



# Canadian Adverse Events Following Immunization Surveillance System (CAEFISS): Technical annex for annual vaccine safety reports—Supplemental material

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## Purpose

The purpose of this technical annex is to provide detailed information on the Canadian Adverse Events Following Immunization Surveillance System (CAEFISS) and the processes undertaken to produce the Vaccine Safety Annual Report 2018–2019 as well as other surveillance-related products. Information included in this Supplemental consists of information on CAEFISS, the Canada Vigilance Program, the Vaccine Vigilance Working Group, as well as the methods and analysis employed to produce annual reports. Also included in this Supplemental are vaccine safety definitions, limitations and tables on the following: 1) vaccine abbreviations and marketed product/trade names; 2) Medical Case Review (MCR) of adverse events following immunization (AEFI) categories/sub-categories in CAEFISS for analysis; and 3) severity classification for primary AEFI in the MCR.

## Background

### Canadian Adverse Events Following Immunization Surveillance System

The CAEFISS is a federal/provincial/territorial public health post-market vaccine safety surveillance system. Its primary objectives are as follows: 1) to continuously monitor the safety of marketed vaccines in Canada (see **Table A1** in **Appendix**); 2) to identify increases in the frequency or severity of previously identified vaccine-related reactions; 3) to identify previously unknown AEFIs that could possibly be related to a vaccine; 4) to identify areas that require further investigation and/or research; and 5) to provide timely information on AEFI reporting profiles for vaccines marketed in Canada that can help inform immunization programs and guidelines (1).

Adverse events following immunization reported to CAEFISS have a temporal association (i.e., occurs following receipt of

vaccine) with a vaccine and have no other clear cause at the time of reporting. A causal relationship between immunization and the event that follows does not need to be proven and submitting a report does not imply or establish causality. Sometimes the vaccinee's medical history, recent disease, concurrent illness/condition and/or concomitant medication(s) can explain the event(s) (2).

In addition, AEFIs which meet one or more of the seriousness criteria and are unexpected regardless of seriousness (please see definition of "serious adverse event" and "unexpected adverse event" in section "key definitions") are also reported to CAEFISS.

Submitted AEFI reports that are accepted into the CAEFISS database must include the following:

- At least one active immunizing agent (vaccine)
- At least one AEFI and/or an indication of an immunization error
- The name of the province/territory or any other AEFI reporting source (e.g., Department of National Defence, Immunization Monitoring Program ACTIVE, IMPACT)

Submitted reports that are excluded from the CAEFISS database are as follows:

- Where an active immunizing agent has **NOT** been administered (e.g., the subject has **only** received a passive immunizing agent and/or a diagnostic agent and/or a drug product)
- Where an AEFI has **NOT** been indicated in the report
- When reports of phase I–III clinical trials involving investigational vaccines are received
- Where immunization took place outside of Canada (excluding military bases)
- Publication/literature reports
- When vaccines are obtained through Health Canada's Special Access Program



The submission of AEFI reports to CAEFISS is a collaborative process that includes passive as well as active surveillance. Passive surveillance is initiated at the local public health level and relies on reporting of AEFIs by healthcare providers, vaccine recipients or their caregivers. Completed reports are sent to provincial/territorial health authorities where population level public health actions as well as ongoing evaluation of immunization programs take place. Reporting of AEFIs to public health authorities has become mandatory in most provinces and territories in Canada, where reporting is covered using public health policies and practice. These reports are then submitted on a voluntary basis to the Public Health Agency of Canada (PHAC) for inclusion into the CAEFISS database (1). Provincial/territorial health authorities also receive reports from federal authorities that provide immunization within their jurisdiction (including First Nations and Inuit Health Branch, Correctional Services Canada and Royal Canadian Mounted Police). Any AEFIs received by National Defence and the Canadian Armed Forces are reported directly to PHAC. On rare occasions, AEFI reports are submitted to PHAC directly from physicians, pharmacists, travel clinics and the public. These reports are entered into CAEFISS and a copy and/or reporter information is sent to the health authorities of provincial/territorial origin.

Active surveillance has been conducted by the Canadian IMPACT since 1991. IMPACT is a paediatric, hospital-based network funded by PHAC and administered by the Canadian Paediatric Society (3). This network currently includes 12 paediatric centres across Canada, where nurses under the supervision of paediatric and/or infectious disease medical specialists screen hospital admissions for target AEFIs, including neurologic events (e.g., seizures, Guillain-Barré syndrome), thrombocytopenia, intussusception, vasculitides, and other complications that may have followed vaccination and which led to a hospital admission (4,5).

### Canada Vigilance Program

Health Canada's [Canada Vigilance Program](#) is a post-market surveillance program that collects and assesses reports of suspected adverse reactions to health products marketed in Canada, which includes vaccines. Market Authorization Holders (MAH) are required to report serious adverse events following immunization to the Canada Vigilance Program. From 1987 through 2010, MAHs also reported to PHAC. In January 2011, a change in reporting regulations required MAHs to begin reporting AEFIs directly to the Canada Vigilance Program. The MAHs gradually stopped reporting to CAEFISS by 2014. All MAH reports are therefore excluded from annual reports produced by PHAC; when MAH reports were sent to PHAC, they accounted for 0.6% of all AEFI reports received. The Canada Vigilance Program also receives voluntary reports from healthcare professionals and consumers.

### Vaccine Vigilance Working Group

In Canada, healthcare providers, manufacturers and the public each have a role to play in vaccine pharmacovigilance (6). Federal/provincial/territorial public health officials monitor vaccine safety through the Vaccine Vigilance Working Group. This network includes representatives from all federal/provincial/territorial immunization programs across the country as well as PHAC, Health Canada regulators and the IMPACT active surveillance program. The working group reports to the Canadian Immunization Committee and its activities include the following: 1) preparing national guidelines and procedures for monitoring of AEFIs in Canada; 2) providing a national forum to identify, share and promote best practices regarding vaccine pharmacovigilance; and 3) providing a national vaccine safety sentinel network that can rapidly share and disseminate information to appropriate stakeholders regarding vaccine safety issues or signals (6).

## Canadian Adverse Events Following Immunization Surveillance System report processing and definitions

### Report processing

The AEFI reports have their personal identifiers removed by the reporting authority and are submitted to PHAC where they are recorded into the CAEFISS database (2). The recording process includes data entry, quality assurance to resolve data discrepancies and identification and reconciliation of duplicate reports. Identified serious adverse events (SAE) are prioritized for processing. All reported AEFI information and medical interventions are coded using the International Medical Dictionary for Regulatory Activities, and concomitant treatment and medications are coded using the international Anatomical Therapeutic Chemical Classification System (7,8). This is followed by a systematic MCR by trained health professionals to classify each AEFI report by assigning the single most important reason for reporting (primary AEFI) (see **Table A2** in Appendix). Findings are then communicated to the appropriate stakeholders for any necessary action.

### Definitions

**Active surveillance:** Active surveillance refers to surveillance of targeted AEFIs at selected sentinel sites. In CAEFISS, active surveillance involves nurse monitors from IMPACT who, under the supervision of paediatric and/or infectious disease medical specialists, actively screen hospital admissions for target AEFIs. This may require chart review and consultation with the treating physician, a family member and the child's family doctor, or contact with the province or territory (4,5).

**Adult vaccines:** Adult vaccines include vaccines given to adults aged 18 years and older. Please refer to Provincial and Territorial Routine Vaccination Programs for Healthy, Previously Immunized



Adults on the Government of Canada's website for specific provincial/territorial immunization schedules (9).

**Adverse event following immunization:** An AEFI is defined as any untoward medical occurrence that follows immunization but which does not necessarily have a causal relationship with the administration of the vaccine. The adverse event may be a sign, symptom or a defined illness (10).

**Life-threatening:** The term "life-threatening" in the definition of "serious" refers to an event/reaction in which the patient was at risk of death at the time of the event/reaction; it does not refer to an event/reaction that hypothetically might have caused death if it were more severe (7).

**Market Authorization Holder:** Also referred to as Sponsor or Manufacturer, the MAH is the legal entity that holds the Notice of Compliance, the Drug Identification Number, the medical device licence number or the product licence number, or that has received approval to initiate clinical trials in Canada (11).

**Medical Case Review:** A MCR is performed by trained health professionals to classify each AEFI report by assigning the single most important reason for reporting (primary AEFI). The process involves reviewing each individual AEFI report to prioritize and standardize review of SAEs and facilitate the detection of unexpected events and increases in frequency of expected events. When necessary, follow up to the reporting province/territory also assists with data completeness. Findings are then communicated to the appropriate stakeholders for any necessary action.

**Passive surveillance:** Passive surveillance is the spontaneous reporting of AEFIs from healthcare providers, vaccine recipients or their caregivers to the local public health level. From there reports are sent to province/territory health authorities and then voluntarily sent to PHAC for inclusion into CAEFISS.

**Primary adverse event following immunization:** Primary AEFI is the single most important reason for reporting and is assigned through a systematic MCR process by a trained health professional at PHAC. For MCR classification, national case definitions are used where available, including CAEFISS User Guide definitions for Oculo-Respiratory syndrome, Bell's palsy, arthritis, parotitis, anaesthesia and paraesthesia, and published Brighton Collaboration case definitions for fever, cellulitis at injection site, abscess at injection site, anaphylaxis, encephalitis, myelitis, and acute disseminated encephalomyelitis, aseptic meningitis, Guillain-Barré syndrome and Fisher syndrome, generalized convulsive seizure, hypotonic-hyporesponsive episode, intussusception, persistent crying, rash, thrombocytopenia and unexplained sudden death including sudden infant death syndrome (2,12–25). It involves assessing all reported AEFI information and classifying the report by primary AEFI and severity.

**Publicly funded vaccine:** Publicly funded vaccines are offered for free by province/territories and vary from province/territory to province/territory. Please refer to the publicly funded vaccines in Canada on the Government of Canada's website for more information (26).

**Routine infant and early childhood vaccine:** Routine infant and early childhood vaccines include those given to children who are younger than seven years of age. As immunization schedules vary across provinces/territories, please refer to Canada's Provincial and Territorial Routine (and Catch-up) Vaccination Routine Schedule Programs for Infants and Children on the Government of Canada's website for more information (27).

**School-based vaccine:** School-based vaccines include those given to children aged seven years to younger than 18 years of age. Please refer to Canada's Provincial and Territorial Routine (and Catch-up) Vaccination Routine Schedule Programs for Infants and Children on the Government of Canada's website for specific province/territory immunization schedules for more information (27).

**Serious adverse event:** A SAE is identified based on the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use as an event that results in death, is life-threatening, requires in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity or a congenital anomaly/birth defect. Any medical event that may not be immediately life-threatening but requires intervention to prevent one of the outcomes listed above may also be considered as serious (7).

**Sudden infant death syndrome:** Sudden infant death syndrome is the sudden unexpected death of an infant younger than one year of age (older than 21 days but younger than nine months of age), with onset of the fatal episode apparently occurring during sleep and that remains unexplained after a thorough investigation, including the performance of a complete autopsy and review of the circumstances of death and the clinical history (25).

**Sudden unexpected/unexplained death syndrome:** Sudden unexpected/unexplained death syndrome refers to the unexpected death of a child in the first or second year of life (25).

**Surveillance:** Surveillance is defined as the ongoing, systematic collection, analysis, interpretation and dissemination of data to enable decision-making and action to protect the health of populations (28).

**Temporal association:** Temporal association is an adverse event that occurs within a given timeframe following the administration of a vaccine. Temporal association could be purely coincidental and further assessments are required before a causal link is assigned.



**Temporal criteria:** Temporal criteria are the timelines between vaccination and the occurrence of an adverse event. Please see the CAEFISS User Guide for temporal criteria for specific adverse events (2).

**“Unexpected” adverse event following immunization:** An “unexpected” AEFI is an adverse event whose nature, severity or outcome is not consistent with the term or description used in the approved Product Monograph (6).

**Vaccine:** A vaccine is a biological preparation that improves immunity to a particular disease. In addition to the antigen, it contains multiple components (excipients) and each component may have unique safety implications (28).

**Vaccine pharmacovigilance:** Vaccine pharmacovigilance is the science and activities relating to the detection, assessment, understanding and communication of AEFI and other vaccine or immunization-related issues, and to the prevention of untoward effects of the vaccine or immunization (28).

**Vaccine safety:** Vaccine safety is the process that maintains the highest efficacy and lowest adverse reaction of a vaccine by addressing its production, storage and handling. Vaccine safety is a part of immunization safety (28).

**Vaccine safety signal:** A vaccine safety signal is defined as information (from one or multiple sources) that suggests a new and potentially causal association, or a new aspect of a known association, between an intervention and an adverse event or set of related adverse events, that is judged to be of sufficient likelihood to justify verificatory action (28).

## Data extraction and analysis

All AEFI reports submitted and accepted into the CAEFISS database by April 30 of the publication year, with a date of vaccine administration from January 1 through December 31 of the previous calendar year, are included in the annual reports. In addition, all AEFI reports following vaccines administered from the previous 11 years are included to assess trends over time. Data is extracted from the CAEFISS database in May/June of the publication year.

The extracted AEFI reports are assessed for quality before analysis. Where necessary, further information is solicited from the reporting jurisdiction for incomplete AEFI reports. Duplicate reports are deleted from the CAEFISS database.

Descriptive analyses are conducted using SAS EG 7.1 and Microsoft Excel 2016. Calculations are presented for all vaccines combined and by specific vaccine categories. They include rates by doses distributed, type of surveillance, primary reason for reporting, primary AEFI by seriousness and health care

utilization and outcome for vaccines administered. Sex and age-specific rates are calculated using population estimates as the denominator. Missing data are excluded from the calculations.

Negative binomial regression is used to assess trends over time for overall AEFIs. The  $p$ -values less than 0.05 are considered statistically significant. Type of regression analysis is based on goodness of fit testing.

## Adverse event following immunization reporting rates

The AEFI reporting rates are calculated using vaccine doses distributed data without adjustment for doses returned or wastage as the denominator where possible. Information on total vaccine doses distributed (publicly and privately funded) is provided to PHAC by the MAHs and is considered proprietary information. Statistics Canada annual population estimates are used when a doses distributed-based rate cannot be calculated (29).

The AEFI reporting rates are calculated using doses distributed as a proxy measure and expressed as the number of AEFIs per 100,000 doses distributed per year. Population estimates are used as a denominator when information on doses distributed are not available. Rates using population estimates are calculated by dividing the number of AEFI reports by the population for the same calendar year. The rate is expressed as the number of AEFIs per 100,000 population per year. Population-based rates are for demographic analysis (i.e., age- and sex-specific rates).

It is important to note that the AEFI rates calculated should not be interpreted as AEFI incidence rates. The CAEFISS collects AEFI information on individuals for whom an AEFI report was submitted, not on the total number of individuals who experience an adverse event, as not every adverse event is reported. In addition, CAEFISS does not have information on the total number of individuals vaccinated, thus making the calculation of an incidence rate unfeasible.

## Limitations of adverse event following immunization surveillance

Passive surveillance for AEFIs is subject to limitations such as underreporting, lack of certainty regarding the diagnostic validity of a reported event, missing information regarding other potential causes such as underlying medical conditions or concomitant medications and the differing AEFI reporting practices by jurisdictions within Canada, as not all AEFIs are reportable in all jurisdictions (i.e., vaccination errors, minor local reactions, syncope, etc.), possibly leading to over or under-reporting of milder AEFIs from some provinces/territories. Despite these limitations, passive surveillance is useful for



detecting potential vaccine safety signals that can be further investigated and verified. Seasonality was not analyzed as a potential variable in this report.

There are also limitations associated with active surveillance. IMPACT uses predetermined AEFI targets (e.g., seizure), which may limit its ability to identify new adverse reactions to immunizations. In addition, while IMPACT covers 90% of Canada's tertiary care paediatric beds and hospital admissions, its focus is on admitted paediatric cases, which means less serious AEFIs may not be detected (4,5). Despite these limitations, IMPACT fulfills an important role in vaccine safety surveillance by actively identifying targeted serious AEFIs in the paediatric population.

In addition, the number of doses administered in the population is not available at the national level; therefore, the denominator used in rate calculations is either 1) doses distributed or 2) population statistics. The use of doses distributed as the denominator can underestimate rates, as they do not take wastage into account. Furthermore, doses distributed in one year may not be administered in that same year, further limiting the accuracy of the doses distributed denominator. Despite these limitations, a doses distributed-based denominator for rate calculations was used when possible in this report as a population-based denominator assumes similar distribution of vaccine doses across population subgroups, and this may not be true in all cases.

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## Appendix

**Table A1: Vaccine abbreviations and marketed product/trade names, 2018–2019**

Vaccine	Trade name	Abbreviation	MAH <sup>a</sup>
Cholera – <i>Escherichia coli</i> – Oral	Dukoral®	Chol-Ecol-O	VAL
Diphtheria and tetanus toxoids, acellular pertussis vaccine adsorbed	Infanrix™	DTaP	GSK
	Tripacel®		SP
Combined diphtheria and tetanus toxoids, acellular pertussis, Hepatitis B (recombinant), inactivated poliomyelitis and adsorbed conjugated <i>Haemophilus influenzae</i> type b	Infanrix hexa™	DTaP-HB-IPV-Hib	GSK
Combined diphtheria and tetanus toxoids, acellular pertussis, Hepatitis B (recombinant), inactivated polio	Pediarix™	DTaP-HB-IPV	GSK
Diphtheria and tetanus toxoids, acellular pertussis, <i>Haemophilus influenzae</i> type b	ACTacel®	DTaP-Hib	SP
	ACTacel® Hybrid		GSK
	Infanrix™-Hib		
Diphtheria and tetanus toxoids adsorbed, combined with inactivated poliomyelitis vaccine	Infanrix™-IPV	DTaP-IPV	GSK
	Quadracel®		SP
Diphtheria and tetanus toxoids and acellular pertussis vaccine adsorbed, combined with inactivated poliomyelitis vaccine and <i>Haemophilus influenzae</i> type b conjugate vaccine	Infanrix™-IPV/Hib	DTaP-IPV-Hib	GSK
	Pediacel®		SP
	Pentacel®		
Hepatitis A	Avaxim®	HA	SP
	Avaxim® – Pediatric		GSK
	Havrix® 1440		
	Havrix® 720 (Junior)		
	Vaqta®		Merck
Hepatitis A and B	Twinrix®	HAHB	GSK
	Twinrix® Junior		
Hepatitis – typhoid	ViVAXIM™	HA-Typh-I	SP
Hepatitis B (recombinant), thimerosal free	Engerix® -B	HB	GSK
	Engerix® -B (Pediatric dose)		
	Recombivax HB®		Merck
	Recombivax HB® (Dialysis)		
<i>Haemophilus influenzae</i> type b conjugate	ACT-HIB®	Hib	SP
	Hiberix®		GSK
Quadrivalent human papillomavirus (types 6, 11, 16, 18) recombinant vaccine	Gardasil®	HPV-4	Merck
Human Papillomavirus 9-valent Vaccine, Recombinant	Gardasil® 9	HPV-9	Merck



Table A1: Vaccine abbreviations and marketed product/trade names, 2018–2019 (continued)

Vaccine	Trade name	Abbreviation	MAH <sup>a</sup>
Human Papillomavirus (Types 16 and 18)	Cervarix™	HPV-2	GSK
Influenza vaccine – inactivated (split virus)	Fluviral®	Inf	GSK
	Vaxigrip®		SP
Influenza vaccine – inactivated (subunit)	Influvac®	Inf	BGP
	Agriflu®		SEQ
	Fluad Pediatric®		
	Fluad®		
Influenza vaccine, quadrivalent – inactivated (split virus)	Flulaval® Tetra	Inf	GSK
	Fluzone® Quadrivalent		SP
Influenza vaccine – inactivated (split virus)	Fluzone® High-Dose	Inf	SP
Influenza vaccine (live, attenuated)	Flumist® Quadrivalent	Inf	AZC
Inactivated poliomyelitis	Imovax® Polio	IPV	SP
Japanese encephalitis	IXIARO®	JE	VAL
Multicomponent meningococcal B vaccine (recombinant, adsorbed)	Bexsero	Men-B	GSK
	Trumenba™		Pfizer
Meningococcal – conjugate	Menjugate®	Men-C-C	GSK
	Neis Vac-C®		Pfizer
	Menactra®	Men-C-ACYW-135	SP
	Menveo™		GSK
	Nimenrix™		Pfizer
Measles, Mumps and Rubella	M-M-R® II	MMR	Merck
	Priorix®		GSK
Measles, Mumps, Rubella and Varicella	Priorix-Tetra™	MMR-Var	GSK
	ProQuad™		Merck
Pneumococcal – conjugate – valent	Prenar®	Pneu-C-7	Pfizer
	Synflorix™	Pneu-C-10	GSK
	Prenar® 13	Pneu-C-13	Pfizer
Pneumococcal – Polysaccharide – valent	Pneumovax® 23	Pneu-P-23	Merck
Rabies	Imovax® Rabies	Rab	SP
	RabAvert®		GSK
Rotavirus	Rotarix™	Rot-1	GSK
	RotaTeq®	Rot-5	Merck
Tetanus toxoid, diphtheria	Td Adsorbed	Td	SP
Tetanus toxoid, reduced diphtheria toxoid and acellular vaccine adsorbed	Adacel®	Tdap	SP
	Boostrix™		GSK
Tetanus toxoid, reduced diphtheria toxoid and acellular vaccine adsorbed combined with inactivated poliomyelitis vaccine	Adacel® – Polio	Tdap-IPV	SP
	Boostrix® – Polio		GSK
Tetanus and diphtheria toxoids, inactivated poliomyelitis vaccine	Td Polio Adsorbed	Td-IPV	SP
Typhoid – injection	Typhim Vi®	Typh-I	SP
Typhoid vaccine live oral attenuated TY21A	Vivotif® (capsules)	Typh-O	CV
Varicella	Varilrix®	Var	GSK
	Varivax® III		Merck
Yellow Fever	YF-Vax®	YF	SP
Herpes Zoster vaccine (non-live recombinant)	Shingrix	RVZ	GSK
Live, attenuated virus varicella-zoster vaccine	Zostavax® II	LVZ	Merck

Abbreviations: AZC, AstraZeneca Canada; BGP, BGP Pharma Inc.; CV, Crucell Vaccines Inc.; GSK, Glaxo Kline Smith; MAH, Marketing Authorization Holder; Merck, Merck Canada; Pfizer, Pfizer Canada; SEQ, Seqirus Canada; SP, Sanofi Pasteur; VAL, Valneva Canada

<sup>a</sup> Marketing Authorization Holder distributes the vaccine, and may be different from the manufacturer



**Table A2: Primary adverse event following immunization categories and sub-categories**

Primary AEFI	Primary AEFI sub-category
Allergic or allergic-like events	Anaphylaxis
	Other allergic events <sup>a</sup>
	Oculo-respiratory syndrome (ORS)
Infection/syndrome/systemic symptoms (ISS)	Fever only
	Infection
	Influenza-like illness (ILI)
	Rash with fever and/or other illness
	Syndrome as indicated in AEFI reports (e.g., Kawasaki)
	Systemic (when several body systems are involved)
Neurologic events	Aseptic meningitis
	Ataxia/cerebellitis <sup>b</sup>
	Bell's palsy
	Encephalitis/Acute disseminated encephalomyelitis (ADEM)/myelitis
	Guillain-Barré syndrome (GBS)
	Other paralysis lasting more than 1 day
	Seizure
	Other neurologic event <sup>c</sup>
Rash alone	Generalized
	Localized
	Location not specified/extent unknown
Immunization anxiety	Presyncope
	Syncope
	Other anxiety-related event <sup>d</sup>
Vaccination site reactions	Abscess (infected or sterile)
	Cellulitis
	Extensive limb swelling (ELS) <sup>e</sup>
	Pain in the vaccinated limb of 7 days or more
	Other local reaction <sup>f</sup>
Vaccination error	Vaccination error
Other	Arthralgia
	Arthritis
	Gastrointestinal event
	Hypotonic-hyporesponsive episode (HHE)
	Intussusception
	Anaesthesia/paraesthesia
	Parotitis
	Persistent crying
	Sudden infant death syndrome (SIDS)
	Sudden unexpected/unexplained death syndrome (SUDS)
	Thrombocytopenia
Other event <sup>g</sup>	

Abbreviation: AEFI, adverse event following immunization

<sup>a</sup> "Other" includes, but is not limited to, hypersensitivity and urticarial

<sup>b</sup> "Cerebellar ataxia" is defined as sudden onset of truncal ataxia and gait disturbances. Of note, this assumes absence of cerebellar signs appearing with other evidence of encephalitis or Acute Disseminated Encephalomyelitis (ADEM), in which case it would be classified according to the Brighton-Collaboration case definition (28)

<sup>c</sup> "Other" includes, but is not limited to, seizure like phenomena and migraine

<sup>d</sup> "Other" includes, but is not limited to, dizziness and dyspnoea

<sup>e</sup> Extensive limb swelling of an entire proximal and/or distal limb segment with segment defined as extending from one joint to the next (29)

<sup>f</sup> "Other" includes, but is not limited to, vaccination site pain and vaccination site swelling

<sup>g</sup> "Other" includes, but is not limited to, lymphadenopathy and arthralgia



**Table A3: Severity classification for primary adverse event following immunization (AEFI) in the Medical Case Review**

Severity	Criteria
Serious	<ul style="list-style-type: none"> <li>Fatal outcome</li> <li>Results in hospitalization or prolongation of hospitalization for <math>\geq 24</math> hours</li> <li>Results in persistent or significant disability/incapacity</li> <li>Congenital anomaly or birth defect</li> <li>Life-threatening</li> </ul>
High Impact	<ul style="list-style-type: none"> <li>Results in hospitalization for <math>&lt; 24</math> hours</li> <li>Requires medically supervised observation outside of hospital</li> <li>Requires <math>\geq 3</math> separate physician assessments during acute AEFI episode</li> <li>Requires outpatient intravenous therapy (e.g., for antibiotics or rehydration)</li> <li>Prevents performance of daily activities for <math>\geq 4</math> days</li> </ul>
Moderate Impact	<ul style="list-style-type: none"> <li>Results in 1–2 unscheduled urgent or non-urgent physician assessments</li> <li>Requires emergency medical services to come to immunization clinic</li> <li>Results in a new drug prescription or increased dose of an existing drug</li> <li>Prevents performance of daily activities for 1–3 days</li> </ul>
Low Impact	<ul style="list-style-type: none"> <li>Requires treatment limited to immunization clinic setting by on-site staff</li> <li>Requires health professional advice/reassurance without a scheduled visit</li> <li>Requires non-prescription medication for symptomatic relief</li> <li>Prevents performance of daily activities for <math>&lt; 24</math> hours</li> <li>No discernible impact</li> </ul>

Abbreviation: AEFI, adverse event following immunization