

Safety Platform for Emergency vACcines



SPEAC COVID-19 AESI List and Related Resources

5.1.2e

5.1.2e



EU-EEA NITAG Collaboration
Webinar
COVID-19 Vaccine Safety – Feb 4,
2021

Talk Overview

1. **CEPI – Brighton – SPEAC: very brief project overview**
2. **Process behind COVID-19 AESI list**
3. **AESI related new Brighton case definitions – Plans / Timelines**
4. **AESI related resources and tools**
5. **Brighton website as a resource to download AESI case definitions and SPEAC tools**



This project has been funded in whole by CEPI

CEPI – Brighton – SPEAC: very brief project

overview

CEPI

Coalition for Epidemic Preparedness Innovations

- Multiple target pathogens: Lassa Fever, MERS, Nipah virus, Rift Valley Fever, Chikungunya and 'Disease X'
- Multiple vaccine platforms: Viral vectors (e.g. Measles, VSV, MVA, Chimpanzee adenovirus), DNA, RNA, molecular clamp, live attenuated, recombinant subunit
- Multiple sponsors each with their own approach

 Brighton
collaboration

 SPEAC

CEPI – Brighton – SPEAC: very brief project overview

CEPI

Coalition for Epidemic Preparedness Innovations

- Multiple target pathogens: Lassa Fever, MERS, Nipah virus, Rift Valley Fever, Chikungunya and 'Disease X'
- Multiple vaccine platforms: Viral vectors (e.g. Measles, VSV, MVA, Chimpanzee adenovirus), DNA, RNA, molecular clamp, live attenuated, recombinant subunit
- Multiple sponsors each with their own approach

 Brighton
collaboration

Brighton Collaboration

- Founded in 2000 with a goal to build trust in the safety of vaccines via rigorous science.
- Mission to develop internationally accepted standards for monitoring safety throughout the vaccine life cycle
- Has put out over 60 adverse event case definitions, guidance on collection and reporting vaccine safety data, several vaccine safety templates

 SPEAC

CEPI – Brighton – SPEAC: very brief project overview

CEPI

Coalition for Epidemic Preparedness Innovations

- Multiple target pathogens: Lassa Fever, MERS, Nipah virus, Rift Valley Fever, Chikungunya and 'Disease X'
- Multiple vaccine platforms: Viral vectors (e.g. Measles, VSV, MVA, Chimpanzee adenovirus), DNA, RNA, molecular clamp, live attenuated, recombinant subunit
- Multiple sponsors each with their own approach

 Brighton
collaboration

Brighton Collaboration

- Founded in 2000 with a goal to build trust in the safety of vaccines via rigorous science.
- Mission to develop internationally accepted standards for monitoring safety throughout the vaccine life cycle
- Has put out over 60 adverse event case definitions, guidance on collection and

 SPEAC

Safety Platform for Emergency vACcines

- Brighton project initiated in 2019, funded by CEPI, and operating under the umbrella of the Task Force for Global Health
- Aims to support CEPI's goal of high quality, standardized and harmonized evaluation of vaccine safety across their vaccine portfolio

SPEAC 'Toolbox'

- **Goals/Objectives:**
 - facilitate harmonized approach to safety data collection & assessment
 - anticipate vaccine safety issues that could arise during clinical trials
- **Step 1: define 'adverse events of special interest' (AESI) for each target disease based on landscape analyses/literature review**
 - Events associated with immunization in general; e.g. **anaphylaxis**
 - Events associated with specific vaccine platforms; e.g. **live vaccines: aseptic meningitis;**
 - Events associated with wild type target disease; related to viral replication and/or immunopathogenesis
- **Step 2: For each AESI, make available:**
 - Brighton case definitions if not yet published
 - Tools to facilitate harmonized approach to AESI data collection, investigation and assessment
 - Risk factors and background rates
 - ICD / MedDRA codes for AESI as a whole and key case definition terms

AESIs Related to Immunization +/- Vaccine Platforms

Group 1: relevant to vaccination in general and b) specific vaccine platforms

Body System	AESI	Rationale for Inclusion as an AESI
Neurologic	Generalized convulsion	1, 2, 4
	Guillain-Barré Syndrome (GBS)	2, 3
	Acute disseminated encephalomyelitis (ADEM)	3
Hematologic	Thrombocytopenia	1, 2
Immunologic	Anaphylaxis	1, 2
	Vasculitides	3
Other	Local/systemic SAEs (regulatory criteria)	1, 2

Group 1b: relevant to specific vaccine platforms

Body System	Vaccine Platform Specific AESIs	Rationale for Inclusion as an AESI
Neurologic	Aseptic meningitis Encephalomyelitis	1 (live viral vaccines)
Immunologic	Arthritis	2 (r-VSV platform)
Other	Myocarditis	2 (MVA platform)

1. Proven association with immunizations
2. Proven association with a vaccine platform and/or adjuvant relevant to CEPI vaccine development
3. Theoretical concern based on immunopathogenesis
4. Theoretical concern related to viral replication (for live-attenuated vaccines)
5. Theoretical concern because it has been demonstrated in an animal model with one or more candidate vaccines

Talk Overview

1. **CEPI – Brighton – SPEAC: very brief project overview**
2. **Process behind COVID-19 AESI list**
3. **AESI related new Brighton case definitions – Plans / Timelines**
4. **AESI related resources and tools**
5. **Brighton website as a resource source**



Process behind COVID-19 AESI list

Landscape Analysis for Target Disease Associated AESI

- **Process for Lassa Fever, MERS, Nipah, Rift Valley Fever, Chikungunya**
 - Identify 8-10 recent review articles (primary references)
 - Articles reviewed, summarized and AESI list created independently by two experts
 - Secondary references of interest identified from those cited in primary references
 - Seek consensus on AESI list
- **COVID-19 – emerging disease with evolving understanding of clinical features**
 - Initial AESI list developed in early February based on first reports out of China
 - Hospitalized patients reported by Huang(n=41), Chen(n=99), Guan(n=1099), Wang(n=138)
 - 44,672 confirmed cases reported by China CDC
 - daily screening of published reports in PubMed and input from SPEAC EB members to update list (May25)
 - May 27th: updated AESI list presented to and adopted by WHO Global Advisory Committee on Vaccine Safety

COVID-19 AESI List as presented to and adopted by GACVS in May 2020

	AESI (red font indicates existing case definition)	Rationale to include as an AESI ¹
1	Enhanced disease following immunization	1 FI measles & RSV, HIV; 2 Chimeric YF Dengue; 5 SARS / MERS-CoVs
2	Multisystem inflammatory syndrome in children	3, 4
3	Acute respiratory distress syndrome	3, 4
4	Acute cardiovascular injury (Microangiopathy, Heart failure, Stress cardiomyopathy, Coronary artery disease Arrhythmia, Myocarditis)	3, 4
5	Coagulation disorder (Thromboembolism, Hemorrhage)	3, 4
6	Acute kidney injury	3, 4
7	Generalized convulsion	1, 2
8	Guillain Barré Syndrome	3, 4
9	Acute liver injury	3, 4
10	Anosmia, ageusia	3, 4
11	Chilblain – like lesions	3, 4
12	Single Organ Cutaneous Vasculitis	3, 4
13	Erythema multiforme	3, 4
14	Anaphylaxis	1, 2
15	Acute aseptic arthritis	2 (r-VSV)
16	Meningoencephalitis	1
17	Acute disseminated encephalomyelitis	4
18	Thrombocytopenia	1, 2, 3, 4

Process behind COVID-19 AESI list

Unique to Landscape Analysis for COVID-19 AESI: Need to

- Following the May GACVS meeting, an ongoing process of systematic review was initiated
- Search term strategy adapted by adding 'exclusionary terms' to improve efficiency of review
 - All retrieved articles loaded into an excel spreadsheet and screened by 1 reviewer
 - Since the aim was to identify new entities associated with COVID-19, articles on already identified AESI were screened in for compilation purposes but not read in full
- 1st period: May 16 – August 8 : 4679 citations identified with 1980 (42.3%) screened in
 - A few new entities were flagged but no additions were made to the AESI list
- 2nd period: August 8 – Nov 9: 3901 citations identified with 2141 (55%) screened in
 - 3 new AESI were added to the list. All had been flagged in the 1st period and for each there were several new reports in the 2nd period
 - Subacute thyroiditis
 - Acute pancreatitis
 - Acute rhabdomyolysis
- The full report for both periods, along with the excel spreadsheet which lists all included citations and links to the articles can be downloaded from the Brighton website

Process behind COVID-19 AESI list

Unique to Landscape Analysis for COVID-19 AESI: Need to

update!

Recommendations from the 2nd period COVID update:

Add 3 new entities to the AESI list. Defer CD prioritization until search for existing international case definition but conduct literature search for background rates and identify ICD 9/10-CM and MedDRA codes

- **Subacute thyroiditis:** *multiple case reports with onset 2-8 weeks after COVID illness. Well known association with several other viral infections.*
- **Pancreatitis:** *at least 36 case reports affecting all age groups, male♀ can be COVID-presenting complaint, be concurrent, or occur later as part of multi-organ damage*
- **Rhabdomyolysis:** *at least 32 case reports affecting all ages but predominantly male (29:3); can be COVID-presenting complaint, be concurrent or onset during hospital course; clear association with acute kidney injury and failure*

Revise search strategy for 3rd Quarter review (due Mar 9): focus on still emerging evidence related to

- **Long term COVID complications** ('long-haul syndrome' & others),
- **Pregnancy & pediatric outcomes.**

• Also focus on more in depth review of existing citations regarding need for added cardiovascular CDs



Confidential · This project has been funded in whole by CEPI

Talk Overview

1. **CEPI – Brighton – SPEAC: very brief project overview**
2. **Process behind COVID-19 AESI list**
3. **AESI related new Brighton case definitions – Plans / Timelines**
4. **AESI related resources and tools**
5. **Brighton website as a resource source**



AESI related new Brighton case definitions – Plans / Timelines COVID-19 AESIs by Organization & Case Definition(CD)

System	AESI	SPEAC	CDCP	FDA	EMA
Neurologic	GBS				
	ADEM				
	Encephalitis / Myelitis / Encephalomyelitis				
	Aseptic meningitis				
	Generalized convulsion				
	Anosmia/ageusia				
	Bell's palsy				
	Narcolepsy/cataplexy				
	Other demyelinating diseases				
Immunologic	VAED				
	Anaphylaxis				
	Thrombocytopenia/ITP				
	Vasculitides				
	MIS-Child & Adult				
	Kawasaki disease				
	Arthritis				
	Non-anaphylactic allergic reactions				
Cardiologic	Myocarditis / pericarditis				
	Acute myocardial infarction				
	Other Cardiac(heart failure, stress cardiomyopathy, arrhythmia, coronary artery disease, microangiopathy)				

System	AESI	SPEAC	CDCP	FDA	EMA
Hematologic	Thrombosis / Thromboembolism (Stroke,DVT,PE)				
	Bleeding / DIC				
	Thrombotic thrombocytopenic purpura				
Respiratory	ARDS				
Dermatologic	Chilblain-like lesions				
	Erythema multiforme				
Other	Acute kidney injury				
	Acute liver injury				
	Acute pancreatitis				
	Acute appendicitis				
	Subacute thyroiditis				
	Rhabdomyolysis				
	Adverse pregnancy outcomes				
	Death(BCCDs: maternal/neonatal/fetal/ SUDS	*			

* Sudden death in >2 year olds

CD Published

CD in Press

CD submission soon

Not on AESI List

CD Working Group to Form

CD not yet started



Talk Overview

1. **CEPI – Brighton – SPEAC: very brief project overview**
2. **Process behind COVID-19 AESI list**
3. **AESI related new Brighton case definitions – Plans / Timelines**
4. **AESI related resources and tools**
5. **Brighton website as a resource source**



AESI related resources and tools

- **Resources:** using the published case definition and updating with recent review articles and systematic search for published background rates
 - **Risk Factors:** age, gender, genetics, geography, season, comorbidity, infections, vaccines, drugs
 - **Background rates:** by location, age, gender if available
- **Tools:** to facilitate gathering information needed to meet the Brighton case definition and to determine level of certainty
 - **Data abstraction and interpretation form:** for use in medical record review context
 - **Tabular checklist of key case definition criteria:** with rules to apply their value to determine level of certainty
 - **Pictorial decision tree algorithm:** alternate format to help to assess level of certainty based on available data



Talk Overview

1. **CEPI – Brighton – SPEAC: very brief project overview**
2. **Process behind COVID-19 AESI list**
3. **AESI related new Brighton case definitions – Plans / Timelines**
4. **AESI related resources and tools**
5. **Brighton website as a resource source**



We build trust in the safety of vaccines through rigorous science.

Brighton Collaboration is working diligently to fight the coronavirus disease (COVID-19) pandemic. For Brighton Collaboration resources and tools relevant to COVID-19, please click here!

www.brightoncollaboration.u



PAGES

- About
- News
- Publications & Tools
- Projects
- VSQ
- COVID-19
- Jobs
- Resources



MOST RECENT POSTS

- Webinar on Anaphylaxis to COVID-19 Vaccines
JANUARY 18, 2021 / 0 COMMENTS
- VSQ – Q1 2021
JANUARY 4, 2021 / 0 COMMENTS
- COVID-19 AESI List 2nd Quarterly Update (December 2020)
DECEMBER 30, 2020 / 0 COMMENTS

POSTS TRENDING TODAY

- Vaccine-associated Enhanced Disease: Case Definition and Guidelines...
35 views | posted on October 19, 2020
- Priority List of Adverse Events of Special Interest: COVID-19
36 views | posted on June 10, 2020
- SPEAC
15 views | posted on May 9, 2019

MOST VIEWED POSTS EVER

- Priority List of Adverse Events of Special Interest: COVID-19
4.2k views | posted on June 10, 2020
- Vaccine-associated Enhanced Disease: Case Definition and Guidelines...
2.8k views | posted on October 19, 2020
- SPEAC
1k views | posted on May 9, 2019

CONTACT INFO

- Address:**
The Task Force for Global Health, 330 W. Ponce de Leon Ave. Decatur, GA 30030
- Phone:**
1-404-371-0466
- Email:**
bc-coordinator@taskforce.org



project has been funded in whole by CEPI



Brighton Collaboration is working diligently to fight the coronavirus disease (COVID-19) pandemic.

The Coalition for Epidemic Preparedness Innovations (CEPI) has partnered with the Brighton Collaboration (BC), through the Task Force for Global Health (TFGH), to harmonize the safety assessment of CEPI-funded vaccines via its Safety Platform for Emergency vACcines (SPEAC) Project. SPEAC is creating resources and tools to facilitate COVID-19 vaccine safety clinical trials and pharmacovigilance. Each is described briefly below, along with a link to the specific content page for all AESI. Further information regarding availability for each AESI is provided at the content page.

All recent BC news, webinars, publications and related tools relevant for COVID-19 can be found by clicking [here](#).

To view a complete list of BC publications and related tools, please click here. Publications and related tools are organized in a Google spreadsheet that is sortable and filterable by each column. Direct clickable links to publication DOIs are provided.

For updated external repositories of publications for COVID-19 vaccine clinical trials, please click [here](#).

BC Resources and Tools Relevant for COVID-19:

COVID-19 AESI list: Literature Review and Quarterly Updates Documents that describe the methods, including search terms and references used to develop the May 2020 AESI list and quarterly updates (September 2020, December 2020, Mar&Jun2021).

Excel spreadsheet with updated citations, tabbed by AESI

www.brightoncollaboration.us

US

BC Resources and Tools Relevant for COVID-19

- COVID-19 AESI List – Lit review & Quarterly Updates
- Webinars
- BRAVATO Templates
- AESI Case Definitions
 - Already published BC Case Definitions
 - Draft BC Case Definitions
- Glossary of Terms
- AESI Case Definition Companion Guides
 - Risk Factors
 - Background Rates
 - Diagnosis, Data Analysis and Presentation
 - ICD-9/10-CM, MedDRA Codes
 - Data Abstraction & Interpretation Forms
 - Tabular Checklist & Level of Certainty Algorithm
- Pictorial Level of Certainty Algorithm

Confidential | Internal Use Only

Brighton Collaboration Publications

File Edit View Insert Format Data Tools Extensions Help Last edit was made on 18 November 2020 by Lisa Chun

100% \$ % .0 .00 123 10

A1

A	B	C	D	E	F	G	H	I	J
4	If you have any questions on how to use or navigate this spreadsheet, please contact bc-coordinator@taskforce.org								
6	Notification of newly added content will be noted on the Brighton Publications main page .								
9	How to use this spreadsheet:								
11	All Brighton Collaboration articles can be found under "PUBLICATIONS" tab, organized by publication types, (sub) categories.								
13	Source: Brighton Collaboration Case Definition Working Group (BC CD WG),								
14	Global Alignment of Immunization Safety Assessment in Pregnancy (GAIA),								
15	Viral Vector Vaccine Safety Working Group (V3SWG), Brighton Collaboration (BC)								
16	BC Global Research in Paediatrics (GRIP), and Safety Platform for Emergency Vaccines (SPEAC)								
18	Publication Type: Case definition, Background, Guideline, Safety Template								
20	Category: Guideline articles are broken down by "Clinical Trials" or "Surveillance"								
21	Background articles are broken down by "Case Definition", "Guideline", or "Safety Template"								
22	Case definition articles are broken down by body system (e.g., neurologic, respiratory, etc.), outcome type (e.g., fatal), or host group (e.g., pregnancy, fetal, neonatal, etc.)								
25	Sub-Category: Guideline articles are broken down by "General" or "Pregnancy"								
26	Case definition articles are broken down by systemic classification								
28	COVID-19 Related: SPEAC AESI; other organization AESI (e.g., FDA, CDCP, EMA, WHO)								
29	To access COVID-19 AESI Case Definition filtered view: Under "Publications" tab, click "Data" --> "Filter View" --> "SPEAC COVID-19 AESI"								
30									
32	Title, Year, PMID, DOI: Descriptive information on article listed								
34	Supplemental Material: Columns labelled Supp1, Supp2, Supp3, Supp4 etc may be populated with links to additional case definition resources. The types of supplemental material are listed, with descriptions below. Since some AESI may have several supplements, and others 1 or none, rather than label the Supplemental columns, the linked material will be identified in								

+ INSTRUCTIONS PUBLICATIONS

Confidential · This project has been funded in whole by CEPI

Brighton Collaboration Publications

File Edit View Insert Format Data Tools Extensions Help Last edit was made on 18 November 2020 by Lisa Chun

100%

A1

A B C D E F G H I J

4 If you have any questions on how to use or navigate this spreadsheet, please contact bc-coordinator@taskforce.org

6 Notification of newly added content will be noted on the [Brighton Publications main page](#).

9 **How to use this spreadsheet:**

11 All Brighton Collaboration articles can be found under "PUBLICATIONS" tab, organized by publication types, (sub) categories.

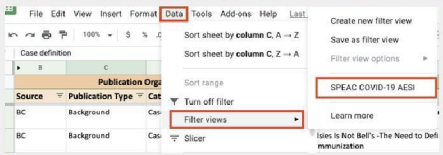
13 **Source:** Brighton Collaboration Case Definition Working Group (BC CD WG),
Global Alignment of Immunization Safety Assessment in Pregnancy (GAIA),
14 Viral Vector Vaccine Safety Working Group (V3SWG), Brighton Collaboration (BC)
15 BC Global Research in Paediatrics (GRIP), and Safety Platform for Emergency Vaccines (SPEAC)
16

18 **Publication Type:** Case definition, Background, Guideline, Safety Template

20 **Category:** Guideline articles are broken down by "Clinical Trials" or "Surveillance"
21 Background articles are broken down by "Case Definition", "Guideline", or "Safety Template"
22 Case definition articles are broken down by body system (e.g., neurologic, respiratory, etc.), out-
23 type (e.g., fatal), or host group (e.g., pregnancy, fetal, neonatal, etc.)

25 **Sub-Category:** Guideline articles are broken down by "General" or "Pregnancy"
26 Case definition articles are broken down by systemic classification

28 **COVID-19 Related:** SPEAC AESI; other organization AESI (e.g., FDA, CDCP, EMA, WHO)
29 **To access COVID-19 AESI Case Definition filtered view:**
Under "Publications" tab, click "Data" -> "Filter View" -> "SPEAC COVID-19 AESI"



32 **Title, Year, PMID, DOI:** Descriptive information on article listed

34 **Supplemental Material:** Columns labelled Supp1, Supp2, Supp3, Supp4 etc may be populated with links to additional case definition resources. The types of supplemental material are listed, with descriptions below. Since some AESI may have several supplements, and others 1 or none, rather than label the Supplemental columns, the linked material will be identified

36 **AESI Companion Guide:** The CEPI-SPEAC project outputs include several resources and tools. To facilitate their use these are being collated into a single guide for each AESI. Included in each guide are: Risk factors; background rates; tabular summaries of recommendations for real time investigation, data analysis and presentation; ICD9/10-CM and MedDRA codes; data abstraction and interpretation form for medical chart review; 2 formats (tabular & pictorial) for summarizing case data and determining level of certainty

38 **WG-CD Algorithm:** For some case definitions, the Working Group developed an algorithm for determining level of certainty in conjunction with the case definition that is available as a supplement to the publication. (e.g. SNHL)

40 **WG-CD Guidelines:** Given length restrictions, for some case definitions the section for guidelines on data collection, presentation and analysis has to be put into a separate supplement. (e.g. SNHL)

42 **WG-CD CRF:** Clinical report from that can be used for the AESI (e.g., Bell's Palsy)

44 **WG-CD Literature Search:** Extensive literature searches are a standard part of the Brighton process for creating new case definitions and may be available as a supplement to the publication.

46 **WG-CD Peer Review:** All Brighton case definitions undergo a standard peer review process. Results are collated into an excel spreadsheet which may be provided as supplemental material (e.g. SNHL)

48

50

51

INSTRUCTIONS PUBLICATIONS



Safety Platform for Emergency vACcines

SO2- D2.5.2.1 - AESI Case Definition Companion
Guide for 1st Tier AESI

Acute Myelitis

Work Package: WP2 Standards and tools
V2.0 – November 5th, 2020
Authors: Barbara Law

by CEPI






1.1. Myelitis Risk Factors

TABLE 1. MYELITIS RISK FACTORS 1-9

Age	o Children have a lower incidence than adults. Bimodal peaks between ages 10-19 and 30-39 years. ⁵
Gender	o May be higher in females due to it being seen commonly in multiple sclerosis ⁵ but no known gender predisposition for acute transverse myelitis
Genetics	o No evidence for familial or ethnic predisposition ⁵
Geography	o No evidence for geographic variation in incidence other than a higher reported incidence in Finnish children ⁴ (see 4.2 Myelitis background rates)
Comorbidity	o May be part of the presentation of other diseases which would be important for causality assessment: o Connective tissue / autoimmune diseases: sarcoidosis, Behcet disease, Sjogren disease, Systemic lupus erythematosus, anti-phospholipid antibody syndrome, mixed connective tissue disease, systemic sclerosis, urticarial vasculitis, perinuclear ANCA systemic vasculitis o Neoplastic disease as a paraneoplastic syndrome o Thyroid disease o Nutritional deficiency: Vitamin B12, vitamin E; copper o Conditions that cause spinal cord compression: A-V malformation; spinal cord tumors, abscess o Post-transplant Graft versus host disease o Common variable immunodeficiency o Conditions that resulted in spinal cord radiation
Infection (one study suggests 12% of cases ⁶)	o Viral: Varicella-zoster virus, enteroviruses, Herpes simplex type-2, Cytomegalovirus most common; but many others have been reported including: Epstein-Barr virus; West Nile virus; Echoviruses; Coxsackieviruses A and B; Poliovirus 1, 2 and 3; enterovirus D68, 70 and 71), Influenza A and B; Hepatitis A, B, C and E; Human immunodeficiency virus; HTLV, Human herpesvirus 6; Measles; Mumps; Rubella; Herpes Zoster, Zika virus, Dengue, Parvovirus B19; Human coronavirus, Hantavirus; Chikungunya; Japanese, St. Louis, Murray Valley, Tick-borne encephalitis viruses; Vaccinia virus o Bacterial: Mycobacterium tuberculosis; Borrelia burgdorferi (Lyme disease); Treponema pallidum (neurosyphilis); Mycoplasma pneumoniae, Campylobacter jejuni, Chlamydia species, Legionella pneumoniae, Brucellosis, Group A & B beta hemolytic streptococci, Salmonella paratyphi B, Acinetobacter baumannii, Orientia tsutsugamushi (scrub typhus) o Parasitic: Toxocara species; Schistosoma species, Gnathostoma spinigerum, Echinococcus granulosus, Toxoplasma gondii, Acanthamoeba species, Trypanosoma brucei, Taenia solium, Gnathostoma spinigerum, Paragonimus westermani, Neurocysticercosis

NOTE: These etiologies are relevant to causality assessment when acute myelitis is an AEFI. These are all known etiologies and would exclude vaccine unless a vaccine strain is found.




SPEAC
Safety Platform for Emergency vACoines

S02-D2.5.2.1 - AESI Case Definition Companion
Guide for 1st Tier AESI

Acute Myelitis

Work Package W5 Standards and Tools
V2.0 - November 17, 2020
Authors: Barbara Lear



	<ul style="list-style-type: none"> o Fungal: Actinomyces, Blastomyces, Coccidioides immitis, Aspergillus, Cryptococcus, Cladophialophora bantiana
Vaccine	<ul style="list-style-type: none"> o Institute of Medicine 2011⁷ reviewed evidence for link between MMR, VZV, influenza, Hepatitis A/B, HPV, D/T/aP, meningococcal vaccines and ADEM and concluded evidence was inadequate to accept or reject a causal relationship. They noted that immune-mediated mechanisms included autoantibody, T cells and molecular mimicry. o Updated review of evidence published since 2011 IOM report for similar range of vaccines had similar conclusion to IOM regarding no evidence to accept/reject causality⁸ • Risk window for myelitis as a vaccine product related reaction⁹ <ul style="list-style-type: none"> o Inactivated or subunit vaccines –Immune-mediated mechanism for myelitis likely similar to ADEM, where recommended risk window for individuals is 2-42 days and for epidemiologic studies 5-28 days for primary analysis, and 2-42 days for secondary analysis o Live attenuated vaccines – this should be based on the incubation period for the vaccine strain, adding as above, 5-28 days for primary analysis and 2-42 days for secondary analysis following the end of the incubation period.
Other disorders that may cause acute myelopathy (exclude acute myelitis)	<ul style="list-style-type: none"> o Neoplasm o Toxic/metabolic encephalopathy o Vascular disorder o Drugs/toxins: TNF alpha inhibitors, sulfasalazine, epidural anesthesia, chemotherapeutic agents, heroin, benzene, toxin from brown recluse spider o Trauma


 Safety Platform for Emergency vACines

SO2- D2.5.2.1 - AESI Case Definition Companion
 Guide for 1st Tier AESI

Acute Myelitis

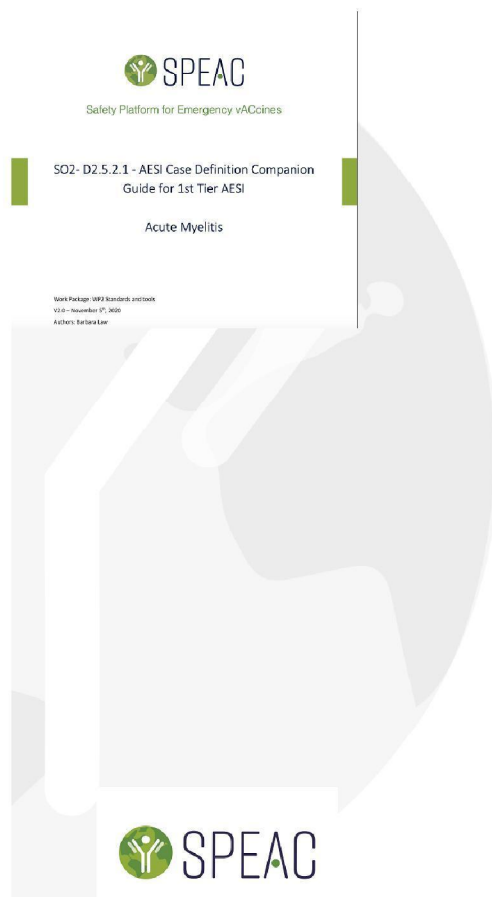
World Pharmacovigilance Standards and Tools
 V1.0 - November 2020
 Authors: Barbara Lee



2.1 Myelitis Background Rates

TABLE 1. MYELITIS BACKGROUND RATES

Country ^{reference}	Study years	Population (age in years)	Incidence rate per 100,000 patient years [95% confidence interval] (total cases)		
			All	Males	Females
USA-N California ⁹ (Kaiser Permanente members)	1998-2004	10-17		0.7[0.1-2.5] (2)	0.4 [0.01-2.0](1)
		18-25	NA	0.4[0.01-2.3] (1)	1.1[0.2-3.2] (3)
		26-62		2.4[1.7-3.2] (42)	4.9[4.0-6.0] (104)
USA-Albuquerque NM ¹⁰	1980-1990	All ages (500,000)	.46 (33)		
Canada ¹¹ (total population-2006 census)	2004-2007	All<18 (2006 census)	0.2[0.15-0.3] (48)		
Australia ¹² 1. New South Wales 2. Western Australia	1995-1998	<15 (Bureau of Statistics)	1. 0.36 (19)		
			2. 0.32 (5)		
Finland ⁴	2007	0-17	7.27		
		18-44	4.06		
		45-64	5.39		
		≥64	9.04		
Israel ¹³	1955-1975	0-9	0.40		
		10-19	1.93		
		20-29	1.42		
		30-39	0.89		
		40-49	1.51		
		50-59	1.97		
		60-69	1.77		
≥70	3.0				



3.1. Myelitis Case Definition¹ Key Caveats for Diagnosis, Data Analysis and Presentation

- Key elements of Case Definition (CD)
 - There are 3 levels of certainty based on clinical and laboratory features
 - Characteristic spinal cord biopsy findings of myelitis are all that are needed to meet level 1 but it is recognized this will rarely be obtained. Of critical importance to meet level 2 or 3 is documentation of at least one feature of myelopathy plus evidence of spinal cord inflammation (fever, CSF pleocytosis, characteristic CT/MRI findings in myelitis) and absence of alternative diagnoses.
 - If there are features of encephalitis or ADEM in addition to myelitis – the tools in sections 4.5, 4.6 and/or 4.7 can be used to determine the level of certainty for myelitis but the encephalitis/ADEM tools should also be used to assess the case. They can be found in the Companion Guide to Encephalitis and the Companion Guide to ADEM.
 - Myelitis may present in combination with encephalitis. If so and both reach the same level of certainty the case is one of encephalomyelitis. If so but both reach different levels of certainty specify separately for each.
 - Myelitis may also present as part of acute disseminated encephalomyelitis. A level 3A of certainty can be used to specify cases where there are insufficient data to allow distinction between Level 3 myelitis and Level 3 ADEM. However, if one of the two entities achieve a higher level of certainty that should be the basis for categorization: e.g., level 2 myelitis and level 3 ADEM should be reported as level 2 myelitis.
- Recommendations for real time assessment
 - Neurologic consultation should be obtained when possible, as early as possible in the illness course.
 - Fever is one criterion for inflammation and should be documented following the Brighton case definition of temperature ≥ 38.0 C by any measurement.
 - Other criteria for inflammation require CSF exam for pleocytosis and spinal cord imaging with CT &/or MRI.
 - Recommended frequency of neurologic assessment is at initial presentation to medical care, at the clinical nadir (defined as when clinical status is at the worst), at all subsequent points of significant change in neurologic status until the end of the clinical course (recovery, death or end of follow-up).
- Data Collection Guidelines
 - Document all myelitis CD criteria that are met by each case. As an aid, the SPEAC data abstraction form can be used to record the data (See section 4.5).
 - If multiple CSF, CT and/or MRI studies are done record all dates and results
 - Document all therapies given with dates
 - Document concurrent signs, symptoms and diseases other than those associated with the myelitis event



Safety Platform for Emergency vACCines

SO2- D2.5.2.1 - AESI Case Definition Companion
Guide for 1st Tier AESI

Acute Myelitis

Work Package: WP2 Standards and Tools
V2.0 - November 17, 2020
Authors: Barbara Luv



4.1 Myelitis Diagnostic Codes: ICD-9/10-CM and MedDRA

TABLE 1. NARROW SEARCH TERMS FOR ENCEPHALITIS, MYELITIS AND ACUTE DISSEMINATED ENCEPHALOMYELITIS (ADEM)

Codemapper Number & Concept ¹⁴		Diagnostic Coding System Term and Codes ^{15,16}			
Number	Name	Term	MedDRA	ICD9CM	ICD10C
C0026975	Myelitis	Myelitis	10028524		
		Myelitis NOS	10028526		
C1719356	Myelitis following immunization procedures			323.52	
C0751343	Myelitis, Postinfectious	Postinfectious myelitis		323.63	
C1719367	Other causes of myelitis			323.82	
C0026976	Myelitis, transverse		10028527	341.2	G37.9
C0270627	Myelitis, Acute Transverse			341.2 341.20	G37.3
C0014059	Encephalomyelitis, Acute Disseminated	Acute disseminated encephalomyelitis	10000709		
C1719722	Infectious acute disseminated encephalomyelitis (ADEM)			323.61	
C2875015	Acute disseminated encephalitis and encephalomyelitis, unspecified				G04.00
C3263956	Postinfectious acute disseminated encephalitis and encephalomyelitis (postinfectious ADEM)				G04.01
C3263957	Postimmunization acute disseminated encephalitis, myelitis and encephalomyelitis				G04.02
		Post immunization	10014502		



5.1. Myelitis Data Abstraction and Interpretation Form for Medical Chart Review

Instructions are provided with each table. The focus is on the specific data needed to meet and/or exclude myelitis based on the Brighton case definition.¹ This form will be most applicable to situations where a hospital/other institutional chart is available and used retrospectively to gather the information needed to validate that a case coded as myelitis meets or does not meet the Brighton case definition. It may also serve as a guide for the type of data to be collected and investigations to be done at the time a possible case is identified or reported during a clinical trial or active surveillance for cases as part of pharmacovigilance. Separate forms are available in both the developers’ toolbox and Brighton collaboration website for encephalitis and ADEM and should be used if symptoms/signs of encephalopathy or focal cortical signs accompany the spinal cord manifestations. A neurologic glossary of terms is available as well.

Four tables are included in the form.

- Table 1 is a guide to likely sources of information for the key case definition clinical and laboratory criteria.
- Table 2 is the main data abstraction form. Use it to record data from the chart and based on the evidence to assign a value to each case definition criterion. Space is limited and additional paper can be used as appropriate to capture key clinical and laboratory data.
- Table 3 should be used to summarize the criterion values as determined once table 2 is completed.
- Table 4 is the key to determine the level of certainty based on the summary data in Table 3. It follows the logic of the Brighton case definition.

TABLE 1. MYELITIS KEY CASE DEFINITION CRITERIA, LIKELY AND ACTUAL SOURCES OF INFORMATION

Criterion	Criterion category	Likely sources of information	Actual sources of information
A3	Spinal cord histopathology	Surgical procedure(s) to obtain tissue samples; laboratory results – specifically pathology/histopathology reports; post-mortem findings	
D	Spinal cord abnormal symptoms & signs	Admitting history & physical; neurologic consultation(s); other consultation(s); discharge summary;	
E/F	Evidence for spinal cord inflammation	Temperature chart; CSF laboratory results; CT scan/MRI finding(s)/report(s); other neuroimaging study report(s)	
X1	Exclusion criterion – alternative diagnosis for spinal abnormalities	Discharge summary; Discharge diagnosis; Follow-up post discharge including hospital readmission; Neurologic clinic visits; Investigations/specialty consultations for alternative diagnoses (neoplasm, vascular disorder, infection, toxic/metabolic encephalopathy)	

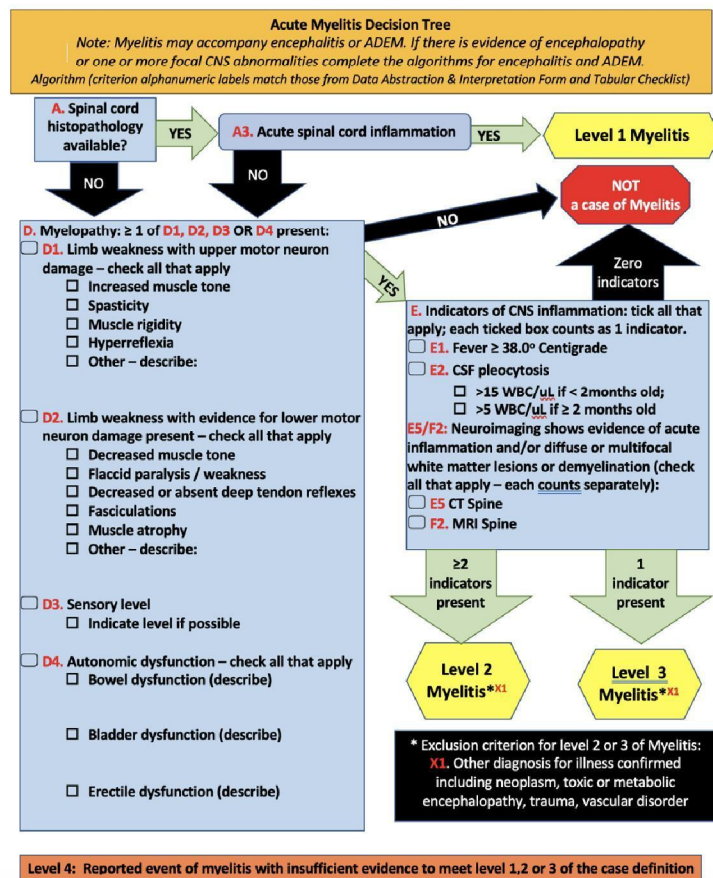
SPEAC
Safety Platform for Emergency vACcines

SO2- D2.5.2.1 - AESI Case Definition Companion Guide for 1st Tier AESI

Acute Myelitis

Work Package V02 Standards and Tools
V2.0 - November 9th, 2022
Authors: Barbara Law

SPEAC



Annex I

Updated tabular presentation of the COVID-19 AESI including status of associated Brighton case definitions

AESI <small>Rationale to include as AESI (1, 2, 3, 4 and/or 5)</small>	Brighton Case Definition Status
AESI included because they are seen with COVID-19 Disease ^{3,4}	
Acute respiratory distress syndrome	Submitted (Vaccine) ⁶
Multisystem inflammatory syndrome (children & adults)	Submitted (Vaccine) ⁶
Acute cardiovascular injury <small>(includes myocarditis/pericarditis, microangiopathy, heart failure, stress cardiomyopathy, coronary artery disease arrhythmia)</small>	Myocarditis/pericarditis near completion. Others not yet started
Coagulation disorder <small>(includes thrombotic disorders, bleeding disorders)</small>	Thrombosis near completion. Bleeding disorder WG to be formed
Anosmia, ageusia	WG to be formed
Chilblain – like lesions	WG to be formed
Erythema multiforme	Not yet started
Single Organ Cutaneous Vasculitis	Published ⁶
Acute kidney injury	Published lab-based criteria (see *)
Acute liver injury	Published lab-based criteria (see #)
Acute pancreatitis <small>NEW (Dec 2020)</small>	Not yet started
Rhabdomyolysis <small>NEW (Dec 2020)</small>	Not yet started
Subacute thyroiditis <small>NEW (Dec 2020)</small>	Not yet started
AESI included because they have a proven or theoretical association with immunization in general	
Anaphylaxis ^{1,2}	Published ⁶
Thrombocytopenia ^{1,2,3,4}	Published ⁶
Generalized convulsion ^{1,2}	Published ⁶
Acute disseminated encephalomyelitis ⁴	Published ⁶
Guillain Barré Syndrome ^{3,4}	Published ⁶
AESI included because they have a proven or theoretical association with specific vaccine platform(s)	
Acute aseptic arthritis <small>nVSV</small>	Published ⁶
Aseptic meningitis <small>Live vaccines</small>	Published ⁶
Encephalitis / Encephalomyelitis <small>Live vaccines</small>	Published ⁶
Idiopathic Peripheral Facial Nerve Palsy <small>Intranasal ECoil Heat Labile Toxin Adjuvanted Vaccine</small>	Published ⁶
Vaccine associated enhanced disease <small>1(Formalin inactivated measles/RSV/ HIV), 2(Chimeric YF Dengue), 5 (SARS / MERS-CoVs)</small>	In press (Vaccine) ⁶



SPEAC COVID-19 Updated AESI list based on May 16-Nov 9 systematic literature review. This and entire review document can be downloaded here: https://brightoncollaboration.us/wp-content/uploads/2021/01/SO2_D2.1.2_V1.2_COVID-19_AESI-update_V1.3.pdf

AESI Case definition Companion Guides will soon be posted for the following:

- Anaphylaxis
- Thrombocytopenia
- Aseptic meningitis
- Encephalitis
- ADEM
- GBS
- Facial Nerve Palsy

By April should have Guides for VAED, ARDS, MIS-C/A, Myocarditis, Thrombosis.

