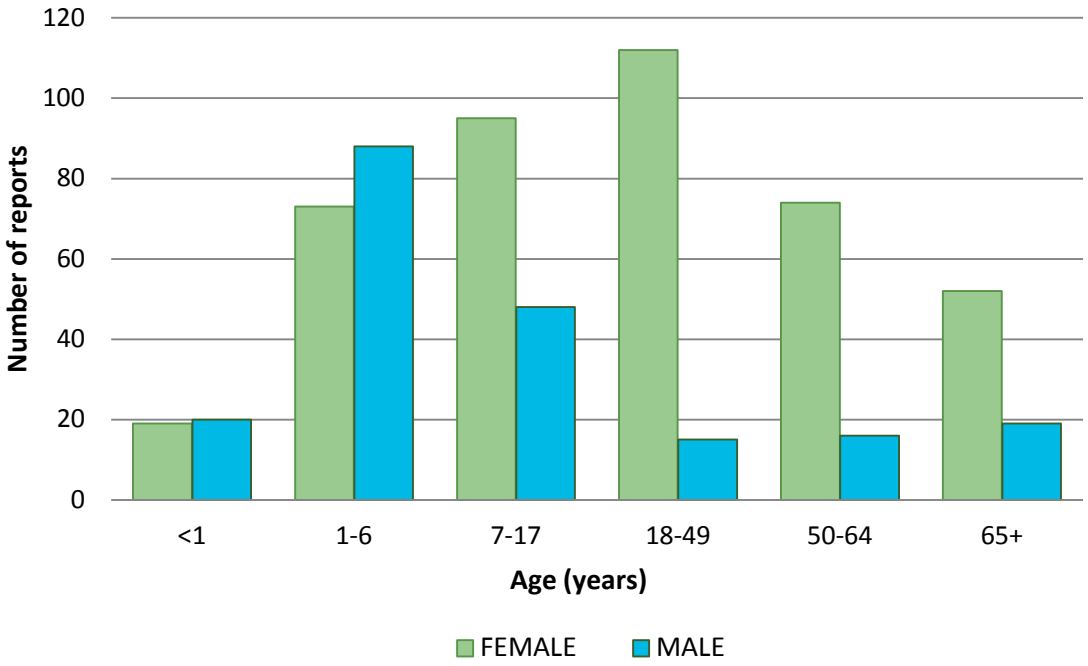
Notes:

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

The distribution of AEFI reports by age was weighted toward younger ages with over half of all reports for individuals 18 years of age and under (31.7% and 22.7% in those less than 7 years of age and 7 to 17 years of age, respectively). The proportion of AEFI reports decreased with increasing age with 20.1%, 14.3% and 11.3% among those 18 to 49, 50 to 64, and ≥65 years of age.

Among overall AEFI reports by sex, females outnumbered males slightly more than 2:1 with 67.4% (n=425) of reports among females. The distribution of AEFI reports by sex varies with age. While there is a slight predominance of males among reports in children under 7 years of age, female predominance begins among those 7 to 17 years of age and is most pronounced in adults 18 years of age and older (82.6% female) compared with those younger than 18 years (54.5% female) (Figure 4). 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 7 to 17 years of age.

Figure 4. Age and sex distribution of confirmed AEFIs reported following vaccines administered in 2012



In reports with health care utilization information completed, medical consultation was sought in 76% (471/620) of reports while 18% (115/628) had an emergency room visit and 4% (24/614) were admitted to the hospital. In the majority of AEFI reports, individuals had recovered at the time of reporting (65%; 408/631); whereas, in 20% (126/631) of reports individuals had not yet recovered with 3% (21/631) experiencing residual effects and 12% (76/631) having an "unknown" outcome.

AEFI reports by agent

The majority of the 631 AEFI reports in 2012 were associated with one agent (84.0%); 10.1% of reports were associated with two agents and 5.9% were associated with three or more agents. The highest number of agents in a single report was five. The most frequently reported agents among all confirmed AEFI reports were Inf (28.7%), Tdap (9.7%), DTaP-IPV-Hib (9.0%) and DTaP-IPV (8.4%) vaccines. The highest reporting rates of AEFI by agent were observed with DTaP-IPV (103.9 per 100 000 doses distributed), followed by BCG (82.6 per 100 000 doses distributed), rabies (40.8 per 100 000 doses distributed), HPV4 (26.7 per 100 000 doses distributed) and HB (21.1 per 100 000 doses distributed (Table 1).

Agent-specific reporting rates of serious AEFIs ranged from 0 to 3.5 per 100 000 with the highest reporting rate associated with MMRV. Specific agents with the highest proportion of serious AEFIs relative to all AEFIs for the same agent included HA-Typh-I (33%), Men-C-C (26.7%), Rot-1 (26.1%),

MMRV (25%) and Pneu-C-13 (21.4%). Among the 56 serious AEFIs, the reporting burden was concentrated among reports with Inf (42.9% of all serious AEFI reports), Pneu-C-13 (16.1%), DTaP-IPV-Hib (12.5%), Rot-1 (10.7%) or HB (10.7%) as one of the reported agents. See Appendix 3 for a complete list of agent acronyms and corresponding trade names.

Table 1. Number, percent, and rate of confirmed AEFI reports, by agent administered in 2012

Agent[1]	Doses distributed [2]	Number and proportion of reports by agent (N=631)		Reporting rate by agent (per 100, 000 doses distributed)	Number and proportion of serious reports by agent[4] (N=56)		Serious reporting rate by agent (per 100,000 doses distributed)	Proportion of serious reports within agent %[5]
		n	%[3]		n	%		
BCG	1 210	1	0.2	82.6	0	0	0	0
Chol-Ecol-O	-	1	0.2	-	0	0	-	0
DTaP-IPV	51 015	53	8.4	103.9	1	1.8	2.0	1.9
DTaP-IPV-Hib	561 380	57	9.0	10.2	7	12.5	1.5	12.3
HA	-	1	0.2	-	0	0	-	0
HAHB	-	10	1.6	-	1	1.8	-	10.0
HA-Typh-I	-	3	0.5	-	1	1.8	-	33.3
HB	236 940	50	7.9	21.1	6	10.7	2.5	12.0
HPV2	-	1	0.2	-	0	0	-	0
HPV4	172 280	46	7.3	26.7	4	7.1	2.3	8.7
Inf	3 722 720	181	28.7	4.9	24	42.9	0.6	13.3
IPV	34 477	3	0.5	8.7	0	0	0	0
JE	-	1	0.2	-	0	0	-	0
Men-C-ACWY	117 776	22	3.5	18.7	3	5.4	2.5	13.6
Men-C-C	154 775	15	2.4	9.7	4	7.1	2.6	26.7
MMR	288 720	33	5.2	11.4	5	8.9	1.7	15.2

Agent[1]	Doses distributed [2]	Number and proportion of reports by agent (N=631)		Reporting rate by agent (per 100, 000 doses distributed)	Number and proportion of serious reports by agent[4] (N=56)		Serious reporting rate by agent (per 100,000 doses distributed)	Proportion of serious reports within agent %[5]
		n	%[3]		n	%		
MMRV	28 420	4	0.6	14.1	1	1.8	3.5	25.0
Pneu-C-13	446 740	42	6.7	9.4	9	16.1	2.0	21.4
Pneu-P-23	203 712	40	6.3	19.6	5	8.9	2.5	12.5
Rab	9 812	4	0.6	40.8	0	0	0	0
Rot-1	245 618	22	3.5	9.0	6	10.7	2.4	27.3
Td	314 790	10	1.6	3.2	0	0	0	0
Tdap	664 820	61	9.7	9.2	3	5.4	0.5	4.9
Tdap-IPV	143 805	10	1.6	7.0	0	0	0	0
Td-IPV	24 155	1	0.2	4.1	0	0	0	0
Typh-I	-	6	1.0	-	0	0	-	0
Typh-O	-	2	0.3	-	0	0	-	0
Var	371 223	53	8.4	14.3	1	1.8	0.3	1.9
YF	-	8	1.3	-	0	0	-	0
Zos	-	30	4.8	-	1	1.8	-	3.3

Notes:

1. Only those agents with AEFI reports in 2012 are shown. See Appendix 3 for a list of these agents and corresponding vaccine products and agent abbreviations.
2. Doses distributed are obtained from Ontario Government Pharmaceutical and Medical Supply Service (OGPMSS) for publicly funded vaccines only.
3. Each AEFI report may include one or more agents. Percentages will not sum to 100%. The denominator is 631 (total number of confirmed AEFI reports).
4. Proportion across all AEFI reports that are serious (denominator n=56). Each serious report may be associated with one or more agents. Percentages will not sum to 100%.
5. Proportion of reports within each agent that are serious (denominator is the total number of agent-specific confirmed AEFIs).

AEFI reports by event

The majority of reports were associated with one adverse event category (73.5%; 464/631) while 21.9% of reports were associated with two categories (138/631) and 4.6% (29/631) were associated with 3 or more adverse event categories (the highest number of adverse event categories in a single report was 4). The most frequently reported events were injection-site reactions (including pain, redness, swelling, nodule, abscess and cellulitis) which were present in 40.0% (252/631) of all AEFI reports, while rash and allergic skin reactions were also relatively common (21.7% and 20.8% respectively). "Other severe/unusual events" were reported in almost one fifth of all reports (19.5%) (Table 2).

Table 2. Number and distribution of confirmed AEFI reports following vaccines administered in 2012, by adverse event category

Adverse event category[1]	Reports with adverse reaction[2]		Serious AEFI[6]	
	N	%[3]	N	%
Abscess - infected	4	0.6	1	25
Abscess - sterile	7	1.1	0	0
Adenopathy/lymphadenopathy	5	0.8	0	0
Allergic reaction–other	25	4.0	1	4.0
Allergic reaction–skin	131	20.8	6	4.6
Anaesthesia/paraesthesia[4]	6	1.0	0	0
Anaphylaxis‡	18	2.9	18	100
Arthritis/arthralgia	12	1.9	1	8.3
Bell's palsy[5]	3	0.5	3	100
Cellulitis	59	9.4	7	11.9
Convulsions/seizures[5]	12	1.9	12	100
Encephalopathy/encephalitis[5]	2	0.3	2	100
Fever ≥ 38°C	47	7.4	10	21.3
Guillain-Barré syndrome (GBS)[5]	1	0.2	1	100

Adverse event category[1]	Reports with adverse reaction[2]		Serious AEFI[6]	
	N	%[3]	N	%
Hypotonic-hyporesponsive episode (HHE)	5	0.8	1	20
Local/ injection-site reaction (< 4 days)	61	9.7	1	1.6
Local/ injection-site reaction (≥ 4 days)	122	19.3	2	1.6
Local/ injection-site reaction (extending beyond nearest joint)	11	1.7	0	0
Nodule	21	3.3	0	0
Oculo-respiratory syndrome (ORS)	4	0.6	0	0
Other severe/unusual events	123	19.5	11	8.9
Paralysis other than Bell's palsy[5]	3	0.5	3	100
Parotitis	2	0.3	0	0
Persistent crying/ screaming	5	0.8	1	20
Rash	137	21.7	3	2.2
Severe vomiting/ diarrhea[4]	5	0.8	1	20

Notes:

1. See Appendix 1 for a complete description of adverse event categories and corresponding values in iPHIS.
2. Includes only those event categories where the number was ≥1. For a complete list of possible values in iPHIS and corresponding event categories, please refer to Appendix 1.
3. Adverse event categories are not mutually exclusive. Each report may include one or more events. Percentages will not sum to 100%. The denominator is 631 (total number of confirmed AEFI reports).
4. These categories reflect new values added to the "adverse event reaction(s)" field in iPHIS on Jan.1, 2013.
5. Medically important events as defined by the definition of serious AEFIs in Appendix 2.
6. Proportion within each adverse -event category that are serious (denominator is the total number of event-specific confirmed AEFIs).

Serious AEFIs

There were 56 reports of AEFIs that were classified as serious representing 8.9% of all reports. Among serious AEFI reports, 57.1% (n=32) were related solely to a medically important event, 30.4% were related solely to a hospital admission of >24 hours (n=17) and 12.5% (n=7) had both a hospital admission of >24 hours and a medically important event. Among all hospital admissions (n=24), the median length of stay was 2.5 days (range 1 to 18 days). There were 19 (79.2%) hospital admissions among those <18 years of age, of which 11 (57.9%) were detected and investigated by IMPACT. Among all medically important events (n=39), the most frequently reported was "Anaphylaxis" (n=18; 46.2%) and "Convulsions/seizures" (n=12; 30.1%), followed by "Bell's palsy" (n=3; 7.7%), "Encephalitis/encephalopathy" (n=2; 5.1%) and "Guillain-Barré syndrome" (GBS) (n=1; 2.6%). There were no reports of death temporally associated with receipt of a vaccine.

There were a total of 18 reports of anaphylaxis temporally associated with 20 agents: eight Inf, three HPV4, two HB, two Tdap, one HB and Men-C-ACWY administered concomitantly, one MMRV and DTaP-IPV administered concomitantly and one HA-Typh-I. All anaphylaxis reports were assessed using the Brighton Collaboration case definition (22) and six (33.3%) met the case definition of anaphylaxis (four were level one, one was level two and one was level three). Nine (50.0%) reports did not meet the Brighton Collaboration case definition based on information contained in the report and three (16.7%) reports did not contain enough information to complete an assessment.

There were 12 reports of "Convulsions/seizures" temporally associated with 19 agents: three MMR, Men-C-C and Pneu-C-13 administered concomitantly, three Inf, one HB, one HB and Men-C-ACWY administered concomitantly, one Var, one Zos, one HAHB and one DTaP-IPV-Hib. The age range was 1 to 69 years and seven (58.3%) reports from vaccine recipients that were under 5 years of age. Among these seven reports, all were febrile seizures and five were admitted to hospital. There was one additional hospital admission in an older child.

Both of the encephalopathy/encephalitis reports were temporally associated with administration of influenza vaccine, one in which HPV4 was concomitantly administered. Upon case-level review, one report was incorrectly classified as "Encephalopathy/encephalitis" while the other was a suspected viral encephalitis report that was admitted to hospital 28 days following receipt of HPV4 and influenza vaccines with symptoms of nausea, vomiting and altered level of consciousness. There were three reports of "Bell's palsy" and one report of "Guillain-Barré syndrome" (GBS), all temporally associated with receipt of influenza vaccine in adults and with no related hospital admissions.

Among 17 serious reports with a hospital admission related to a "non-medically important event," the reported events were "Cellulitis" (n=6), "Other severe/unusual events" (n=5), "Fever" (n=4), "Hypotonic–hyporesponsive episode (HHE)" (n=1) and "Abscess—infected" (n=1). This included one report of anaphylaxis, reported as "Other severe/unusual events." Among reports of cellulitis resulting in hospital admission, four were in children between 1 and 9 years of age (one associated with

administration of Pneu-P-23, one Inf, one Inf with Pneu-P-23 administered concomitantly and one DTaP-IPV-Hib) and two were in adults (both associated with administration of Pneu-P-23).

Risk factors

Among all reports, 19.2% (n=121) had risk factor information completed in iPHIS. The most frequently reported risk factor was "Chronic illness/underlying medical condition" (67.6%; n=94), followed by "Other" (22.3%; n=31) and "Immunization program error" (5.8%; n=8). The remaining were "Immunocompromised" (2.9%; n=4), "Pregnant" (0.7%; n=1) and "Unknown" (0.7%; n=1). Table 3 provides a summary where the report indicated that the AEFI was preceded by an "Immunization program error" (n=8).

Table 3. Summary of AEFI reports following vaccines administered in 2012 where "Immunization program error" was selected under "Risks" in iPHIS

Age (years)	Agent	Error	Adverse event category	Additional case details
1-6	Var (Varivax® III)	Wrong site	Local/injection site reaction (≥ 4 days)	Administered in vastus lateralis (thigh) in a child >1 year of age
7-17	DTaP-IPV (Quadracel®)	Vaccine not indicated for age	Sterile abscess	Vaccine administered to a child > 7 years of age
7-17	DTaP-IPV (Quadracel®)	Vaccine not indicated for age	Local/injection site reaction (≥ 4 days)	Vaccine administered to a child > 7 years of age
18-49	MMR (M-M-R® II)	Wrong diluent	Local/injection site reaction (≥ 4 days)	Agent diluted with Pneu-P-23 (Pneumovax®23) instead of diluent provided
65+	Pneu-P-23 (Pneumovax® 23)	Vaccine not indicated	Rash	Two doses of same vaccine received previously
65+	Pneu-P-23 (Pneumovax® 23)	Wrong site	Local/ injection site reaction (< 4 days)	Vaccine administered in the right "hip area"
65+	Pneu-P-23	Incorrect needle	Cellulitis	1" needle used to administer

Age (years)	Agent	Error	Adverse event category	Additional case details
	(Pneumovax® 23)	length		vaccine subcutaneously in arm
65+	Zos (Zostavax®)	Vaccine contraindicated	Rash	Recent dx of lymphoma; zoster-like rash; onset on day 20 after vaccine (no lab confirmation of vaccine virus)

Discussion

This report represents the first comprehensive annual assessment of vaccine safety in Ontario. It fulfils a previous recommendation made for annual reporting of Ontario AEFI data to facilitate ongoing assessment of vaccine safety and to provide relevant and timely information for health professionals and the public about the safety of vaccines administered in Ontario.[13]

The following discussion is based on analysis of AEFI information entered into iPHIS that was 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 annual reporting rate of 4.7 per 100 000 population for AEFI in Ontario in 2012 is lower than annual (per population) reporting rates from passive AEFI surveillance systems in other jurisdictions. For example, the most recent annual AEFI reporting rates estimated from passive surveillance systems in Australia and the US (10.4 and 7.4 per 100 000 population, respectively).[23-25] From a national perspective, Ontario represents approximately 22.9% of all AEFI reports made by all provincial/territorial health authorities to CAEFISS compared with representing 38.7% of the national population. The estimated national reporting rate based on AEFIs reported by provincial/territorial health authorities to CAEFISS is 9.4 per 100 000 population (Canadian Adverse Events Following Immunization Surveillance System Database Search, July 15th, 2013. Public Health Agency of Canada; unreferenced). It is important to note that a higher overall reporting rate of AEFIs (across all agents) does not necessarily suggest a vaccine safety concern; rather, it is an indicator of a robust passive vaccine safety surveillance system. We anticipate that Ontario's overall reporting rate will increase given that its rate is lower than the national rate as well as rates reported from other passive vaccine safety surveillance systems and the increased focus on vaccine safety surveillance including the publication of annual provincial vaccine safety reports. The quantity of AEFI reports to a passive vaccine safety surveillance system contributes to establishing a clear historical baseline which can be used to identify future vaccine safety signals.

In Ontario, the increase in the annual reporting rate, particularly between 2011 and 2012, likely reflects an increased focus on AEFI reporting in the province. This includes activities undertaken to enhance AEFI surveillance in 2012 and 2013, including the release of new guidelines for provincial AEFI surveillance (e.g., surveillance case definitions, iPHIS User Guide), delivery of AEFI surveillance training, and professional education on vaccine safety (e.g., PHO Rounds). This increase may also be attributable in part to the addition of new publicly funded programs (e.g., rotavirus vaccine) in 2011 which would increase the total number of vaccines administered in the province. Annual monitoring will demonstrate whether this trend towards increased reporting of AEFIs in the province continues.

The increased proportion of cases classified as "Confirmed" provincially in 2012 reflects a shift away from the use of other case classifications (e.g., "Persons under investigation" and "Does not meet"). This

is most likely the result of active ongoing follow-up in 2012 and year-end data quality measures implemented by PHO and conducted by PHUs, aimed in part to improve the validity of AEFI case classification. Misclassification of AEFIs was first identified in early 2012 when it was noted anecdotally that the case classification field was being used to reflect a causation assessment (e.g., "Confirmed" implied that the vaccine caused the event). This was further validated by the HPV4 AEFI assessment which found substantial misclassification of reports.[13] These findings led to the clarification of the definitions of "Confirmed" and "Does not meet" in the Infectious Diseases Protocol (Appendix B: AEFI).[17]It is expected that the proportion of AEFI reports that are confirmed will continue to increase with the uptake of new surveillance case definitions and continued active, ongoing data-quality follow-up and efforts to standardize AEFI surveillance practices.

AEFI reports by month of vaccine administration demonstrate a wide variation. The most prominent peak (October–November) reflects delivery of the universal influenza immunization program (UIIP) which accounts for almost half of all vaccine doses distributed in Ontario in a given year, as well as initiation of school-based vaccination programs (HB, Men-C-ACWY & HPV4) in the fall. Another small peak (February) may again be related to subsequent doses administered as part of school-based immunization programs and the PHUs' *Immunization of School Pupils Act (ISPA)* assessment and enforcement activities.

The age distribution of AEFI reports is as expected with a concentration of reports among those less than 18 years of age, the age group for whom the greatest number of doses is recommended in the publicly funded routine immunization schedules.[26] A variation in sex ratio by age is consistent with what has been observed in other passive AEFI surveillance systems.[24, 27, 28] The over-representation of females in the adolescent age group is expected because HPV4 vaccine is provided only to Grade 8 females. Among adults it may be related to higher uptake of vaccine among females [29], higher proportion of females among health care workers who are targeted for specific vaccines [30], as well as differences in health-seeking behaviour between males and females.[31, 32]

With respect to outcome, most reports indicated that the vaccine recipient had recovered at the time of reporting suggesting that most events were mild and/or self-limited. It is important to note that outcome is assessed at the time of reporting of the event in iPHIS and there is no subsequent follow-up to assess when recovery occurred or if there were permanent sequelae from the event where the outcome values "Not yet recovered" or "Residual effects" were selected.

The most frequently reported agents by proportion of all AEFI reports, is generally consistent with vaccine distribution volume by agent; however, this comparison includes only those vaccine doses distributed by OGPMSS. Reflecting this overall trend, influenza is the most frequently reported agent with the highest volume distribution. One notable exception is DTaP-IPV (Quadracel®) which is a reported agent in 8.4% of all AEFIs. However, the vaccine accounts for 0.6% of all of the vaccine doses distributed by OGPMSS. DTaP-IPV also had the highest agent-specific reporting rate in 2012 (103.9 per 100 000 doses distributed). There are a number of factors to consider when interpreting this reporting

rate. There were a number of AEFIs reported following administration of DTaP-IPV to individuals who were over the age of 7 and therefore outside the indicated age for this vaccine. For example, when AEFIs reported following administration of DTaP-IPV to individuals over the indicated age for the vaccine (i.e. >7 years) are excluded, the reporting rate decreased to 88.2 per 100 000 doses distributed. The reporting rate may also be over-estimated due to limited distribution of DTaP-IPV vaccine in 2012 (Tdap-IPV [Adacel-Polio®] became available for the four- to six-year-booster in April 2012), combined with continued use of outstanding stock of this vaccine or reporting errors if DTaP-IPV was selected as the agent in iPHIS rather than Tdap-IPV. The latter error was minimized during the data-cleaning process by manual validation of agent-lot-number combinations. In order to further assess the impact of the change from DTaP-IPV to Tdap-IPV on reporting rates in 2012 we assessed the reporting rate for DTaP-IPV over a longer period of time including 2009–11 in which DTaP-IPV was the primary vaccine used for the four- to six-year booster. Between January 1, 2009 and April 30, 2013, the AEFI reporting rate for DTaP-IPV was 38.1 per 100 000 doses distributed.[33] Although this reporting rate is still elevated compared with Tdap-IPV, it is considerably lower than the 2012 estimate. This further suggests that vaccine distribution patterns had a role in elevating the DTaP-IPV reporting rate in 2012.

Regardless, the relatively high frequency of DTaP-IPV reports is consistent with the safety profile of DTaP-IPV vaccine which is known to produce large local reactions in a sizable proportion of recipients (15-20%), as well as the less common reaction of extensive limb swelling (2-6%).[34-37] This event is not associated with significant pain, limitation of recreational activities in the child or negative parental attitudes about the vaccine.[38] The increasing trend towards local reactions after the fourth and fifth doses of DTaP vaccines [34] is reflected in a high frequency of AEFI reports following this vaccine observed in other passive AEFI surveillance systems.[23] The frequency and reporting rate of AEFIs reported following Tdap-IPV is comparatively low, which may reflect a delay in uptake of this vaccine relative to distribution as well as a more favourable safety profile with respect to frequency of local reactions. However, a more in-depth analysis would be required to assess the impact on AEFI reporting due to the replacement of DTaP-IPV with Tdap-IPV vaccine for the four- to six-year booster.

Reporting rates vary widely by agent. Aside from DTaP-IPV discussed above, the second and third highest AEFI reporting rates are from rabies and BCG vaccines; however, reporting rates may be unstable due to the low number of AEFI reports for these agents (one and four respectively). Of note, the next highest reporting rates are from agents that are generally administered by PHUs in the school-based adolescent programs: HB, HPV4 and Men-C-ACWY. This suggests that reporting rates of AEFIs from PHU-administered programs may be higher than from vaccine programs traditionally administered by other providers; however, further analysis is required to fully understand AEFI reporting patterns by agent, immunization provider and reporting source. In general, interpretation of the AEFI reporting rate by all agents and by specific agent is limited by the lack of comparison to previous years. It is expected that subsequent annual reports will allow a comparison of reporting rates over time which will contribute to the interpretation of agent-specific AEFI trends. As previously noted, vaccine distribution patterns may not reflect vaccine administration patterns resulting in either over- or under-estimation of the reporting rate.

The frequency of reported event categories suggests a high burden of reporting of injection-site reactions which were present in almost half of all AEFI reports. In particular, an injection-site reaction of "Pain/redness/swelling lasting less than four days" was present in 9.7% of reports compared with "Pain/redness/swelling lasting greater than four days," present in 19.3% of reports. Given the high reporting burden of injection-site reactions within the surveillance system, changes were implemented on January 1, 2013, which included the discontinuation of reporting of injection-site reactions lasting less than 4 days. In addition, further differentiation of these injection-site reactions through the recent addition of "Pain/redness/swelling lasting 4 to 10 days" and "Pain/redness/swelling lasting 10 days or greater" will assist in assessing the burden of injection-site reporting within the surveillance system. Injection-site reactions will continue to be assessed to determine if further changes are necessary given that injection-site reactions (redness/pain/swelling) are relatively frequent events following all vaccines and are not considered a contraindication to further immunization..

"Other severe/unusual events" were also selected in a high proportion (19.5%) of reports. The frequent use of this value may be related to an important limitation of iPHIS prior to January 1, 2013. During this time, the list of available adverse event values within iPHIS did not correspond directly to provincial AEFI surveillance case definitions which led to frequent use of the "Other severe/unusual events" category to capture all other events that did not fit with existing event categories.[13] As a result, events in this category should not be interpreted as severe nor do they necessarily meet the definition of a serious AEFI. This issue was also demonstrated in the HPV AEFI assessment in which 26% of reports between 2007 and 2011 were classed as "Other severe/unusual events," while further assessment of these reports showed that many were misclassified.[39] With the implementation of updated and aligned iPHIS adverse-event values and case definitions at the beginning of 2013, the proportion of reports with this event selected has already decreased. It is expected that the frequency of this value will continue to decrease in subsequent years.

The proportion of serious AEFIs occurring in this report is similar to a recent HPV4 AEFI assessment using iPHIS data (8.9% vs. 7.5% respectively)(13). Also similar is the proportion of reports classified as "Serious" from the passive AEFI surveillance system in Australia (7%); whereas, the proportion from the Vaccine Adverse Events Reporting System (VAERS) in the United States is higher (13%).[23, 40] While the core definition of serious used by all three systems is the same (i.e., event associated with disability, hospitalization, life-threatening illness or death), there are likely differences in classification based on the data available within each system. For instance, there is no field in iPHIS that accurately captures disability or permanent sequelae resulting from a reported event which may lead to underestimation of this outcome. In addition, the list of "medically important events" included in the definition of serious may vary by jurisdiction.

Although the number of anaphylaxis reports that met the Brighton case definition was low, it should be noted that missing or incomplete information in reports of anaphylaxis is an important limitation to assessing these reports retrospectively. In addition, it is not possible to ascertain if some reports that did not meet the Brighton case definition were true anaphylactic events since epinephrine was

administered and subsequently altered the progression of the event. It is expected that changes to AEFI surveillance guidelines implemented on January 1, 2013, will improve monitoring and investigation of suspected anaphylactic reactions; however, continued focus on obtaining detailed event descriptions is required. Guided reporting tools may assist with specific data capture that is necessary for assessment of events managed as anaphylaxis.[41]

Just less than half of all AEFI reports to PHUs were made by individuals other than physicians and other health care providers, suggesting some degree of under-reporting given the reporting mandate for health care providers under the HPPA. Further evidence of this is seen when comparing the number of AEFI reports in which some medical consultation was sought (76%) with the number of reports reported by physicians (38%).

Limitations

Limitations of this analysis include those which are shared with other passive AEFI surveillance systems, including under-reporting, inconsistent quality and completeness of AEFI reports, and reporting bias.[42] As such, some variables may be either missing/incomplete, including dose number, time to onset and duration of the event, complete description of the reaction, treatment, and outcome. Specific limitations and their impact on interpretation have been included, where relevant.

Currently, Ontario does not have a comprehensive population-based immunization registry to estimate the total cohort of vaccine recipients and subsequently the population-based rate of AEFIs for specific vaccine-event pairs. Instead, the AEFI reporting rate is calculated using the total population or doses distributed to the publicly funded program as the denominator which enables comparison of rates over time and to other jurisdictions. As this is the first annual report on vaccine safety that has been completed in Ontario, there is limited analysis on trends over time.

As previously described, there were substantial changes to AEFI surveillance in the province implemented during the period of time in which the AEFIs in this report were investigated and entered into iPHIS. Where relevant, the impact on interpretation has been noted; however, there may also be an impact on the comparability of this data to subsequent years.

Conclusions and Recommendations

This report presents the first annual assessment of vaccine safety in Ontario. It fulfils the province's important vaccine-safety surveillance objective of reporting to stakeholders on the safety of publicly funded vaccines, as well as contributing to public and professional confidence in vaccines.

Overall, AEFI reports have increased in 2012 compared to the previous two years; however, the rate of reporting relative to population size in Ontario is lower than some other Canadian jurisdictions. AEFI reports by specific agent are primarily driven by the volume of vaccine distributed. Reported events were consistent with the safety profile of many vaccines in which injection-site reactions are most frequent. It is expected that the implementation of revised case definitions and specific adverse event criteria on January 1, 2013, will improve the characterization of AEFIs by event type over time.

We recommend the following actions to continue to improve the quality of vaccine safety surveillance in Ontario.

1. Continue to produce a report that assesses AEFI reports on an annual basis, using an iPHIS data extraction date of May 1 for all AEFIs reported following vaccines administered in the previous calendar year and after an annual data-cleaning process to ensure consistency and comparability of data over time.
2. Develop and implement a knowledge translation plan for the annual report which includes distribution of an annual vaccine safety report to public health units (PHUs), health professionals and members of the public to contribute to openness and transparency of the vaccine safety surveillance system in Ontario
3. Implement an anaphylaxis reporting tool to improve the quality and completeness of reporting of events managed as anaphylaxis and aid in provincial assessment and classification of these events using standard, internationally accepted criteria.
4. Further explore possible explanations for under-reporting of AEFIs and recommend strategies to improve reporting rates in Ontario.

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Appendices

Appendix 1: Adverse event categories

Table A1: Adverse event reaction(s) values in iPHIS pre- and post-January 1, 2013, and adverse event categories for analysis

Adverse event categories 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

Adverse event categories 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
Bell's palsy	Bell's palsy	Bell's palsy
Cellulitis	Cellulitis	Cellulitis
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

Adverse event categories 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
Encephalopathy/ encephalitis	Encephalopathy/encephalitis	Encephalopathy/encephalitis–neuroimaging consistent with encephalitis Encephalopathy/encephalitis–brain pathology consistent with encephalitis Encephalopathy/encephalitis–CSF pleocytosis >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
Guillain-Barré syndrome (GBS)	Guillain-Barré syndrome (GBS)	Guillain-Barré syndrome (GBS)

Adverse event categories 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)
Oculo-respiratory syndrome (ORS)	Oculo-respiratory syndrome (ORS)	ORS–bilateral red eyes ORS–facial oedema ORS–respiratory symptoms

Adverse event categories 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
Other severe/unusual events	Other severe/unusual events N/A[1] N/A[1] N/A[1]	Other severe/unusual events Optic neuritis Auto-immune hepatitis Acute transverse myelitis
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 other than Bell's palsy	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 abscess–non-purulent fluid

Adverse event categories 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
	(sterile)	
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: Definition of a serious AEFI from draft Standard Operating Procedure (SOP) #6 of the Vaccine Vigilance Working Group (VVWG), Public Health Agency of Canada (PHAC), June 2011

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
- requires inpatient hospitalization (in hospital for >24 hours, or for at least all or part of two consecutive days)
- results in prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect

None of the above, but is a medically important event or reaction defined as one or more of the following (* denotes conditions for which a Brighton Collaboration case definition exists; for purposes of being considered serious, it is sufficient to meet at least a level 3 of diagnostic certainty OR be the diagnosis of an attending physician; ** denotes conditions for which there is no Brighton case definition; an attending physician's diagnosis is required).

Medically important events:

Anaphylaxis*

GBS*

Bell's palsy*

Generalized Seizure *

Aseptic meningitis*

Significant thrombocytopenia*[1]

Intussusception*

Myocarditis**

Narcolepsy*

Pericarditis**

Syncope with injury[2]

Alopecia[3]

Acute bronchospasm requiring urgent medical attention

[1] Defined as a platelet count of <150 PLUS clinical signs or symptoms of spontaneous (non-traumatic) bleeding (petechiae, purpura, sensu stricto, ecchymosis, hemorrhagic oozing of skin lesions including rashes, hematoma, bruising, hematemesis, hematochezia, occult bleeding per rectum, epistaxis,

hemoptysis, hematuria, vaginal bleeding other than menstruation, conjunctival bleeding, intracranial bleeding)

[2] Injury associated with post-immunization syncope requiring urgent medical attention, with or without admission

[3]Considered to be autoimmune in origin

Application of "medically important events" for AEFI surveillance in Ontario

Medically important events are not specifically defined by the International Conference on Harmonisation (ICH). The list above has been proposed by PHAC and requires agreement across jurisdictions. In Ontario, medically important events currently included in the definition of serious are anaphylaxis, Guillain Barré syndrome (GBS), Bell's palsy, paralysis (other than Bell's palsy), seizure, meningitis, encephalopathy/encephalitis, intussusception and thrombocytopenia.

Appendix 3: Vaccine agent abbreviations

Table A2: Vaccine agent abbreviations for agents included in this report

Agent abbreviations used in the report	"Agent" values in iPHIS (as of April 1, 2013)	Product/trade name
BCG	BCG – Bacillus Calmette-Guérin	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 (Paediatric)	Pediacel®, Infanrix™-IPV/Hib, Pentacel®
HA	HA – Hepatitis A (Adult)	Avaxim®, Havrix®, Vaqta®
HA	HA – Hepatitis A (Paediatric)	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®

Agent abbreviations used in the report	"Agent" values in iPHIS (as of April 1, 2013)	Product/trade name
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 – Herpes zoster	Zostavax®

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