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Annual Report on Vaccine Safety in Ontario, 2018

Surveillance Report

November 2019

Public Health Ontario

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Contents

Introduction

Public health surveillance of adverse events following immunization (AEFIs) is essential to monitor the safety of vaccines in Ontario. When viewed collectively, reports of AEFIs provide vital information to help identify previously unrecognized or rare adverse events or an increase in frequency or severity of known adverse events, which then can be further evaluated. In addition, AEFI surveillance provides valuable information to support publicly-funded immunization program planning and communication about the safety of vaccines administered in the province.

AEFI surveillance is a highly collaborative process requiring participation across multiple stakeholders within public health and the broader health care system, as well as individual vaccine recipients and their caregivers. In Ontario, public health units (PHUs) play a central role as the primary recipients of AEFI reports, which they investigate and document according to provincial surveillance requirements. Public Health Ontario (PHO) coordinates the provincial AEFI surveillance system, working closely with PHUs and the Ministry of Health (MOH). For detailed information about roles and responsibilities within Ontario's AEFI surveillance system, as well as the purpose and objectives of conducting AEFI surveillance, please see the Technical Annex of the Annual Report on Vaccine Safety in Ontario (subsequently referred to as the "Technical Annex").

Annual vaccine safety data for Ontario are now available through both the Annual Report on Vaccine Safety in Ontario and the interactive online Vaccine Safety Surveillance Tool.

New in 2018

Further enhancements to the online tool were made to accompany the release of this report.

- PHU-specific comparisons are now available for each vaccine
- Adverse event types are also available by vaccine

Report Objectives and Scope

The objective of this report is to summarize AEFIs reported in Ontario following vaccines administered in 2018. In addition, reporting trends are assessed by comparing AEFIs reported in Ontario following vaccines administered across seven years between 2012 and 2018.

Methods

An AEFI report refers to a report received by the PHU, which pertains to one individual vaccine recipient who experiences one or more adverse events that are temporally associated (i.e., the event occurs *after* administration of the vaccine) with receipt of one or more vaccines administered at the same time (i.e., during the same day).

The Annual Report includes the most up-to-date data and includes delayed AEFI reports received that relate to immunizations administered in previous years. This means that annual numbers may differ slightly from past reports. Trends in reported AEFIs are influenced by many factors, including changes to the publicly-funded immunization program.

Of note in 2018, the following changes were made in the publicly-funded immunization program:

- High-dose influenza vaccine was introduced for persons 65 years and older.
- Rot-5 replaced Rot-1, which resulted in an increase from a two to three dose-series for the routine infant rotavirus immunization program.

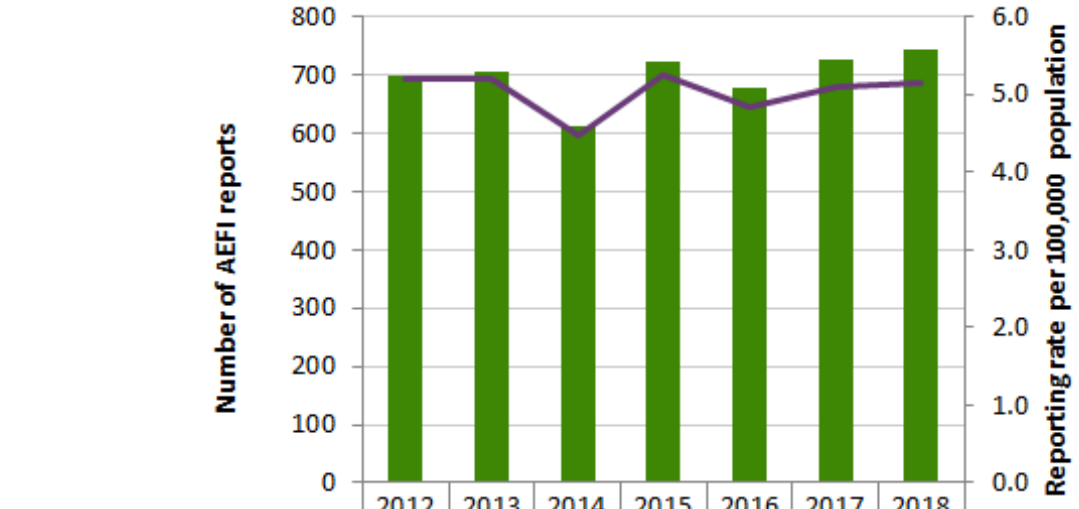
In addition, in 2017 a new non-live recombinant virus vaccine for zoster (RZV) was authorized for use in individuals 50 years and older and available for private purchase.

For a detailed description of Ontario's AEFI surveillance system, definitions, an in-depth explanation of analytic methods and notes on the limitations of AEFI surveillance data, please see the Technical Annex. For a complete list of vaccine acronyms used in this report and a description of immunization program changes in recent years, see Appendix 1 and Appendix 3, respectively, of the Technical Annex.

Results

In Ontario, 742 AEFI reports were received following vaccines administered in 2018, representing a population-based reporting rate of 5.1 per 100,000 population (Figure 1). The annual reporting rate between 2012 and 2018 ranged from 4.5 to 5.2 per 100,000 population with no statistically significant change in trends observed over this seven-year period.

Figure 1. Number of Reports and Reporting Rate of AEFIs per 100,000 Population by Year: Ontario, 2012-18



	2012	2013	2014	2015	2016	2017	2018
Number of AEFI reports	697	706	613	724	678	726	742
AEFI Reporting rate	5.2	5.2	4.5	5.2	4.8	5.1	5.1

AEFI reports: MOH, integrated Public Health Information System (iPHIS) database, extracted [2019/06/27].

Population: IntelliHEALTH Ontario[1,2]

Note: Only includes AEFI reports classified as confirmed, as per provincial AEFI reporting criteria. See the Technical Annex for more information about provincial AEFI surveillance case classifications.

Global Indicator for Vaccine Safety Surveillance

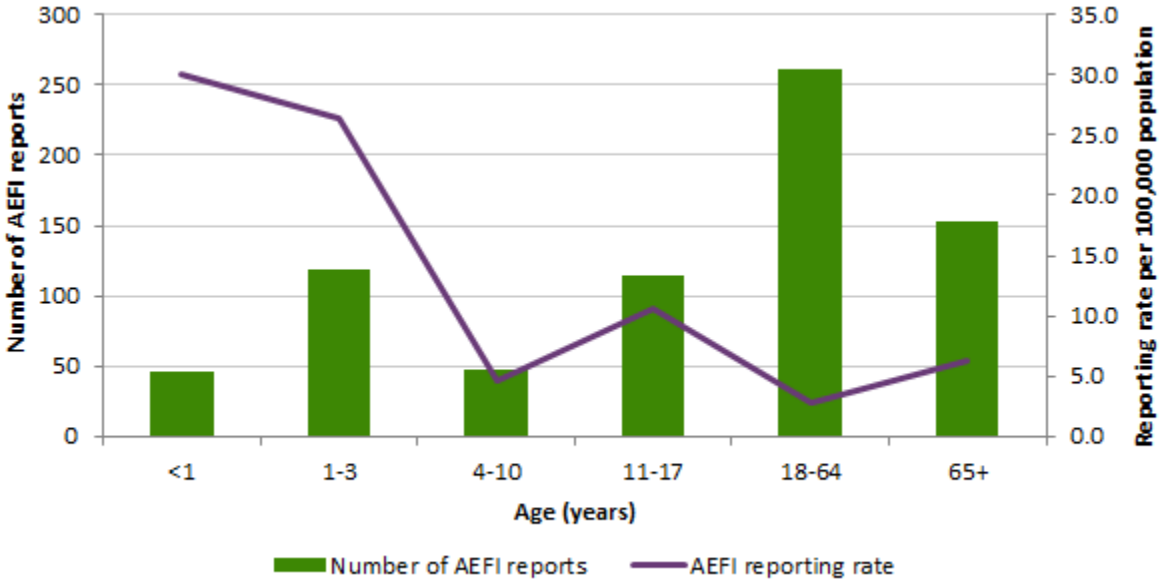
In 2016, the World Health Organization (WHO) adopted a new Global Vaccine Action Plan indicator for vaccine safety surveillance based on the number of AEFIs reported by country per 100,000 surviving infants.[3] A target of 10 per 100,000 was initially set, as this level "reflects if a country has a basic system in place for reporting of safety concerns."[4] In 2016, there were approximately 80 countries with >=40/100,000 and over 40 of those had >=160/100,000.[3] Applying the methodology to the Ontario AEFI surveillance data, the ratio among infants under one year was 32.7 per 100,000 surviving infants.

Age and Sex Distribution

In 2018, persons with AEFI reports ranged in age from two months to 99 years, with a median age of 30 years. Approximately half of all reports were among those younger than 18 years of age (44.2% of total AEFI reports). The majority of all AEFI reports were among females (65.9%).

Among specific age categories, the highest AEFI reporting rate in 2018 was in infants under one year (30.1 per 100,000 population), followed by children aged one to three years (26.3 per 100,000 population) (Figure 2). Among adults 65 years and older, the AEFI reporting rate increased from 5.1 to 6.2 per 100,000 population between 2017 and 2018 (see Vaccine Safety Surveillance Tool).

Figure 2. Number of Reports and Reporting Rates of AEFIs per 100,000 Population by Age Group: Ontario, 2018



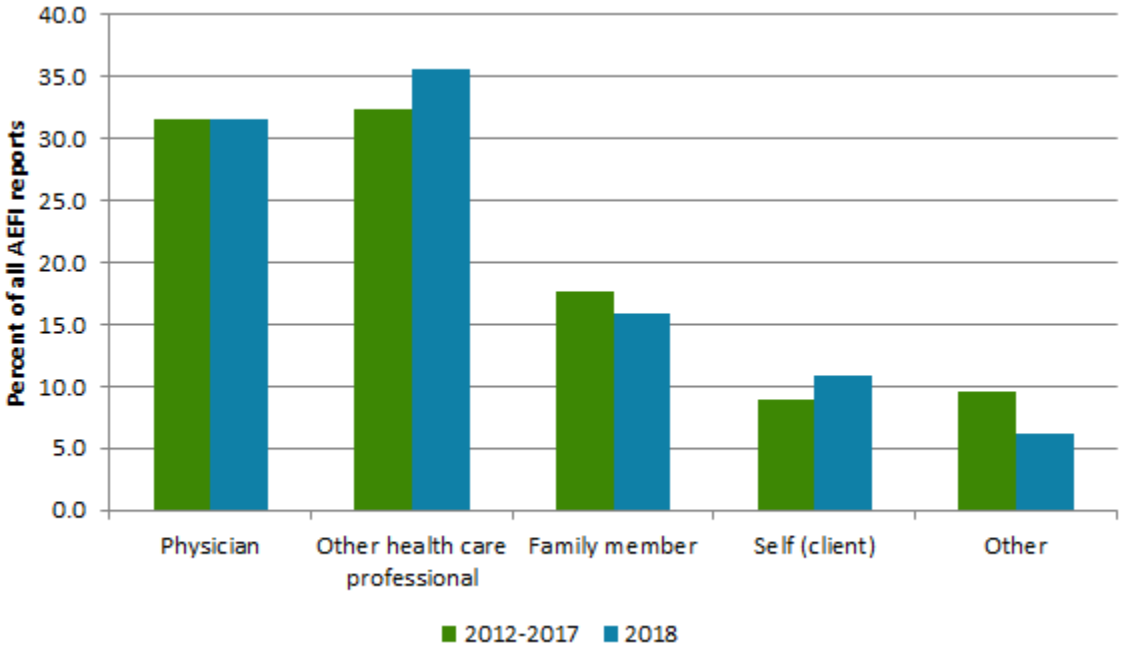
AEFI reports: MOH, integrated Public Health Information System (iPHIS) database, extracted [2019/06/27].

Population: IntelliHEALTH Ontario[1,2]

Reporting Source

In 2018, the majority of AEFIs were reported by physicians and other healthcare professionals (67.2%; 431 of 641 reports with reporting source completed) – consistent with what was observed in previous years (Figure 4). In particular, the proportion of reports from other healthcare professionals (e.g., nurses, pharmacists) has increased over time. Of note, pharmacists started administering influenza vaccines (to adults and children five years of age and older) as part of the universal influenza immunization program (UIIP) in Ontario in 2012. In 2016, pharmacists had an expanded scope of practice to administer other non-publicly funded vaccines.[5]

Figure 3. Percent Distribution of AEFIs by Reporting Source: Ontario, 2012-18



AEFI reports: MOH, integrated Public Health Information System (iPHIS) database, extracted [2019/06/27].

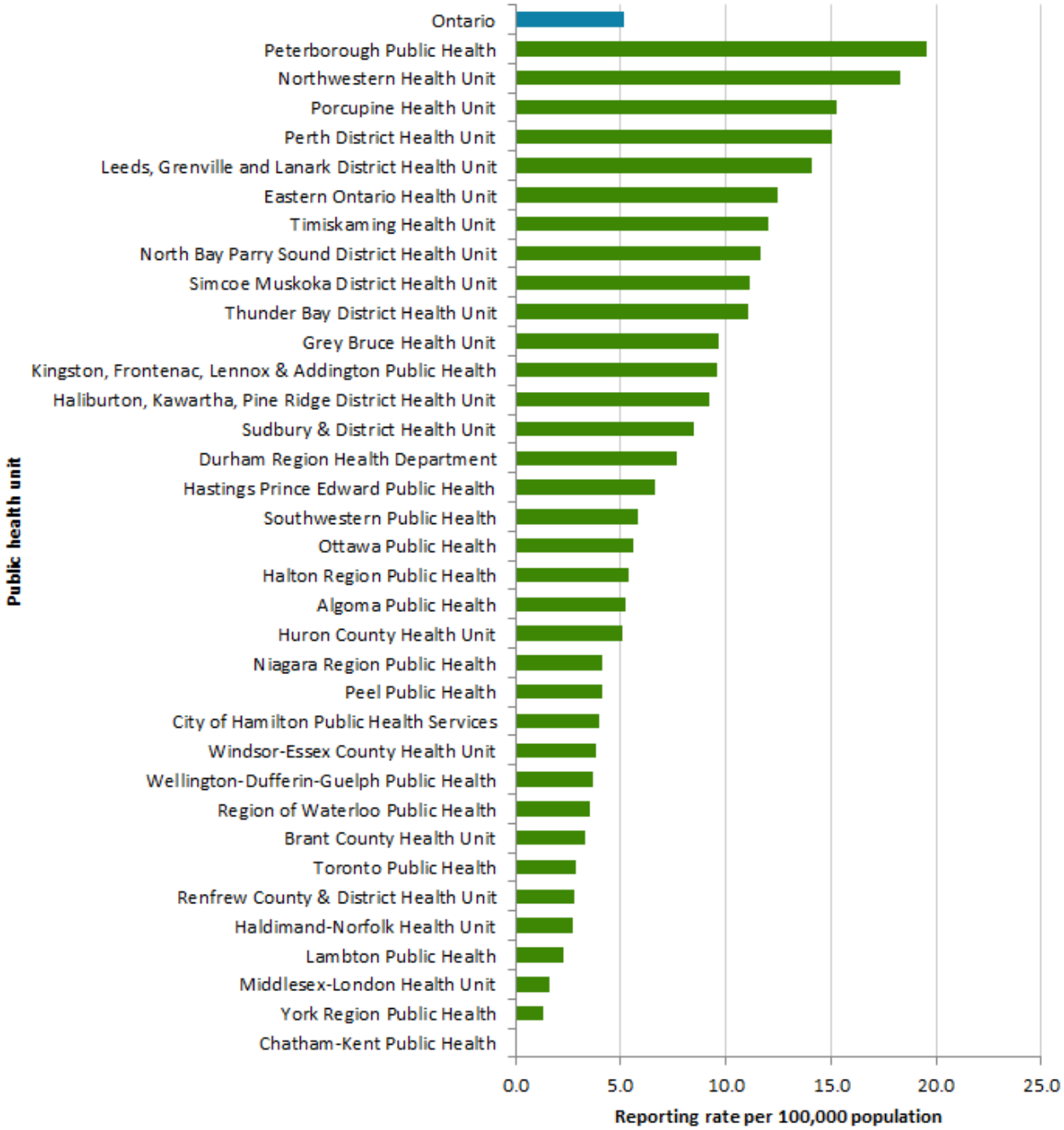
Notes:

- Excludes 489 reports between 2012 and 2018 with unknown reporting source.
- Reporting source 'Other healthcare professional' includes the following iPHIS values: healthcare professionals, hospital, health area, lab and branch office.
- Reporting source 'Other' includes the following iPHIS values: Facility, insurance, other agency, workplace, personnel, friend, detention centre and other (specify).

Geographic Distribution

There was a wide variation in overall AEFI reporting by PHU in 2018, with PHU-specific reporting rates ranging from 0.0 to 19.5 per 100,000 population. Twenty-one PHUs (58.3%) met or exceeded the overall provincial AEFI reporting rate of 5.1 per 100,000 population in 2018, while the remainder (15 PHUs) were below the provincial rate, including the three most populated PHUs (Figure 4). This represents a slightly lower proportion of PHUs exceeding the provincial rate compared to 2017 (61.1%, 21/36 PHUs). One PHU did not report any AEFIs in 2018.

Figure 4. AEFI Reporting Rate per 100,000 Population by Public Health Unit: Ontario, 2018

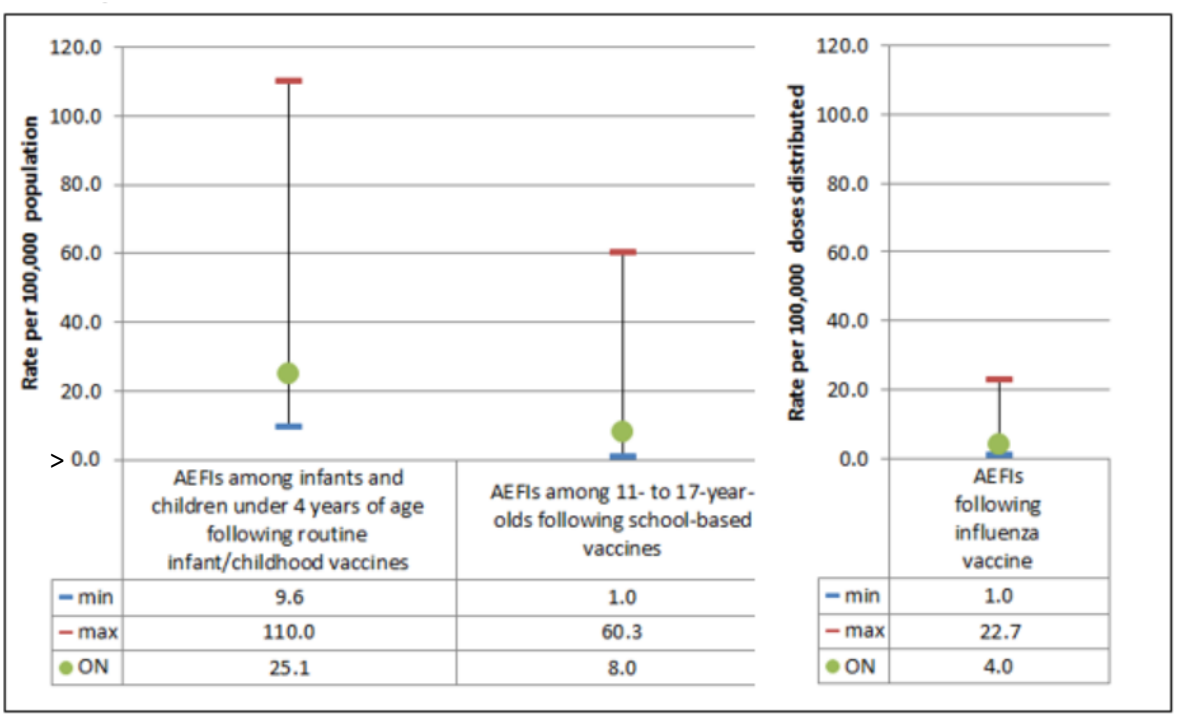


AEFI reports: MOH, integrated Public Health Information System (iPHIS) database, extracted [2019/06/27].

Population: IntelliHEALTH Ontario[2]

There was a wide variation in PHU-specific rates among selected age and vaccine categories (Figure 5). Among infants and children under four years of age, the rate of AEFI reporting for routine infant and early childhood vaccines (typically delivered by a primary health care provider) ranged between 9.6 to 110.0 per 100,000 population, excluding three PHUs with zero AEFIs. This was lower than the seven PHUs that did not report any AEFIs in this age group in 2017. Among 11- to 17-year-olds, the PHU-specific reporting rate for AEFIs following the three vaccines that are administered to adolescents by PHUs in school-based programs ranged between 1.0 to 60.3 per 100,000 population, excluding 13 PHUs with zero AEFIs. This was similar to the 12 PHUs that did not report any AEFIs in 2017. In 2018, 4,217,528 net doses of influenza vaccine were distributed throughout the province (refer to Technical Annex on derivation of doses distributed). Rates of influenza AEFI reports are calculated per 100,000 doses distributed and ranged between 1.0 to 22.7 per 100,000 doses distributed, excluding two PHUs with zero reports. This was lower than the six PHUs that did not report any AEFIs in 2017. Please refer to the online Vaccine Safety Surveillance Tool for the total number of reports and reporting rates for each PHU.

Figure 5. Range[1] in AEFI Reporting Rates by Vaccine Category[2] among Public Health Units: Ontario, 2018



AEFI reports: MOH, integrated Public Health Information System (iPHIS) database, extracted [2019/06/27].

Vaccine doses distributed: MOH, Panorama Enhanced Analytical Reporting, extracted by MOH [2019/06/12].

Notes:

1. PHUs with 0 AEFI reports are excluded from the range. 3, 13 and 2 PHUS reported 0 AEFIs among infant/early childhood, school-based and influenza vaccines, respectively.

2. Routine infant and early childhood vaccines include DTaP-IPV-Hib, Rot-1, Rot-5, Pneu-C-13, MMR, Men-C-C and Var). School-based vaccines include HPV-9, Men-C-ACYW and HB).

Vaccines

In 2018, approximately 8.6 million doses of vaccines were distributed in Ontario for the publicly-funded immunization programs. Using net doses distributed for each routine, publicly-funded vaccine as the denominator, the highest vaccine-specific AEFI reporting rates in 2018 were observed for HPV9, Men-C-ACWY and Pneu-P-23 vaccines (Table 1A). Although influenza vaccine was associated with the highest number of AEFI reports, it had the third lowest AEFI reporting rate due to the high volume of doses distributed.

The vaccine-specific serious AEFI reporting rates for vaccines for which dose distribution data were available ranged between zero and 3.8 per 100,000 doses distributed. Men-C-C and MMR had the highest serious AEFI reporting rates (3.8 and 2.7 per 100,000 doses distributed, respectively). Refer to Serious AEFIs for further information (see Technical Annex for definition).

The number of AEFI reports among other high-risk publicly-funded and non-publicly-funded vaccines is provided in Table 1B. The number of vaccine-specific AEFIs ranged between 1 and 98, with one serious AEFI observed with Men-B.

For annual vaccine-specific reporting rates prior to 2018, please refer to the online Vaccine Safety Surveillance Tool.

Recombinant herpes zoster vaccine (RZV)

In October 2017, a new recombinant herpes zoster vaccine (RZV, Shingrix®) was authorized for use in Canada. RZV AEFIs comprised 13.2% (n=98) of all AEFIs in 2018. The RZV AEFI reporting rate (31.7 per 100,000 doses distributed[6]) was higher than the live virus herpes zoster vaccine (LZV, Zostavax® II) offered through the publicly-funded program (16.3 per 100,000 doses). The most commonly reported reactions among RZV AEFIs were pain, redness, swelling (57.1%), rash (21.4%), and fever (17.3%). Co-administration with another vaccine occurred in 11.2% of RZV AEFIs (n=11). There were no serious AEFI reports following immunization with RZV. Individuals with an RZV AEFI ranged in age from 34 to 93 years (median age 63 years), with a predominance among females (82.7%). The highest number of RZV AEFIs was among 55-59 year olds (n=23, 23.5%, 2.2 per 100,000 population), while 65-69 year olds were associated with the highest rate (n=18, 18.4%, 2.3 per 100,000 population).

Table 1A. Number of Reports of AEFIs and AEFI Reporting Rates per 100,000 Doses Distributed by Routine, Publicly-Funded Vaccine: Ontario, 2018

Vaccine[1]	Number of AEFI Reports	Vaccine-Specific Reporting Rate[2]	Number of Serious Reports[3]	Vaccine-Specific Serious Reporting Rate[2,3]	Doses Distributed[2]
HPV9	72	31.9	0	0.0	225,832
Men-C-ACWY	55	30.7	0	0.0	178,915
Pneu-P-23	63	26.9	2	0.9	234,397
Var	52	23.5	0	0.0	220,883
Men-C-C	42	22.8	6	3.3	183,931
HB	48	18.7	0	0.0	256,849
MMR	54	18.5	7	2.4	292,001
LZV	19	16.3	1	0.9	116,887
DTaP-IPV-Hib	88	15.4	7	1.2	573,151
Pneu-C-13	68	14.5	5	1.1	467,974
MMRV	25	12.9	2	1.0	194,148
Rot-1	21	11.7	1	0.6	179,170
Tdap	77	9.4	1	0.1	821,817
Tdap-IPV	17	7.1	1	0.4	238,852
Inf	168	4.0	5	0.1	4,217,528
Td	6	3.0	0	0.0	202,055
Rot-5	2	2.4	0	0.0	84,599

Table 1B. Number of Reports of AEFIs among High-Risk Publicly-Funded and Non-Publicly-Funded Vaccines: Ontario, 2018

Vaccine[1]	Number of AEFI Reports[3]	Number of Serious Reports[2,3]
RZV[1]	98	0
HAHB	11	0
Rab	7	0
HPV-4	4	0
HA	4	0
Men-B	4	1
YF	3	0
JE		0
Typh-I	2	0
Typh-O	2	0
Chol-E	1	0
Chol-O	1	0
DTaP-IPV	1	0
IPV	1	0
Men-P-ACWY	1	0

AEFI reports: MOH, integrated Public Health Information System (iPHIS) database, extracted [2019/06/27].

Vaccine doses distributed: MOH, Panorama Enhanced Analytical Reporting, extracted by MOH [2019/06/12].

Notes:

1. Only those vaccines with AEFI reports are shown. See Appendix 1 of the Technical Annex for a list of all vaccine abbreviations and corresponding vaccine product/trade names. Vaccines are grouped by main category of recommended age of receipt, as per the *Publicly Funded Immunization Schedules for Ontario – December 2016.*[7]

2. Vaccine-specific reporting rates per 100,000 doses distributed are calculated for routine, publicly-funded vaccines only, due to unknown vaccine distribution for other vaccines within the private market.

3. An AEFI that meets the serious definition is typically associated with an in-patient hospitalization or death (refer to Technical Annex).

Adverse Event Descriptions

The most frequently reported specific adverse event-types (excluding fever in conjunction with another reportable event due to overlap with other reported event types) were pain, redness or swelling at the injection site, followed by rash and skin allergic reactions (Table 2A-2D). At least one injection site reaction was recorded in 49.9% (n=370) of all AEFI reports, three of which were classified as serious (0.8%). Rashes were the second most frequently reported specific adverse event-type, present in 25.7% of reports (n=191); 96.9% were classified as non-serious. Among those AEFI reports with rash, 41.9% (n=80) were associated with administration of live virus vaccines (i.e., MMR, MMRV, Var or LZV) and 52.5% (n=42) of these occurred within five to 42 days of vaccine administration (i.e., within the expected range of time to rash onset for live virus vaccines). Among those occurring within five to 42 days, five were confirmed as vaccine-strain by genotyping, including four that were measles vaccine strain (all following MMR vaccine, including one classified as serious) and one varicella vaccine strain (following LZV, which was classified as serious). Allergic skin reactions comprised 13.6% of all AEFI reports (n=101); only one event was classified as serious. Refer to Serious AEFIs for further information. For annual reporting rates by specific adverse event-types prior to 2018, see Vaccine Safety Surveillance Tool.

Tables 3A – 3C list the 10 most frequent routine, publicly-funded vaccines associated with the three most frequently reported adverse events types described above, in descending order of AEFI reporting rate. Pneu-P-23 was the most commonly associated vaccine with pain, redness and swelling reactions (16.6 per 100,000 doses). Men-C-C was the most frequently associated vaccine for rash reactions (16.9 per 100,000 doses) and HPV-9 was the most frequently associated vaccine for allergic skin reactions (6.6 per 100,000 doses).

Table 2A. Number and Distribution of AEFI Reports by Injection Site Reactions: Ontario, 2018

Adverse Event	Number of AEFI Reports[3]	Percent of All AEFI Reports (%)[4]	Number of Serious AEFI Reports
Cellulitis	66	8.9	2
Infected abscess	1	0.1	0
Nodule	11	1.5	0
Pain/redness/swelling at the injection site	313	42.2	1
Pain/redness/swelling extending beyond nearest joint	80	10.8	0
Pain/redness/swelling 4-10 days	188	25.3	0
Pain/redness/swelling >10 days	66	8.9	1
Sterile abscess	3	0.4	0

Table 2B. Number and Distribution of AEFI Reports by Systemic Events: Ontario, 2018

Adverse Event	Number of AEFI Reports[3]	Percent of All AEFI Reports (%)[4]	Number of Serious AEFI Reports
Adenopathy/lymphadenopathy	4	0.5	0
Arthritis/arthralgia	12	1.6	1
Fever in conjunction with another reportable event	110	14.8	11
Hypotonic-hyporesponsive episode	1	0.1	0
Intussusception[5]	1	0.1	0
Parotitis	1	0.1	0
Persistent crying/screaming	6	0.8	0
Rash	191	25.7	6
Severe vomiting/diarrhea	35	4.7	0
Syncope with injury	6	0.8	0

Adverse Event	Number of AEFI Reports[3]	Percent of All AEFI Reports (%)[4]	Number of Serious AEFI Reports
Thrombocytopenia	2	0.3	2

Table 2C. Number and Distribution of AEFI Reports by Allergic Events: Ontario, 2018

Adverse Event	Number of AEFI Reports[3]	Percent of All AEFI Reports (%)[4]	Number of Serious AEFI Reports
Allergic reaction – skin	101	13.6	1
Event managed as anaphylaxis[5]	10	1.3	2
Oculorespiratory syndrome (ORS)	4	0.5	0

Table 2D. Number and Distribution of AEFI Reports by Neurologic and Other Severe/Unusual Events: Ontario, 2018

Adverse Event[2]	Number of AEFI Reports[3]	Percent of All AEFI Reports (%)[4]	Number of Serious AEFI Reports
Anaesthesia/paraesthesia	15	2.0	0
Bell's palsy	1	0.1	0
Convulsions/seizures	19	2.6	5
Guillian-Barré syndrome[5]	1	0.1	0
Paralysis other than Bell's palsy	1	0.1	1
Other severe/unusual events	74	10.0	7

AEFI Reports: MOH, integrated Public Health Information System (iPHIS) database, extracted [2019/06/27].

Notes:

1. Adverse event categories represent groupings of specific adverse events within a common category. An AEFI report may contain multiple adverse events from different adverse event categories, as well as more than one adverse event within the same adverse event category.

Reports with more than one adverse event within the same category are counted only once in the category totals. Therefore, the sum of adverse event-specific counts within a category may not equal to the category total.

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 see Appendix 2 of the Technical Annex.

3. Each AEFI report may contain one or more specific adverse events. Thus the sum will not equal to the total number of AEFIs reported in 2018.

4. Percentages will not sum to 100%. The denominator is the total number of confirmed AEFI reports with at least one adverse event reported (n=742).

5. Classified as medically important events. See Technical Annex for further detail on the definition of medically important events.

Table 3A. Number and distribution of AEFI reports for pain, redness, swelling at the injection site by vaccine[1]: Ontario, 2018

Ranking	Vaccine	Number of AEFI Reports	AEFI Reporting Rate per 100,000 doses distributed
1	Pneu-P-23	39	16.6
2	Men-C-ACWY	22	12.3
3	HPV-9	25	11.1
4	LZV	10	8.6
5	Var	13	5.9
6	HB	15	5.8
7	Tdap	40	4.9
8	MMRV	9	4.6
9	DTaP-IPV-Hib	21	3.7
10	Pneu-C-13	12	2.6

Table 3B. Number and distribution of AEFI reports for rash by vaccine[1]: Ontario, 2018

Ranking	Vaccine	Number of AEFI Reports	AEFI Reporting Rate per 100,000 doses distributed
1	Men-C-C	31	16.9
2	MMR	40	13.7
3	Var	25	11.3
4	LZV	8	6.8
5	Pneu-C-13	32	6.8
6	DTaP-IPV-Hib	36	6.3
7	HPV-9	12	5.3
8	Rot-1	9	5.0
9	MMRV	8	4.1
10	Men-C-ACWY	7	3.9

Table 3C. Number and distribution of AEFI reports for allergic reaction - skin by vaccine[1]: Ontario, 2018

Ranking	Vaccine	Number of AEFI Reports	AEFI Reporting Rate per 100,000 doses distributed
1	HPV-9	15	6.6
2	Men-C-ACWY	9	5.0
3	HB	11	4.3
4	Men-C-C	6	3.3
5	MMRV	6	3.1
6	Var	6	2.7
7	Pneu-P-23	6	2.6
8	Tdap-IPV	6	2.5

Ranking	Vaccine	Number of AEFI Reports	AEFI Reporting Rate per 100,000 doses distributed
9	DTaP-IPV-Hib	14	2.4
10	MMR	7	2.4

AEFI Reports: MOH, integrated Public Health Information System (iPHIS) database, extracted [2019/06/27].

Notes:

1. Only the 10 vaccines with the highest rates within each adverse event type are shown.

There were 14 AEFIs reported that were classified as medically important events in 2018, representing 1.9% of all reports (please see the Technical Annex for a description of a medically important event). Four of these 14 events also met the definition of a serious AEFI and are therefore described under Serious AEFIs. Of the remaining 10 medically important events, the majority (n=8) were reports of events managed as anaphylaxis among persons who ranged in age from one to 45 years and one report each of intussusception in a two-month old following receipt of Rot-1 and Guillian-Barré syndrome in an adult after receiving HAHB vaccine. There were two additional reports of anaphylaxis that were classified as serious (described below) for a total of 10 events managed as anaphylaxis reported in 2018. Among the 10 reports of anaphylaxis, the most frequently reported vaccines were Inf (five reports) and Men-C-ACYW (three reports, two of which involved co-administration of HB and HPV9). All events managed as anaphylaxis were assessed using the Brighton Collaboration standard definition of anaphylaxis.[8] Two met the Brighton definition at level II of diagnostic certainty. The remaining eight (80.0%) reports did not have sufficient documented evidence to meet levels I, II or III of diagnostic certainty.

Serious AEFIs

There were 21 AEFI reports in 2018 that were classified as serious (please see the Technical Annex for a description of a serious AEFI), representing 2.8% (21/742) of all reports and a serious AEFI reporting rate of 1.5 per 1,000,000 population. All serious AEFI reports were following administration of at least one publicly-funded vaccine (2.4 per 1,000,000 publicly-funded doses distributed). The majority of serious AEFIs (81.0%; n=17) occurred in individuals under 18 years of age, with most in children under four years (n=14). All 21 serious AEFIs in 2018 were admitted to hospital with a mean length of stay of 4.7 days (range 1 to 49 days); there were no reports of death. The proportion of AEFIs defined as serious remained relatively stable between 2012 and 2018 (2.8% to 5.0%).

Based on case-level review, there were five reports of convulsions/seizures – all of which occurred in children two years of age and under and four reports documented as being febrile. In addition, there were three reports of vaccine strain illness, including two that were laboratory-confirmed and one that was presumed to be vaccine strain based on recent immunization and lack of travel history or exposure

to a case. Of the two laboratory-confirmed vaccine strain illnesses, there was one report of measles virus and the other varicella-zoster virus; the latter was reported to have developed a systemic papulovesicular rash. There were two reports each of thrombocytopenia (Immune Thrombocytopenic Purpura or ITP), injection site reactions (both cellulitis with hospitalization related to treatment with intravenous antibiotics) and anaphylaxis (both of which did not have sufficient documented evidence to meet levels I, II or III of diagnostic certainty of the Brighton anaphylaxis case definition). Of the remaining serious AEFI reports, there was one each of Kawasaki Disease (KD), pneumonia, arthralgia, paralysis, transient weakness in the injected arm, apnea and bronchiolitis, and an allergic skin reaction. For more information about specific serious AEFI reports, please refer to the Appendix.

Healthcare Utilization, Outcome and Risk Factors

Tables 4A-4C summarizes the healthcare utilization, outcomes and risk factors associated with AEFI reports in 2018. Among those reports with the corresponding healthcare utilization fields completed in iPHIS, 74.6% (547/733) sought out-patient medical consultation, 16.7% (123/462) had an emergency room visit and 3.0% (22/736) indicated a hospitalization had occurred.

In terms of AEFI outcomes, the majority of individuals had recovered at the time of reporting (67.9% of all AEFI reports), followed by those who were not yet recovered, but likely to recover (23.1%). In a small proportion of reports (2.8%), the outcome was reported as "residual effects," which is defined as residual disability or sequelae related to the reported event. None of the cases reported to have residual effects met the definition of a serious AEFI. Due to the relatively short follow-up time for AEFIs reported in iPHIS, it is uncertain whether these residual effects represent long-term residual disability or events which will resolve, but had not yet resolved at the time of reporting.

An affirmative response to at least one of the three medical risk factors that are collected for provincial AEFI surveillance (i.e. required in iPHIS), was observed in 19.9% of all AEFI reports. Of these, most (89.8%) reported having a chronic illness/underlying medical condition, followed by being immunocompromised and being associated with an immunization program error. Among immunization program errors, six reports included administration errors (e.g., incorrect land-marking or needle selection, and wrong route/dose administered), five included a report of non-adherence to vaccine indications or recommendations for use and one included both a report of an administration error and non-adherence to vaccine indications and recommendations.

Table 4A. Number and Distribution of AEFI Reports by Healthcare Utilization: Ontario, 2018

Healthcare utilization	Number of AEFI Reports[3]	Percent of All AEFI Reports with a known response (%)
Medical consultation	547	74.6
Emergency room visit	123	16.7

Healthcare utilization	Number of AEFI Reports[3]	Percent of All AEFI Reports with a known response (%)
Hospitalization	22	3.0

Table 4B. Number and Distribution of AEFI Reports by Outcomes: Ontario, 2018

Outcomes	Number of AEFI Reports[3]	Percent of All AEFI Reports (%)
Recovered	502	67.9
Not yet recovered/likely to recover	171	23.1
Residual effects	21	2.8

Table 4C. Number and Distribution of AEFI Reports by Risk Factors: Ontario, 2018

Risk Factors	Number of AEFI Reports[3]	Percent of AEFI reports with at least 1 medical risk factor (%)
Chronic illness	132	89.8
Immunocompromised	16	10.9
Immunization program error	13	8.8

AEFI Reports: MOH, integrated Public Health Information System (iPHIS) database, extracted [2019/06/27].

Notes on Interpretation

We describe in this report adverse events that were temporally associated and not necessarily causally linked to vaccines. Our assessment was based on data from iPHIS only and not comprehensive chart review. We provided reporting rate estimates for comparison to other passive surveillance systems and for monitoring reporting trends over time; they should not be interpreted as incidence rates. It is important to note that in the context of a passive AEFI surveillance system, a higher overall reporting rate of AEFIs (across all vaccines) does not necessarily suggest a vaccine safety concern; rather, it is an indicator of a robust passive vaccine safety surveillance system. The quantity of reports contributes to establishing a clear historical baseline that can be used to identify future vaccine safety signals.

Discussion

Overall, we found a low rate of AEFI reporting in Ontario following vaccines administered in 2018 and no unexpected vaccine safety issues.

The provincial AEFI reporting rate increased slightly in 2018 (5.1 per 100,000 population) compared to previously published 2017 data (4.9 per 100,000 population); however, this increase was likely due to the high proportion of RZV AEFIs, without which the overall rate would have declined this year. Ontario's AEFI reporting rate has been consistently lower relative to other jurisdictions. Some differences in rates are expected across different geographic areas due to variability in reporting requirements, case definitions, immunization programs and population demographic characteristics. As a comparison, the Canadian national AEFI reporting rate was 7.2 per 100,000 population in 2018[9] and the Australian annual reporting rate was 12.3 per 100,000 population in 2015.[10] The causes of Ontario's low reporting rate are likely multifactorial, including under-reporting by healthcare providers; [11-13] which is discussed in further detail in previous reports.[14-18] The World Health Organization has introduced an indicator of the functioning of a country's AEFI surveillance system,[19] with a value of 10 reports per 100,000 surviving infants suggesting basic capacity for reporting rather than the quality of the surveillance system. Our analysis yielded a corresponding estimate of 32.7 per 100,000 surviving infants in Ontario in 2018. This was substantially lower than the AEFI reporting ratios for the Region of the Americas and Globally (all WHO regions) that were 486 and 549 AEFI reports per 100,000 surviving infants, respectively, in 2015.[4]

We observed an increase in the reporting rate among adults 65 years and older in 2018 compared to 2017 (6.2 versus 5.1 per 100,000 population). This may be related to uptake of RZV vaccine in this population that was available for private purchase starting in October 2017 and is supported by our analysis of RZV AEFIs within this report, where the highest reporting rate per doses distributed was among those 65 years and older. An increase in reporting following the introduction of new vaccines or expansion of vaccines in new populations has previously been observed in our data[18,21] and has also been reported elsewhere.[20] Other age- and sex-specific trends were similar in 2018, as compared to previous years (see online tool for data); the factors associated with the higher rates observed among infants, young children and females have been previously described.[14-18, 21]

Similar to previous years, wide variation in population-based AEFI reporting by PHUs for both infant and early childhood vaccine programs, school-based programs and influenza vaccine was observed in 2018. The high geographic variability in AEFI reporting rates may in part be related to variability in the interpretation and promotion of AEFI reporting among local health care providers within jurisdictions and different reporting processes for AEFIs across PHUs, all of which drives provincial AEFI reporting. Overall, the number of PHUs with zero reports in 2018 was similar or lower compared to 2017 across all categories. Our analysis is based on reporting rates derived using both population data and vaccine dose distribution data as denominators, both of which have specific limitations which have previously been described.[21] In general, the absence of a population-based provincial immunization registry, which

would allow for an accurate assessment of the number of doses administered to individuals residing in each area, doses distributed data, where available, serves as a proxy and enables a more accurate comparison of AEFI reporting rates across geographic areas by taking into account the differences in vaccine distribution relative to population-based reporting rates.

Vaccine-specific reporting rates in 2018 among routine, publicly-funded vaccines were highest for HPV9, Men-C-ACYW and Pneu-P-23 (using doses distributed in the denominator), although serious reporting rates for all three vaccines were lower than the overall serious AEFI rate. HPV9 and Men-C-ACYW are two vaccines primarily delivered by PHUs within school-based programs, where higher AEFI reporting is typically observed compared to program delivery by other providers.[14-18, 21] In addition, it has been observed that local adverse events are more common following HPV9 compared to HPV4 (HPV9 replaced HPV4 in September 2017).[22] Pneu-P-23 is also known to be a reactogenic vaccine (i.e., injection site reactions), particularly when booster doses are administered at intervals of less than two years.[23] Of note, RZV had the highest number and rate of AEFIs in 2018, despite being available for private purchase only. The RZV AEFI reporting rate was nearly twice as high as the LZV AEFI reporting rate; however; there were no serious RZV AEFIs – in comparison, there was one serious LZV AEFI.

As in previous years, mild events (e.g., injection site reactions and rash) were the most frequently reported reactions. This is expected based on the safety profile of many vaccines and is consistently observed in AEFI surveillance systems in other jurisdictions.[24, 25] Pneu-P-23 was the routine, publicly-funded vaccine most frequently associated with pain, redness and swelling at the injection site, while rash and fever were both most commonly associated with Men-C-C, followed closely by MMR, which is typically co-administered with Men-C-C at 12 months of age. Of note, among reports of immunization errors, three involved RZV and all were related to administration errors where the vaccine was given subcutaneously instead of intramuscularly; injection site reactions were reported for two of the three cases. This suggests that immunizers may be confusing the administration procedure for RZV with LZV, a finding also noted in data from the US Vaccine Adverse Event Reporting System (VAERS).[26]

Serious AEFIs were very rarely reported in 2018. Despite a slight increase in the overall AEFI reporting rate, the rate of serious AEFIs was slightly lower than last year. Similar to previous years, the types of serious AEFIs reported were most often related to rare events that are known to be reported following vaccination, including one report of KD and two reports of ITP. Thrombocytopenia is known to have a causal relationship with measles-containing vaccine (and to a lesser degree, other vaccines) and although KD is consistently reported in passive AEFI surveillance, a causal link to immunization has not been established[27]

Among serious AEFIs, there were two reports of muscle weakness and paralysis (one paralysis and one arthritis/arthralgia) and both were reported during the winter of 2018. This timeline overlaps with a widely reported increase in cases of acute flaccid paralysis/myelitis (AFP or AFM) observed in Canada and the United States.[28,29] It is possible that reporting of these AEFI events was stimulated by heightened awareness of reporting of AFP-type events during that time. There was also one serious AEFI of transient arm weakness; however, this was reported in early 2018, prior to the increase in AFP/AFM cases in late 2018.

For a description of the limitations of the AEFI surveillance system, please see the Technical Annex.

Conclusions

This report summarizes AEFIs reported in Ontario following vaccines administered in 2018, as well as reporting trends since 2012. Overall, a low rate of AEFI reporting continued to be observed in the province, though a wide range in reported AEFI rates was found among PHUs. No unexpected vaccine safety issues were identified – the most commonly reported events were mild (e.g., injection site reactions). Serious events were very rare and the majority of individuals had recovered at the time of reporting. Ongoing surveillance of AEFIs in Ontario is needed to monitor vaccine safety and to assess and interpret trends within the context of changes to provincial immunization programs, with the goal of improving reporting within the surveillance system.

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Appendix: Summary of Serious AEFIs, 2018

Event description based on case-level review	Number of AEFI reports	Age group (years)	Associated vaccines	Additional information
Convulsion/seizure	5	1-3	DTaP-IPV-Hib, Inf (Q-LAIV), MMR, Men-C-C, Penu-C-13,	4 reports with documented fever. One with a report of rash, onset 17 days after receiving vaccine.
Thrombocytopenia	2	1-3 4-10	MMR, MMRV, Men-C-C, Pneu-C-13, Tdap-IPV	2 reports of Immune Thrombocytopenic Purpura.
Local reaction	2	<1 4-10	DTaP-IPV-Hib, MMRV	2 reports of cellulitis; hospitalizations related to treatment with intravenous antibiotics.
Anaphylaxis	2	1-3 18-64	Inf	Brighton level: IV (both cases)
Vaccine strain illness	3	1-3 65+	DTaP-IPV-Hib, MMR, Men-C-C, LZV	1 report of laboratory-confirmed measles vaccine strain. 1 presumptive measles vaccine strain based on recent immunization and lack of recent travel or exposure to a confirmed case (PCR positive, genotype indeterminate). 1 report of laboratory-confirmed varicella vaccine strain.
Kawasaki Disease	1	1-3	MMR, Men-C-C, Penu-C-13	Onset of fever and rash 3 and 5 days respectively, after receiving vaccine.

Event description based on case-level review	Number of AEFI reports	Age group (years)	Associated vaccines	Additional information
Pneumonia	1	18-64	Tdap, Pneu-P-23	Onset of left upper quadrant pain and fever 2 days after immunization.
Arthritis/arthralgia	1	11-17	Inf	Diagnosed with fever of unknown etiology with differential diagnosis of viral infection causing arthralgia.
Paralysis	1	1-3	DTaP-IPV-Hib	Refusal to walk and unable bear weight two weeks after receiving vaccine.
Transient arm weakness	1	1-3	DTaP-IPV-Hib, Inf, Men-B	
Apnea and bronchiolitis	1	<1	DTaP-IPV-Hib, Pneu-C-13, Rot-1	NP swab positive for enterorhinovirus.
Allergic skin reaction	1	18-64	Pneu-P-23	

AEFI Reports: MOH, integrated Public Health Information System (iPHIS) database, extracted [2019/06/27].

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