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Annual Report on Vaccine Safety in Ontario, 2017

Technical Annex

November 2018

Public Health Ontario

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Contents

Purpose

The purpose of this document is to provide standard technical information to support Public Health Ontario's (PHO) Annual Report on Vaccine Safety in Ontario, 2017 and related surveillance products. Technical information includes a brief background on vaccine safety surveillance in Canada, adverse event following immunization (AEFI) surveillance reporting processes in Ontario and an in-depth explanation of analytic methods used in the report, as well as notes on interpretation and limitations of AEFI surveillance data.

Vaccine Safety Surveillance in Canada

In Canada, vaccines are highly regulated and monitored to ensure they are as safe as possible. 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.[2] The National Advisory Committee on Immunization (NACI) independently reviews the available evidence on safety and efficacy.[3] 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.

> **An AEFI (adverse event following immunization) is 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.**[1]

Following approval of a new vaccine, post-marketing surveillance is initiated to ensure the ongoing monitoring of safety in the population receiving the vaccine. Individual case reports of AEFIs represent an important source of data because they have the potential to identify previously unrecognized or rare AEFIs or an increase in frequency or severity of known AEFIs, which can be further evaluated.

In Canada, post-marketing surveillance is a shared responsibility between Health Canada, the vaccine manufacturers, the Public Health Agency of Canada (PHAC), provinces and territories, as well as local public health authorities. PHAC and Health Canada coordinate post-marketing vaccine safety surveillance nationally, while provinces and territories coordinate surveillance of AEFIs occurring within their jurisdiction in collaboration with their local partners. Reports of AEFIs made directly to vaccine manufacturers are sent to Health Canada, while AEFIs reported to provincial and territorial (P/T) public health authorities are reported to the Canadian Adverse Event Following Immunization Surveillance System (CAEFISS), maintained by PHAC. AEFI reports received by vaccine manufacturers may also be voluntarily reported to CAEFISS; however, any serious reports are required by law to be reported by them directly to Health Canada.

Public Health Surveillance of Adverse Events Following Immunization in Ontario

The public health aim of surveillance of AEFIs in Ontario is early detection and timely response to real or perceived vaccine safety issues and to lessen any impact on the health of individuals and immunization programs. In addition, AEFI surveillance provides important information to support and inform immunization program planning and evaluation.

Ontario's specific AEFI surveillance objectives are to:

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

In recent years, several initiatives have been implemented to support Ontario's AEFI surveillance objectives, including: revised provincial case definitions for AEFIs, enhanced surveillance guidelines and forms, improved training and resources for public health units (PHUs) and information for health care providers. In 2013, PHO initiated the Annual Report on Vaccine Safety in Ontario, an annual comprehensive assessment of AEFIs reported following vaccines administered in Ontario in the preceding year. In 2017, PHO also launched the Vaccine Safety Surveillance tool, an interactive online tool allowing users to explore, manipulate and download vaccine safety data. Both the report and the online tool were created to facilitate ongoing assessment of vaccine safety in the province and to provide relevant, transparent and timely information about vaccine safety to support health care professionals, reassure the public that vaccines are continuously monitored for safety and build confidence in vaccines and immunization programs.

Methods of the Annual Report on Vaccine Safety

AEFI Reporting Process

In Ontario, initial reports of AEFIs are directed to local PHUs either by telephone or by faxing or mailing the Ontario AEFI reporting form. Reports originate from health care providers, vaccine recipients or their caregivers. The *Health Protection and Promotion Act (HPPA)* mandates reporting of AEFIs by specified healthcare providers (e.g., registered nurses, pharmacists and physicians); as of May 1, 2018, the Act was updated to require reporting of AEFIs for all vaccines authorized for use in Canada by all health care providers who administer immunizations.[4] PHUs also receive reports from IMPACT (Immunization Monitoring Program ACTive), which is a paediatric hospital-based active surveillance network that monitors select vaccine-preventable diseases and AEFIs in Canada. The two Ontario sites are in Toronto (Hospital for Sick Children) and Ottawa (Children's Hospital of Eastern Ontario).

AEFI reports received by PHUs are investigated, assessed and documented according to provincial surveillance guidelines, as required by the Ontario Public Health Standards (OPHS), which was updated in 2018 to reflect changes to the *Health Protection and Promotion Act*, RSO 1990, c. H.7.[4,5] PHUs also provide support and advice to vaccine recipients or their parents and health care providers in their community. This may include recommendations with respect to additional follow-up and whether to receive further doses of vaccine for vaccine recipients who experience an AEFI.

AEFI reports are entered by PHUs into the integrated Public Health Information System (iPHIS), the electronic reporting system for reportable diseases and adverse events in Ontario. AEFI reports are required to be reported in iPHIS within five business days of receipt of initial notification to a PHU.[6,7] The minimum data elements for the majority of AEFI reports analysed in the vaccine safety report for the current year are specified in the iPHIS AEFI User Guide (2015)[7] and RRO 1990, Reg. 569: REPORTS under the *Health Protection and Promotion Act*, RSO 1990, c. H.7.[4] In spring 2018, an updated version of the iPHIS AEFI User Guide (2018)[8] was implemented and revised legislation[4] to expand reporting requirements were enacted, which will guide the entry of new AEFI reports.

PHO conducts provincial surveillance of AEFIs and provides advice and support for local PHUs in the investigation and management of AEFI reports. This role was transferred from the Ministry of Health and Long-Term Care (MOHLTC) on January 1, 2012. The MOHLTC continues to be responsible for public health legislation and standards, which enable the reporting and collection of information required for provincial surveillance. PHO transmits AEFI data to PHAC on a monthly basis for inclusion in CAEFISS, the national database containing AEFIs reported from all provinces and territories in Canada.

AEFI Surveillance Definitions

Provincial AEFI surveillance definitions are described in Appendix B (Adverse Events Following Immunization) of the Ontario Public Health Standards (OPHS), Infectious Diseases Protocol, 2015.[9] According to Section 3.0 (Case Classification) of Appendix B, AEFI reports are to be classified and entered in iPHIS as "Confirmed" or "Does not meet" based on the following definitions:

Confirmed

Any reported event in a vaccine recipient which follows immunization and 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 (DNM)

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

Section 5.0 (Clinical Evidence) includes specific definitions to guide further classification of AEFI reports by event-type.[9] Each adverse event definition includes specific criteria, which define each type of event, as well as temporal criteria.

Definitions of Key Terms

Vaccine

A generic active immunizing agent and includes one or more vaccine products (e.g., "influenza vaccine" refers to all influenza vaccine products). Standard acronyms for vaccines are used in the report (e.g., MMR for measles, mumps and rubella vaccine). A complete list of these acronyms and corresponding products and trade names can be found in Appendix 1.

Adverse Event

In the context of provincial surveillance reporting, an adverse event refers to an event which is temporally associated with receipt of vaccine and meets the corresponding event-specific provincial surveillance criteria. These criteria can be found in Appendix B (Adverse Events Following Immunization) of the OPHS, Infectious Diseases Protocol, 2015 and include clinical and temporal components.[9] In the Annual Report on Vaccine Safety in Ontario, adverse events are presented both individually and according to event categories. See Appendix 2 for a complete description of all specific adverse events under provincial surveillance and corresponding categories and adverse event values available in iPHIS. Of note, both the event criteria and adverse event values in iPHIS were updated on January 1, 2013. Appendix 2 also includes mapping of these values before and after this change was implemented.

AEFI Report

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). One individual may have multiple AEFI reports if they experience adverse events following multiple doses in a series of different vaccines administered on different days.

Temporal Criteria

Temporal criteria are estimated timelines between vaccination and onset of symptoms. Specific adverse events and their temporal criteria are described in Appendix B (Adverse Events Following Immunization) of the OPHS, Infectious Diseases Protocol, 2015.[9] Events described in the report are assumed to fall within their temporal criteria; however, some adverse events may be reported, which have occurred outside of these timelines, but were assessed by the PHU to be clinically significant.

Serious AEFI

Serious AEFIs are defined as an AEFI that results in death, is life-threatening, requires in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity or in a congenital anomaly/birth defect. This definition is based upon International Conference on Harmonisation (ICH) E2A and E2D guidelines.[10,11]

Of note, specific components of the above serious definition, including persistent or significant disability/incapacity and congenital anomaly/birth defect, are not systematically captured in iPHIS due to the relatively brief follow-up period of AEFIs reported in Ontario. As a result, AEFIs in Ontario that meet the serious definition typically have an in-patient hospitalization or are reported to have died. In-patient hospitalization is defined as having a hospitalization recorded in iPHIS with a discharge date that is at least one day following the admission date.

Medically Important Events

Some selected adverse events can be defined as "medically important," based on the World Health Organization's (WHO) guidance, regardless of whether they meet the serious AEFI definition. These types of events may jeopardize the patient or may require intervention to prevent an outcome described in the serious definition (e.g., hospitalization); "medically important" events may be defined after applying medical and scientific judgement.[1] In Ontario, the following specific events under surveillance that align with this definition include: acute disseminated encephalomyelitis (ADEM), events managed as anaphylaxis, encephalitis/encephalopathy, Guillain-Barré syndrome (GBS), intussusception, meningitis, myelitis and thrombocytopenia.

Medically important events which do not otherwise meet the serious definition are described separately in the Annual Report on Vaccine Safety in Ontario. Those that also meet the serious definition are described in the section on serious AEFIs. Events managed as anaphylaxis, regardless of whether they meet the serious definition, are further assessed using the internationally recognized case definition for

anaphylaxis following vaccination from the Brighton Collaboration.[12] All medically important events and serious AEFIs are reviewed individually by PHO to provide detailed assessment and descriptions within the annual report.

Data Preparation & Extraction

In the spring of each year, PHO leads a data clean-up initiative in collaboration with PHUs to address any data quality issues present in AEFI reports that are associated with vaccines administered in the previous calendar year. PHO electronically sends each PHU a list of AEFI reports from iPHIS that have specific data quality issues. PHUs then review and update these cases according to the instructions provided. PHO provides support to PHUs as needed and actively follows up throughout the data cleaning process to address any outstanding data issues.

Data for the annual report were extracted from iPHIS on May 11, 2018. The data extract includes all reports of AEFIs that were reported in Ontario on or after January 1, 2012. This includes all AEFI reports with a vaccine administration date between January 1 and December 31 of 2017, which are the focus of this annual report, as well as all AEFI reports following vaccines administered in the preceding years starting in 2012 for an updated assessment of temporal trends. Reports of AEFIs reported in 2011 and earlier are excluded due to data quality issues. Historical trend data may change slightly from year-to-year due to late reporting and delayed data entry of adverse events occurring from previous years.

Analysis of Epidemiologic Data

Descriptive analysis of AEFIs is limited to reports with a case classification of "confirmed" in iPHIS and with at least one active immunizing agent associated with the report. The following AEFI reports were excluded from the analysis:

- AEFI reports with a case classification other than "confirmed" or a disposition of "does not meet definition," "entered in error" or "closed- duplicate – do not use" in iPHIS
- AEFI reports that are **only** associated with diagnostic agents (e.g., tuberculin skin test) and/or passive immunizing agents (e.g., immune globulin), with no active immunizing agents administered at the same time. These reports are not within the scope of provincial AEFI surveillance.[9]
- AEFI reports in non-residents of Ontario
- AEFI reports with a vaccine administration date not occurring between January 1, 2012 and December 31, 2017

Temporal trends are assessed by year of vaccine administration. Age categories for analysis are based on key age milestones within the provincial immunization schedule (<1 year, 1-3 years, 4-10 years, 11-17 years, 18-64 years, 65+ years). Proportions are calculated based on reports with completed data fields in iPHIS; therefore the denominator varies by variable of analysis. AEFI reporting source is the source of the initial AEFI report to the PHU and not necessarily the only source of information in the AEFI investigation. Reporting source categories presented were derived from drop-down values available in

iPHIS, where physicians are listed as a separate category from 'other health professionals,' which includes nurses and pharmacists. Reporting rates were mapped using ArcMap® 10.3 to visualize the geographic distribution of AEFI reporting in the province by PHUs. For each map, reporting rates were grouped into quartile intervals. Determination of the interval to rash onset following administration with live virus vaccines (MMR, Var, MMRV, Zos) was based on a quantitative analysis of entered data (i.e. onset date of adverse event, administration date and interval to onset date) and a review of case notes; in the event of any discrepancies, a manual review was undertaken to determine the most likely value.

All analyses were performed using SAS Enterprise Guide version 7.1 and Microsoft Excel 2010. Trends in reporting rates over the entire study period were assessed using Poisson regression and p-values less than 0.05 were considered statistically significant. This project has been assessed to be outside the scope of evidence generating initiatives requiring review by the PHO Ethics Review Board.

Reporting Rates

Reporting rates for AEFIs are calculated using both doses distributed and population-based denominators. Overall reporting rates (i.e., all vaccines combined) by demographic groups (e.g., age, sex and geography) are calculated using population-based denominators in the absence of information about doses administered within these groups. Population-based denominators are derived from Ontario population estimates and projections.[13,14] Net doses distributed is used for vaccine-specific reporting rates for publicly-funded universal vaccines as a proxy for doses administered. Net doses distributed are estimated using vaccine distribution data extracted from Panorama through the Panorama Enhanced Analytic Reporting tool, which is the provincial information system for vaccine supply management. These estimates are adjusted for wasted or reusable vaccine returned to the Ontario Government Pharmaceutical and Medical Supply Service (OGPMSS). Influenza vaccine doses also include doses that are distributed to third-party wholesale distributors as part of the Universal Influenza Immunization Program (UIIP). Vaccine-specific reporting rates for high-risk publicly-funded, travel and non-publicly-funded vaccines are not calculated due to unknown vaccine distribution within the private market.

Reporting rates by the type of provider (i.e., primary care providers vs. school-based programs primarily delivered by PHUs) are estimated using a combined reporting rate for specific vaccines and age categories, which are primarily delivered by one provider-type (e.g., primary care providers for infant/toddler vaccines, PHUs for school-based vaccines). Reporting rate ratios are calculated for comparison of reporting rates by sex within specific age groups and are presented as a ratio of the female reporting rate to the male reporting rate.

Limitations of AEFI Surveillance

General limitations of AEFI surveillance data presented in the Annual Report on Vaccine Safety in Ontario are similar to other passive AEFI surveillance systems. These include inconsistent quality and completeness of AEFI reports and reporting bias including under-reporting, particularly for mild or common reportable events, as well as stimulated (elevated) reporting which can occur in response to media coverage of a potential AEFI and subsequently increased public awareness.[15] Additionally, the provincial AEFI surveillance system does not include an unimmunized group for comparison. Therefore determining whether immunization is associated with an increased risk of a specific adverse event is not possible; further study would be required.

A further limitation of the analysis of AEFI surveillance data in Ontario is the lack of a population-based provincial immunization registry to estimate the number of individuals who were immunized or doses which were administered to individuals. This would enable estimation of AEFI incidence rates, including specific events, by vaccine type. In lieu of this, AEFI reporting rates are estimated using either the entire population irrespective of immunization status or vaccine doses distributed as the denominator. In this analysis, population-based denominators are used for overall system reporting rates (all vaccines combined) and for overall demographic analysis. This approach enables comparison of overall AEFI reporting trends over time and across geographic areas; however, population-based reporting rates have limitations as a proxy for true AEFI incidence where there are variations in vaccine uptake (i.e., coverage) over time or between geographic areas. Doses distributed are widely used in analyses of passive AEFI surveillance systems[15,16] and can be a reasonable proxy for doses administered for established programs with known vaccine wastage. When the amount of wastage is unknown and underestimated, this can result in underestimates of reporting rates. Additionally, in the context of new or discontinued vaccines/programs, the AEFI reporting rate using doses distributed as the denominator can be temporarily rendered invalid due to fluctuations in vaccine distribution caused by stockpiling, delayed vaccine use or large returns of unused/expired doses.

There have been substantial changes to AEFI surveillance in the province since 2012, including revised case definitions and updates to the iPHIS application on January 1, 2013. While these changes have resulted in improvements to iPHIS data quality, they do impact comparability of AEFI surveillance data and analyses of trends over time. Therefore, to facilitate comparisons over time, in-depth trend analysis is limited to AEFIs following vaccines administered on or after January 1, 2012. Finally, trends in reported AEFIs can be influenced by changes to the publicly-funded program. See Appendix 3 for details of program changes in recent years that may impact AEFI surveillance data presented in the report.

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Appendix 1: Vaccine Abbreviations, iPHIS Values and Marketed Product/Trade Names

Vaccine abbreviations	"Agent" values in iPHIS (as of April 1, 2013)	Product/trade name currently marketed in Canada
BCG	BCG - Bacillus Calmette Guerin	BCG vaccine
Chol-Ecol-O	Chol-Ecol-O - Cholera - E.Coli (Oral)	Dukoral®
Chol-O	Chol-O – Cholera Oral	No product currently marketed in Canada
DTaP-IPV	DTap-IPV - Diphtheria, Tetanus, Acellular Pertussis, Polio	Infanrix®-IPV, Quadracel®
DTaP-IPV-Hib	DTap-IPV-Hib - Diphtheria, Tetanus, Acellular Pertussis, Inactivated Poliomyelitis, Haemophilus b (Pediatric)	Pediacel®, Infanrix®- IPV/Hib, Pentacel®
HA	HA – Hepatitis A, HA - Hepatitis A (Adult), HA - Hepatitis A (Pediatric)	Avaxim®, Avaxim® - Pediatric, Havrix®, Havrix® 720 Junior, Vaqta®
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, Engerix®-B (Pediatric), Recombivax HB®, Recombivax HB® (Dialysis)
Hib	Hib - Haemophilus influenza type b	Act-HIB®, Hiberix®
HPV2	HPV2 - Human Papilloma Virus	Cervarix®
HPV4	HPV4 - Human Papilloma Virus	Gardasil®
HPV9	HPV9 - Human Papilloma Virus	Gardasil®9
Inf	Inf - Influenza	Agriflu®, Influvac®, Flumist® Quadrivalent, Fluad®, Fluad®Pediatric, Flulaval™ Tetra, Fluviral®, Fluzone®, Fluzone® HD, Fluzone® Quadrivalent, Vaxigrip®

Vaccine abbreviations	"Agent" values in iPHIS (as of April 1, 2013)	Product/trade name currently marketed in Canada
IPV	IPV - Inactivated Poliomyelitis (Vero Cell)	Imovax® Polio
JE	JE - Japanese Encephalitis	Ixiaro®
Men-B	Men-B – Meningococcal - B	Bexsero®
Men-C-ACWY	Men-C-ACWY - Meningococcal - Conjugate ACWY	Menactra®, Menveo™, Nimenrix®
Men-C-C	Men-C-C - Meningococcal - Conjugate C	NeisVac-C®, Menjugate®
MMR	MMR - Measles, Mumps, Rubella	M-M-R®II, Priorix®
MMRV	MMRV - Measles, Mumps, Rubella, Varicella	Priorix-Tetra®, ProQuad™
Pneu-C-13	Pneu-C-13 - Pneumococcal Conjugate 13 Valent	Prevnar® 13
Pneu-P-23	Pneu-P - Pneumococcal - Polysaccharide 23 Valent	Pneumovax® 23
Rab	Rab - Rabies (Purified Chick Embryo Cell), Rab - Rabies Vaccine Inactivated (Diploid Cell)	RabAvert®, Imovax® Rabies
Rot-1	Rot-1 - Rotavirus	Rotarix®
Rot-5	Rot-5 - Rotavirus	Rota Teq®
Td	Td - Diphtheria, Tetanus - Adult	Td Adsorbed
Tdap	Tdap - Tetanus, Diphtheria, Acelluar Pertussis	Adacel®, Boostrix®
Tdap-IPV	Tdap-IPV - Tetanus, Diphtheria, Acelluar Pertussis, Inactivated Poliomyelitis (Adult)	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®

Vaccine abbreviations	"Agent" values in iPHIS (as of April 1, 2013)	Product/trade name currently marketed in Canada
Typh-O	Typh-O - Typhoid Oral	Vivotif®
Var	Var - Varicella	Varilrix®, Varivax® III
YF	YF - Yellow Fever	YF-VAX®
Zos	Zos - Zostavax[1]	Zostavax® II

Notes:

1. As of February 2018, Zos agent values in iPHIS were updated to distinguish between the live virus (Zos (LZV) – live virus zoster vaccine) and non-live recombinant vaccines (Zos (RZV) – recombinant zoster vaccine).

Appendix 2: Adverse Event Values in iPHIS and Corresponding Categories for Analysis

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

Adverse event category used in current analysis	Adverse event name used in current analysis	Current "Adverse event reaction(s)" values in iPHIS (as of January 1, 2013)	Former "Adverse event reaction(s)" values in iPHIS (Jan. 1–Dec. 31, 2012)
Neurologic events	Acute disseminated encephalomyelitis (ADEM)	Acute disseminated encephalomyelitis (ADEM)	Acute disseminated encephalomyelitis
Systemic events	Adenopathy/ lymphadenopathy	Adenopathy/ lymphadenopathy	Lymphadenitis
Allergic events	Allergic reaction - skin	Allergic reaction - skin	Allergic reaction – dermatologic/mucosa
Allergic events	Allergic reaction - other	N/A	Allergic reaction – gastrointestinal[1] Allergic reaction - cardiovascular[1]
Neurologic events	Anaesthesia/ paraesthesia	Anaesthesia/ paraesthesia[2]	N/A
Allergic events	Event managed as anaphylaxis	Event managed as anaphylaxis	Anaphylaxis – cardiovascular Anaphylaxis – dermatologic/mucosal Anaphylaxis – gastrointestinal Anaphylaxis – respiratory
Systemic events	Arthritis/arthralgia	Arthritis/arthralgia	Arthritis – joint redness Arthritis – joint swelling Arthritis – sensation of warmth over joint
Neurologic events	Bell's palsy	Bell's palsy	Bell's palsy

Adverse event category used in current analysis	Adverse event name used in current analysis	Current "Adverse event reaction(s)" values in iPHIS (as of January 1, 2013)	Former "Adverse event reaction(s)" values in iPHIS (Jan. 1–Dec. 31, 2012)
Injection site reactions	Cellulitis	Cellulitis	Cellulitis
Neurologic events	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
Neurologic events	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

Adverse event category used in current analysis	Adverse event name used in current analysis	Current "Adverse event reaction(s)" values in iPHIS (as of January 1, 2013)	Former "Adverse event reaction(s)" values in iPHIS (Jan. 1–Dec. 31, 2012)
			present, provide details in seizure section)
Systemic events	Fever in conjunction with another reportable event	Fever in conjunction with another reportable event	Fever ≥38°C
Neurologic events	Guillian-Barré syndrome (GBS)	Guillian-Barré syndrome (GBS)	Guillian-Barré syndrome (GBS)
Systemic events	Hypotonic-hyporesponsive episode (HHE)	Hypotonic-hyporesponsive episode (HHE)	Hypotonic-hyporesponsive episode – limpness Hypotonic-hyporesponsive episode – pallor/cyanosis Hypotonic-hyporesponsive episode – reduced responsiveness/unresponsiveness
Injection site reactions	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
Systemic events	Intussusception	Intussusception	Intussusception
Neurologic events	Meningitis	Meningitis	Meningitis
Neurologic events	Myelitis	Myelitis	Myelitis Acute transverse myelitis
Injection site reactions	Nodule	Nodule	Nodule (discrete, well-demarcated, firm soft tissue mass or lump)
Allergic	Oculorespiratory	Oculorespiratory	ORS – bilateral red eyes

Adverse event category used in current analysis	Adverse event name used in current analysis	Current "Adverse event reaction(s)" values in iPHIS (as of January 1, 2013)	Former "Adverse event reaction(s)" values in iPHIS (Jan. 1–Dec. 31, 2012)
events	syndrome (ORS)	syndrome (ORS)	ORS – facial oedema ORS – respiratory symptoms
Other severe/ unusual events	Other severe/ unusual events	Other severe/unusual events	Other severe/unusual events Optic neuritis Autoimmune hepatitis Allergic reaction – respiratory
Injection site reactions	Pain/redness/ swelling lasting less than 4 days	N/A	Severe pain – lasting fewer than 4 days[1] Severe swelling – lasting fewer than 4 days[1]
Injection site reactions	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
Injection site reactions	Pain/redness/ swelling (extending beyond nearest joint)	Pain/ redness/swelling (extending beyond nearest joint)	Severe swelling – extending past nearest joint(s)
Neurologic events	Paralysis other than bell's palsy	Paralysis	Paralysis other than bell's palsy
Systemic events	Parotitis	Parotitis	Parotitis
Systemic events	Persistent crying/screaming	Persistent crying/screaming	Screaming episode/persistent crying
Systemic events	Rash	Rash	Rash – generalized Rash – localized at injection site Rash – localized at non-injection site

Adverse event category used in current analysis	Adverse event name used in current analysis	Current "Adverse event reaction(s)" values in iPHIS (as of January 1, 2013)	Former "Adverse event reaction(s)" values in iPHIS (Jan. 1–Dec. 31, 2012)
Systemic events	Severe vomiting/diarrhea	Severe vomiting/diarrhea[2]	N/A
Injection site reactions	Sterile abscess	Abscess at the injection site (sterile)	Sterile abscess – non-purulent fluid
Systemic events	Syncope with injury	Syncope with injury[2]	N/A
Systemic events	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 3: Changes to the Publicly-Funded Immunization Programs in Ontario (2010-17)

Time period	Vaccine program changes

September 2017	• HPV9
	  • Replacement of HPV-4 with HPV-9 for the school-based immunization program: two-dose HPV9 school-based program offered to Grade 7 students
	  • HPV9 vaccine eligibility until the end of Grade 12 for Grade 7 students who did not receive or complete the HPV9 immunization series in Grade 7.
	  • Replacement of HPV-4 with HPV-9 for high risk males nine to 26 years of age who have not initiated their HPV4 immunization series
	• DTaP-IPV discontinued and DTaP-IPV-Hib eligibility is expanded to all children five to six years of age who have not completed their primary immunization vaccine series with diphtheria, tetanus, pertussis and polo
	• As a result of DTaP-IPV discontinuation, Hib routine eligibility is expanded to children five to six years of age.
	• Fluad® is no longer publicly-funded for seniors

September 2016	• HPV4
	  • Two-dose HPV4 school-based program moved to Grade 7 (from Grade 8) for 2016-17 school year and expanded to males, as well as females (previously only girls in Grade 8 were eligible); program also offered to Grade 8 females during same school year
	  • Vaccine series publicly-funded for high risk males nine to 26 years old
	• Zoster vaccine for individuals 65 to 70 years of age and one time catch-up in 2016 for individuals born in 1945

September 2015	• Addition of quadrivalent influenza vaccine (inactivated and live attenuated) to the Universal Influenza Immunization Program (UIIP) for children ages six months to 17 years and two to 17 years, respectively • HPV4 program for Grade 8 girls switched from a three-dose to a two-dose schedule
December 2014	• Meningococcal B vaccine for high risk children aged two months to 17 years • Meningococcal ACYW vaccine; for high risk individuals nine months to 55 years of age (previously two to 55 years); booster doses and expanded high risk criteria • One dose of pertussis (Tdap) vaccine for all adults ≥18 years of age,

Time period	Vaccine program changes
	regardless of whether Tdap was received in adolescence • Pneumococcal conjugate 13 vaccine for high risk individuals ≥50 years of age
September 2012	• Extended HPV4 vaccine eligibility until the end of Grade 12 for girls who did not receive or complete the three-dose HPV immunization series in Grade 8. • One-time HPV 4 catch-up from Sept. 2012 to June 30, 2014 for females who were in Grade 8 during 2007/08 school year who have received at least one dose by June 30, 2013; could complete the series by June 30, 2014
May 2012	• Replacement of DTaP-IPV (Quadracel®) with Tdap-IPV (Adacel-IPV®, Boostrix®-Polio) for the four- to six-year-old booster dose
September 2011	• New influenza vaccine products implemented for Universal Influenza Immunization Program including Fluad® (for high-risk persons 65 years of age and older) and Agriflu® for all those aged six months and older, as well as a full dose of trivalent influenza vaccine (TIV) for infants and children six to 35 months of age and removal of egg allergy as a contraindication to TIV
August 2011	• Rotavirus vaccine (Rot-1/Rotarix®) for infants at ages two and four months • Routine second dose of varicella vaccine administered as the combined agent MMRV at four to six years of age (previously second dose of MMR vaccine was administered at 18 months of age) • Second dose varicella vaccine catch-up program for children born on or after January 1, 2000 and at least four years of age • Pertussis vaccine for all adults 19 to 64 years of age who have not received an adolescent booster at 14 to 16 years of age • Hib vaccine for high risk individuals ≥5 years of age • Pneu-C-13 vaccine one time catch-up in 2011 for low-risk children <3 years of age and high risk children <5 years of age with completed series of Pneu-C-7 and/or Pneu-C-10
January 2011	• Catch-up program: Grade 7 students who missed one or both doses of the hepatitis B vaccine can complete the series by the end of Grade 8.
November 2010	• Replacement of Pneu-C-10 (Synflorix™) with Pneu-C-13 (Prevnar® 13), which resulted in the reduction from four to three doses of pneumococcal conjugate vaccine for low-risk children

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