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

V3.0 – February 13th, 2021

Authors: Barbara Law

Nature: Report | Diss. level: Public

TABLE OF CONTENTS

DOCUMENT INFORMATION

Master Service Agreement		Service order	SO2
Project acronym	SPEAC	Full project title	Safety Platform for Emergency Vaccines
CEPI Project Lead	Nadia Tornieporth / Jakob Cramer		
CEPI Project Manager	Brett Barnett		
CEPI Contract Manager	Nishat Miah		

Deliverable number	SO2 D2.5.2.1	Title	Transform Tier 1 AESI Tools
Work package number	WP2	Title	Standards and tools

Delivery date		Changes on due date ☑	Actual date	13-Feb-2021
Status	Draft ☐ Final ☑	Old due date: 01/11/2020	Version	3.0
Nature	Report ☑ Toolbox ☐ List ☐ Template ☐ Guidance ☐ Handbook ☐ Questionnaire ☐			
Dissemination Level	Public ☑ Confidential ☐			

SPEAC Project Lead	Robert Chen	E-mail: robert.chen@cepi.net
Scientific Coordinator	Miriam Sturkenboom	E-mail: miriam.sturkenboom@cepi.net

Reviewer 1	Steve Black	E-mail: steve.black@cepi.net
Reviewer 2	Wan-Ting Huang	E-mail: wan-ting.huang@cepi.net

Main Author(s)	Barbara Law	E-mail: barbara.law@cepi.net
WP Leader	Barbara Law	E-mail: barbara.law@cepi.net

Description of the deliverable	This deliverable collates into a single document all SPEAC Acute Myelitis resources (Risk factors, background rates, ICD9/10-CM & MedDRA codes), tools (data abstraction & interpretation form, tabular summary of key case definition criteria and algorithm for level of certainty determination, pictorial level of certainty algorithm) and guidance (real time investigation, data collection, analysis and presentation). This guide can be used by stakeholders to assess the occurrence of myelitis in several settings, including as an adverse event following immunization.
Key words	Myelitis, Brighton case definition, risk factors, background rates, ICD-9-CM, ICD-10-CM, MedDRA, case definition level of certainty.

DOCUMENT HISTORY

NAME OF DOCUMENT	DATE	VERSION	CONTRIBUTOR(S)	DESCRIPTION
SO2-D2.5.2.1 Transform Tier 1 AESI Tools	October 9 2020	V1.0	Barbara Law	First draft
SO2-D2.5.2.1 AESI Case Definition Companion Guide for Tier 1	October 28 2020	V1.1	EB	Review and comments
SO2-D2.5.2.1 AESI Case Definition Companion Guide for Tier 1	November 5 2020	V2.0	Barbara Law	Revised draft
SO2-D2.5.2.1 AESI Case Definition Companion Guide for Tier 1	February 13 2021	V3.0	Barbara Law Marta Rojo Villaescusa	Revise text to match other Tier 1 Companion Guides Add more Background Rates from Systematic Review

DEFINITIONS & ACRONYMS

ADEM	Acute Disseminated Encephalomyelitis
AESI	Adverse Events of Special Interest
ANCA	Anti-Neutrophil Cytoplasmic Autoantibody
AV	Arteriovenous (referring to an AV malformation)
BC	Brighton Collaboration
CD	Case Definition
CEPI	Coalition for Epidemic Preparedness and Innovation
CM	Clinical Modification (Relates to numbered versions of ICD codes)
CSF	Cerebrospinal Fluid
CT	Computed Tomography
CUI	Concept Unique Identifier
DTaP	Diphtheria Tetanus acellular Pertussis (vaccine)
HPV	Human Papillomavirus
ICD	International Classification of Diseases
MedDRA	Medical Dictionary for Regulatory Activities
MMR	Measles Mumps Rubella (vaccine)
MRI	Magnetic Resonance Imaging
NA	Not Applicable
RBC	Red Blood Cell
SPEAC	Safety Platform for Emergency Vaccines
TNF	Tumor Necrosis Factor
UMLS	Unified Medical Language System
VZV	Varicella Zoster Virus
WBC	White Blood Cell

THIS PROJECT HAS BEEN FUNDED IN WHOLE BY CEPI.

INTRODUCTION

1. Background

CEPI has contracted with the Brighton Collaboration, through the Task Force for Global Health, to harmonize the safety assessment of CEPI-funded vaccines via its Safety Platform for Emergency vACcines (SPEAC) Project.

A key aspect of this harmonization has been creation of lists of priority potential adverse events of special interest (AESI) that are relevant to vaccines targeting CEPI target diseases.

SPEAC Work Package 2 is creating resources and tools for the AESI including:

1. Tabular summaries of risk factors and background rates for each AESI.
2. Guidance on AESI real time investigation, data collection, analysis and presentation.
3. Spreadsheet summaries of ICD9/10 and MedDRA codes for each AESI.
4. Tools to facilitate capturing the specific clinical data needed to meet AESI case definitions across a variety of settings applicable to clinical trials, epidemiologic studies and individual case causality assessment. These include:
    a. Data abstraction and interpretation forms to facilitate capturing data from medical charts and applying it to determine a given AESI case definition level of certainty.
    b. Tabular checklists that are a stand-alone tool useful for summarizing key clinical data needed to determine the level of diagnostic certainty for a given case definition.
    c. Tabular logic and pictorial decision tree algorithms, also stand-alone tools, to facilitate correct application of key clinical data to determine the level of diagnostic certainty for each AESI.
    d. Glossary of terms relevant to anaphylaxis and the neurologic AESI.

To guide timelines for the activities above, the AESIs have been prioritized into 4 tiers as shown in the Table below (process described in SO1-D2.0 Addendum to SO1-D2.2 & 2.3 Landscape Analyses Priority Tiers for All CEPI Vaccine Development AESI). This is available in the Developers Toolbox and on the Brighton Collaboration website.

TABLE 1. AESI PRIORITIZED BY TIER

Tier 1	Tier 2	Tier 3	Tier 4
Anaphylaxis	Vaccine associated enhanced disease	Sensorineural hearing loss	Acute/Chronic inflammatory rheumatism
Thrombocytopenia	Acute respiratory distress syndrome	Anosmia/ageusia	Total/partial loss of vision
Generalized convulsion	Acute cardiovascular injury	Chilblain like lesions	Optic neuritis
Aseptic meningitis	Coagulation disorder	Erythema multiforme	Alopecia
Encephalitis	Acute kidney injury	Acute aseptic arthritis	Neonatal sepsis
Myelitis	Acute liver injury	Single organ cutaneous vasculitis	Neonatal encephalopathy
Acute disseminated encephalomyelitis	Stillbirth	Maternal death	Neonatal neuro-developmental delay
Guillain Barré & Miller Fisher Syndromes	Spontaneous abortion and ectopic pregnancy	Neonatal death	
Peripheral facial nerve palsy	Pathways to Preterm birth & Preterm birth		

To simplify access to AESI specific tools and resources, companion guides to the Brighton AESI case definition are now being prepared for each AESI separately. That is the purpose of this deliverable, which focuses on myelitis.

2. Objective of this deliverable

To collate SPEAC and BC tools, resources and guidance that have been developed for acute myelitis.

3. Methods

The methods for developing each of the tools included in this guide were detailed in previously completed SPEAC deliverables as follows:

- Myelitis risk factors and background rates and risk factors: SO1-D2.4 Tier 1 AESI: Risk Factors and Background Rates
- Myelitis Case definition key caveats for diagnosis, data analysis and presentation: SO1-D2.7 Guidance for CEPI Developers
- Myelitis Diagnostic Codes: SO2-D2.3 Tier 1 AESI: ICD-9/10-CM and MedDRA Codes
- Myelitis Data Abstraction, Tabular checklist and Level of Certainty algorithms: SO2-D2.5.1.1-Tools for Tier 1 AESI Data Collection and Interpretation

The methods are briefly described in Appendix 8 of this Guide along with links to source documents which have more detailed methodology.

4. Results

The outputs are provided as separate appendices to simplify printing as needed. These are provided as shown below.

1. Myelitis Risk Factors
2. Myelitis Background Rates
3. Myelitis Case Definition key caveats for diagnosis, data analysis and presentation
4. Myelitis Diagnostic Codes: ICD-9CM, ICD-10CM, MedDRA
5. Myelitis Data Abstraction and Interpretation Form for Medical Chart Review
6. Myelitis Tabular checklist for key case definition criteria and level of certainty algorithm
7. Myelitis Pictorial level of certainty algorithm
8. Summary of methods. Also provides links, as appropriate, to the original deliverable documents with more detailed methodology.

5. Recommendations & discussion

This guide brings together many resources and tools related to the AESI of myelitis including risk factors, background rates, guidance for real time investigation, ICD-9/10-CM and MedDRA codes for data entry or database searching and provides tools for collecting and interpreting clinical data to apply the Brighton myelitis case definition and determine the level of diagnostic certainty. The choice of tabular or pictorial algorithm is up to the user in terms of what is best suited to the situation and the assessor. SPEAC recommends that the tools be used in order to assign level of certainty for all identified AEFI with features of myelitis. This standard, harmonized approach will facilitate signal detection and assessment as well as the capacity to combine data across trials for meta-analyses.

One particular point to be noted for myelitis is that it may present with features that indicate central nervous system involvement including encephalitis or acute disseminated encephalomyelitis. These three entities are defined in a single Brighton case definition[1,] but each has their own definition with levels of certainty. Similarly, it makes sense to present risk factors and background rates separately. Thus, separate companion guides are available for encephalitis and myelitis. The three guides can be used together for data collection and assessment of level of certainty as appropriate to the clinical presentation of illness.

6. References

1. Sejvar JJ, Kohl KS, Bilynsky R et al. Encephalitis, myelitis and acute disseminated encephalomyelitis (ADEM): Case definitions and guidelines for collection, analysis and presentation of immunization safety data. Vaccine 2007; 25:5771-5792. Doi:10.1016/j.vaccine.2007.04.060.
2. West TW. Transverse Myelitis – A Review of the Presentation, Diagnosis, and initial management. Discovery Medicine 2013; 16(88): 167-77.
3. Absoud M, Greenberg BM, Lim M et al. Pediatric transverse myelitis. Neurology 2016; 87(Suppl2): S46-S52.
4. Black S, Eskola J, Siegrist CA. Importance of background rates of disease in assessment of vaccine safety during mass immunization with pandemic H1N21 influenza vaccines. Lancet 2009; 374:2115-22.
5. Bhat A, Naguwa S, Cheema G, Gershwin ME. The epidemiology of transverse myelitis. Autoimmun Rev 2010; 9(5): A395-9.
6. Debette S, De Seze J, Pruvo JP et al. Long-term outcome of acute and subacute myelopathies. J Neurol 2009; 256(6): 980-8.
7. IOM (Institute of Medicine). 2011. Adverse effects of vaccines: Evidence and Causality. Washington, DC: The national Academies Press.
8. Dudley MZ, Halsey NA, Omer SB et al. The state of vaccine safety science: systematic reviews of the evidence. Lancet ID 2020; published online April 9. https://doi.org/10.1016/S1473-3099(20)30130-4.
9. Rowhani-Rahbar A, Klein NP, Dekker CL et al. Biologically plausible and evidence-based risk intervals in immunization safety research. Vaccine 2012; 31:271-7.
10. Klein NP, Ray P, Carpenter D et al. Rates of autoimmune diseases in Kaiser Permanente for use in vaccine adverse event safety studies. Vaccine 2009 (need full citation)
11. Jeffery DR, Mandler RN, Davis LE. Tranverse myelitis. Retrospective analysis of 33 cases, with differentiation of cases associated with multiple sclerosis and parainfectious events. Arch Neurol 1993; 50:532-5.
12. Sechi E, Shosha E, Williams JP et al. Aquaporin-4 and MOG autoantibody discovery in idiopathic transverse myelitis epidemiology. Neurology 2019; 93(4): e414-e420. Doi: 10.1212/WNL.0000000000007828.
13. Kane MS, Sonne C, Zhu S, Malhotra A, Van Haren K, Messacar K, et al. Incidence, risk factors and outcomes among children with acute flaccid myelitis: a population-based cohort study in a California Health Network between 2011 and 2016. Pediatr Infect Dis J. 2019; 38(7):667–72. https://doi.org/10.1097/inf.0000000000002276
14. Banwell B, Kennedy J, Sadovnik D et al. Incidence of acquired demyelination of the CNS in Canadian children. Neurology 2009; 72:232-239.
15. Torisu H, Kira R, Ishizaki Y, Sanefuji M, Yamaguchi Y, Yasumoto S, et al. Clinical study of childhood acute disseminated encephalomyelitis, multiple sclerosis, and acute transverse myelitis in Fukuoka Prefecture, Japan. Brain Dev 2010;32: 454–62. https://doi.org/10.1016/j.braindev.2009.10.006
16. D'Souza RM. Retrospective hospital-based searches for cases of acute flaccid paralysis. Aust NZ J Public Health 2001; 26: 45-49.
17. Young J, Quinn S, Hurrell M, Taylor B. Clinically isolated acute transverse myelitis: prognostic features and incidence. Mult Scler 2009;15:1295–302 https://doi.org/10.1177/1352458509345906
18. Berman M, Feldman S, Alter M et al. Acute transverse myelitis: incidence and etiologic considerations. Neurology 1981; 31:966-971.
19. Holroyd KB, Aziz F, Szolics M, Alsaadi T, Levy M, Schiess N. Prevalence and characteristics of transverse myelitis and neuromyelitis optica spectrum disorders in the United Arab Emirates: a multicenter, retrospective study. Clin Exp Neuroimmunol. 2018;9(3):155–61. https://doi.org/10.1111/cen3.12458
20. Willame C, Codd C, van der Aa L et al. Incidence rates of autoimmune diseases in European Healthcare databases: a contribution of the ADVANCE project. Drug Safety 2021, Jan 19. https://doi.org/10.1007/s40264-020-01031-1.
21. Becker BFH, Avillach P, Romio S, van Mulligen EM, Weibel D, Sturkenboom MCJM, Kors J. CodeMapper: Semi-automatic coding of case definitions. A contribution from the ADVANCE project. Pharmacoepidemiology and Drug Safety, 2017 (8) 26: 998-1005. Doi:10.1002/pds.4245

22. McCray AT, Burgun A, Bodenreider O. Aggregating UMLS semantic types for reducing conceptual complexity. Studies Health Technology Information, 2001 84(Pt 1): 216-20. PMID: 11604736; PMCID: PMC4300099.
23. Rogers F. Medical subject headings. Bull Med Libr Assoc, 1963. 51(1): 114-6. PMID: 13982385; PMCID: PMC197951.
24. Brown EG, Wood L, Wood S. The medical dictionary for regulatory activities (MedDRA). Drug Safety, 1999. 0(2):109-17. Doi: 10.2165/00002018-199920020-00002.
25. Schuemie MJ, Jelier R, Kors JA. Peregrine: Lightweight gene name normalization by dictionary lookup. In: Proc of the Second BioCreative Challenge Evaluation Workshop., 2007. 131–133.

APPENDIX 1.
Myelitis Risk Factors

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 appendix 2, 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: AV 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]) *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.*	o Viral: Varicella zoster virus, enteroviruses, Herpes simplex type-2, Cytomegalovirus most common[2]; 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; Human T-lymphotrophic Virus, 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*, *Camplyobacter jejuni*, *Chlamydia species*, *Legionella pneumoniae*, Brucellosis, Group A & B beta hemolytic streptococci, *Salmonella paratyphi* B, *Acinetobacter baumanii*, *Orientia tsutsugamushi* (scrub typhus) o Parasitic: *Toxocara species*; *Schistosoma species*, *Gnasthostoma spinigerum*, *Echinococcus granulosus*, *Toxoplasma gondii*, *Acanthamoeba species*, *Trypanosoma brucei*, *Taenia solium*, *Gnasthostoma spinigerum*, *Paragonimus westermani*, Neurocysticercosis o Fungal: *Actinomyces species*, *Blastomyces species*, *Coccidioides immitis*, *Aspergillus species*, *Cryptococcus species*, *Cladophialophora bantiana*
Vaccine	o Institute of Medicine 2011[7] reviewed evidence for link between MMR, VZV, influenza, Hepatitis A/B, HPV, DTaP, 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 causality[8]

	• Risk window for myelitis as a vaccine product related reaction[9] 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)	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

APPENDIX 2.
Myelitis Background Rates

2.1 Myelitis Background Rates

TABLE 1. MYELITIS BACKGROUND RATES[10-20]

Country [reference]	Study years	Population (age in years)	Incidence rate per 100,000 person years[95% confidence interval] (total cases)		
			All	Males	Females
AMERICAS					
USA [10] (N California)	1998-2004	10-17 18-25 26-62 **10-62**	**3.1 [2.6-3.6] (153)**	0.7[0.1-2.5] (2) 0.4[0.01-2.3] (1) 2.4[1.7-3.2] (42)	0.4 [0.01-2.0](1) 1.1 [0.2-3.2] (3) 4.9 [4.0-6.0] (104)
USA [11] (Albuquerque NM)	1980-1990	1.5-82	0.46 (33)		
USA [12] (Minnesota, Olmsted County)	2003-2016	0-19 20-39 40-64 ≥65 **All ages** **Age-standardized rate**	-- (0) 1.28[0.51-2.63](7) 1.54[0.74-2.83](10) 0.78[0.10-2.85](2) **0.95[0.06-1.48](19)** **0.86[0.39-1.66]**	--(0) 0.74[0.09-2.66](2) 15.78[0.51-3.68](5) -- (0) **0.72[0.29-1.47](7)** **0.64[0.25-1.36]**	-- (0) 1.81[0.59-4.22](5) 1.50[0.49-3.51](5) 1.39[0.167-5.03](2) **1.17[0.61-2.05](12)** **1.07[0.52-1.93]**
USA [13] (California)	2011-2016	1-18	1.46 (28)		
Canada[14] (Nationwide)	2004-2007	≤18	0.2 [0.15-0.3] (49)		
ASIA					
Japan [15]	1998-2003	2-13	0.44 (4)		
AUSTRALIA / PACIFIC					
Australia[16] 1. New South Wales 2. Western Australia	1995-1998	<15	1. 0.36 (19) 2. 0.32 (5)		
New Zealand [17]	2001-2005	All ages	2.46 [1.82-3.11] (58)	0.97 [0.41-1.53]	3.89 [2.74-5.04]
MIDDLE EAST					
Israel[18]	1955-1975	0-9 10-19 20-29 30-39 40-49 50-59 60-69 ≥70	0.04 0.19 0.14 0.09 0.15 0.20 0.18 0.30		

		All ages	0.13 (62)		
United Arab Emirates [19]	2010-2016	0-89	0.18 (36)		
EUROPE					
European ADVANCE (Accelerated Development of Vaccine benefit-risk Collaboration in Europe)					Project[20]
All country data combined	2003-2014	0-1 2-4 5-14 15-24 25-44 45-64 ≥65 All ages	0.23 [0.13-0.43] 0.47 [0.33-0.43] 0.34 [0.27-0.43] 0.64 [0.55-0.76] 1.36 [1.26-1.46] 1.23 [1.14-1.34] 0.76 [0.67-0.85] 0.97 [0.92-1.01]	0.83 [0.77-0.89]	1.10 [1.03-1.17]
Denmark (Aarhus University Hospital and Staten Serum Institute)	2003-2014 for all	0-1 2-4 5-14 15-24 25-44 45-64 ≥65 All ages	0.1 [0.01-0.44] 0.2 [0.11-0.54] 0.2 [0.15-0.35] 0.6 [0.43-0.72] 1.3 [1.14-1.46] 1.3 [1.20-1.54] 0.9 [0.74-1.10] 0.9 [0.74-1.10] (678)		
Italy (Agenzia regionale di sanità)		0-1 2-4 5-14 15-24 25-44 45-64 ≥65 All ages	-- (0) -- (0) 0.1 [0.01-0.23] 0.3 [0.13-0.50] 0.4 [0.27-0.49] 0.5 [0.36-0.61] 0.4 [0.29-0.55] 0.4 [0.30-0.41] (144)		
Italy (Val Padana)		0-1 2-4 5-14 15-24 25-44 45-64 ≥65 All ages	-- (0) 1.9 [0.48-7.70] -- (0) 0.3 [0.04-2.11] -- (0) 0.5 [0.19-1.09] 0.4 [0.17-1.19] 0.3 [0.17-0.54] (12)		
Italy (Pedianet)		0-1 2-4 5-14 All 0-14	<5 cases overall No rates calculated		
Spain (Base de Datos para la Ivestigación Farmacoepidemiológica en Atención Primaria)		All ages	<5 cases overall No rates calculated		

UK (Royal College of General Practitioners Research and Surveillance Centre)		0-1 2-4 5-14 15-24 25-44 45-64 ≥65 **All ages**	0.3 [0.04-1.87] 0.8 [0.31-2.18] 0.7 [037-1.20] 1.1 [0.68-1.71] 2.2 [1.82-2.75] 1.6 [1.21-2.01] 1.2 [0.84-1.72] 1.5 [1.28-1.68] (213)		
UK (The Health Improvement Network)		0-1 2-4 5-14 15-24 25-44 45-64 ≥65 **All ages**	0.6 [0.28-1.11] 0.9 [0.55-1.41] 0.6 [0.44-0.82] 0.9 [0.70-1.18] 2.0 [1.83-2.27] 1.6 [1.44-1.84] 0.9 [0.69-1.06] 1.4 [1.27-1.46] (783)		

APPENDIX 3

Myelitis Case Definition Key Caveats for Diagnosis, Data Analysis and Presentation

3.1. Myelitis Case Definition[1] 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 respective Companion Guides available in both the Developers' toolbox and Brighton collaboration website.
    - 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 ADEM. 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 achieves 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
  - Document date of last observation / follow-up and use the categories below for:
    - Neurologic/Functional Outcome
      - Recovered, no sequelae, back at premorbid baseline status
      - Recovered, neurologic sequelae present at time of final follow-up
      - Died
      - Outcome unknown
      - Another outcome (describe)
    - Disposition
      - Disposition to home, independent living
      - Disposition to home, dependent living

- Disposition to pre-illness residence other than home (nursing home, skilled facility etc), independent living or pre-illness baseline status
- Disposition to assisted living or rehabilitation
- Died
- Disposition unknown
- Other disposition (describe)

- Data Analysis Guidelines
  - Classify reported events in of five categories:
    - Level 1 myelitis
    - Level 2 myelitis
    - Level 3 myelitis
      - Level 3A – insufficient data to allow for a distinction between level 3 myelitis and level 3 ADEM
    - Level 4: reported event of myelitis but insufficient evidence to meet any level of the myelitis definition
    - Level 5: Not a case of myelitis
  - If few cases are reported in the trial the concrete time course should be analyzed for each including interval from immunization to onset or first observation or diagnosis based on what is available. The same point should be used consistently for all cases.
  - If multiple cases are reported (e.g., as a study of background incidence or a causality hypothesis testing epidemiologic study) see the analysis guidelines in the published case definition guidelines section 3.2. [1]

APPENDIX 4
Myelitis Diagnostic Codes: ICD-9/10-CM and MedDRA

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

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

UMLS Concept		Diagnostic Coding System Term and Codes			
CUI	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
C0729577	Post-immunization encephalitis	Encephalitis post immunization	10014602 10054373		
C1719353	Encephalitis and encephalomyelitis following immunization procedures			323.51	
C1719358	Encephalitis, myelitis, and encephalomyelitis following immunization procedures			323.5	
C1719361	Postinfectious encephalitis, myelitis and encephalomyelitis			323.6	
C1719360	Other postinfectious encephalitis and encephalomyelitis			323.62	
C1719365	Other causes of encephalitis and encephalomyelitis			323.81	
C1719368	Other causes of encephalitis, myelitis and encephalomyelitis			323.8	
C1719369	Unspecified cause of encephalitis, myelitis and encephalomyelitis			323.9	
C0014038	Encephalitis	Encephalitis	10014581		
		Encephalitis NOS	10014601		
C0751101	Post-vaccinal encephalitis	Encephalitis following immunization procedures	10014588 10056198		
C1719369	Unspecified cause of encephalitis, myelitis and encephalomyelitis			323.9	

APPENDIX 5
Myelitis Data Abstraction and Interpretation Form for Medical Chart Review

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. Similar forms are available in the Companion Guides for encephalitis and ADEM which are available in both the Developers' toolbox and Brighton collaboration website and should be used if symptoms/signs of encephalopathy or focal cortical signs accompany the spinal cord manifestations. The numbering of the lettered criteria is consistent across the data abstraction and interpretation forms and the algorithms for encephalitis, myelitis and ADEM in each of their respective companion guides. For example, the histopathologic criterion A includes A1 and A2 which relate to findings of inflammation and demyelination in brain biopsies typical for encephalitis and ADEM respectively and A3 which relates to similar findings in spinal cord biopsy. Similarly, the exclusion criteria X1 applies to all 3 entities whereas X2, X3 and X4 apply to ADEM only. A glossary of neurologic terms is available as a separate document.

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)	

TABLE 2. ACUTE MYELITIS DATA ABSTRACTION FORM: NOTE: GLOSSARY OF TERMS AVAILABLE AS A SEPARATE DOCUMENT

1. Record specific information, to the extent possible, for all column 1 criteria in the results column 2 below.
2. Use recorded results to circle most appropriate BC CD criterion value based on the formulae in column 3.

1.Data Category	2.Results	3.BCCD Criteria Value Determination
Onset of neurologic illness	a) Date of first symptom(s) onset: (dd/mon/yy): __ / ___ /__ b) Hospital admission? ___Yes ___No ___Uncertain If yes date of admission: (dd/mon/yy): __ / ___ /__	NA
Diagnosis	Admitting diagnosis: Discharge diagnosis:	NA
D. Spinal cord symptoms / signs		
D1 Limb weakness with upper motor neuron damage	___ Yes (check all that apply below) ____No ____Not tested ___Unknown ___increased muscle tone ___spasticity ___muscle rigidity ___hyperreflexia ___Other-describe:	D = YES NO UNKNOWN

<table>
<tr><td></td><td></td><td rowspan="5">D = YES IF ≥ 1 of (D1, D2, D3 or D4) = Yes

D = NO IF (D1 + D2 + D3 + D4) = No

D = UNKNOWN IF (D1 + D2 + D3 + D4) = Not tested OR Unknown OR is a combination of [No or Not tested/Unknown]</td></tr>
<tr><td>D2 Limb weakness with evidence for lower motor neuron damage present</td><td>___ Yes (check all that apply below) ____No ____not tested ___Unknown
___decreased muscle tone ___flaccid paralysis / weakness
___decreased or absent deep tendon reflexes ____fasciculations
___muscle atrophy ___other (Describe):</td></tr>
<tr><td>D3 Sensory level</td><td>___Yes* ____No ___not tested ___Unknown
* indicate level if able: _____</td></tr>
<tr><td rowspan="3">D4 Autonomic dysfunction (can be any 1 of a, b or c)</td><td>a. Bowel dysfunction: __ Yes-describe below __No __Unknown</td></tr>
<tr><td>b. Bladder dysfunction: __ Yes-describe below __No __Unknown</td></tr>
<tr><td>c. Erectile dysfunction: __ Yes-describe below __No __Unknown</td></tr>
<tr><td colspan="2">Laboratory Criteria</td><td></td></tr>
<tr><td>Spinal cord Histopathology Criterion A3</td><td>A3. Spinal cord biopsy results: check all that apply below
1___acute inflammation of the spinal cord
2___meningeal involvement in the inflammation
3___normal histopathology
4___Other- describe:
5___Biopsy not done OR Biopsy done results unknown OR unknown if Biopsy done</td><td>A3 = 1 2 3 4 5</td></tr>
<tr><td rowspan="2">E. Indicators of CNS inflammation Criteria:
E1 - Fever

E2 - CSF pleocytosis</td><td>E1. Fever temperature ≥ 38.0C by any measured method (history of fever insufficient)
___YES (highest temp:) ___NO __UNKNOWN (if no recorded measurement)</td><td>E1 = YES NO UNKNOWN</td></tr>
<tr><td>E2. Cerebrospinal fluid (CSF): ___Not collected ___Unknown if collected
___Collected – Provide results below (sample date dd/mon/yy: __/___/__)
<table>
<tr><th>CSF Parameter</th><th>Result</th><th>Not tested or no result</th></tr>
<tr><td>Opening/Closing pressure(mmHg)</td><td></td><td></td></tr>
<tr><td>WBC count (cells/uL)</td><td></td><td></td></tr>
<tr><td>WBC differential</td><td></td><td></td></tr>
<tr><td>RBC count (cells/uL)</td><td></td><td></td></tr>
</table></td><td>E2 = YES NO UNKNOWN

E2 = UNKNOWN IF CSF not collected OR unknown if collected

IF CSF WBC count available, determine E2 based on age as shown:
• If age <2 months:</td></tr>
</table>

Protein (mg/dl)		
Glucose (mg/dl)		
Gram stain		
Rapid antigen test		
Culture		

Other (describe):

- E2 = NO IF ≤ 15 WBC/ul
- E2 = YES IF >15 WBC/ul

- If age ≥ 2mo:
  - E2 = NO IF ≤ 5 WBC/ul
  - E2 = YES IF >5 WBC/ul

E5, F2
Spine Neuroimaging Caveat: If both Spine CT and MRI done and results differ, seek expert help to decide which most accurately reflects presence or absence of inflammation and/or demyelination consistent with myelitis

Neuroimaging: Check best option for E5&F2; if >1 exam, record most abnormal result; use extra page to record other test dates & results if applicable

	Test	Results (check all applicable)
E5	Spine CT Test Date:	__0. Not done or done but results unavailable or unknown if done __1. Evidence of acute inflammation __2. Normal __3. Not normal but no evidence of acute inflammation __4. Other (Describe)
F2	Spine MRI Test Date:	__0. Not done or done but results unavailable or unknown if done __1. Evidence of acute inflammation __2. Normal __3. Diffuse or multifocal white matter lesions / demyelination __4. Other (describe)

E5 = YES NO UNKNOWN

E5 = YES IF E5=1 &/OR F2=[1 OR 3]

E5 = NO IF E5=[2 OR 3] & F2 = 2 **OR**
IF E5=[2 OR 3] & F2 = 0 **OR**
IF E5 = 0 & F2 = 2

E5 = UNKNOWN IF E5 AND F2 = 0

Caveat: if E5 &/or F2 = 4 seek expert help to determine if the findings are indicative of acute inflammation and/or demyelination

Temporal and Other Exclusionary Criteria

X1. Exclusion criterion

X1 Alternative diagnosis for illness? __Yes * __No __Unknown
*If yes describe (e.g. neoplasm, vascular disorder, infection, toxic/metabolic encephalopathy)

X1 = MET NOT MET

X1 = MET IF = Yes

X1 = NOT MET IF = No or Unknown

TABLE 3. RECORD CRITERION VALUES FROM TABLE 2 (CIRCLE CORRECT VALUE)

A3. Spinal cord histopathology			A3 = 1 2 3 4 5
D. Spinal cord symptoms / signs			D = YES NO UNKNOWN
E. Indicators of CNS inflammation	E1. Fever	YES NO UNKNOWN	Total indicators of CNS inflammation: E = __ 0 if NO / UNKNOWN for E1 + E2 + E5 + F2 __ 1 if YES for only 1 of [E1 or E2 or E5 or F2] __≥2 if YES for ≥2 of [E1 or E2 or E5 or F2]
	E2. Cerebrospinal fluid Pleocytosis	YES NO UNKNOWN	
	E5 Spine CT	YES NO UNKNOWN	
	F2. Spine MRI	YES NO UNKNOWN	
Temporal and Other Exclusionary Criteria			
X1 Exclusion criteria	X1 Alternative diagnosis for illness		X1 = MET NOT MET

TABLE 4. BASED ON INFORMATION RECORDED IN TABLE 3 ABOVE DETERMINE CORRECT LEVEL OF CERTAINTY FOR MYELITIS BASED ON FORMULAE BELOW.

LOC	
Level 1	A3 = 1 (X1 does not apply to Level 1)
Level 2	D = YES AND E = ≥2 AND X1 = NOT MET
Level 3	D = YES AND E = 1 AND X1 = NOT MET
Level 4	Reported case of acute myelitis with insufficient evidence to meet the case definition
Level 5 (Not a case)	D = NO AND/OR E = 0 AND/OR X1 = MET

THIS PROJECT HAS BEEN FUNDED IN WHOLE BY CEPI.

5.2 Supplemental materials for characterizing disease severity and functional outcome scores.[1]

Modified Rankin Scale (Rankin J. Cerebral vascular accidents in patients over the age of 60: prognosis. Scott Med J 1957; 2:200-215)

0 No symptoms at all
1 No significant disability despite symptoms; able to carry out all usual duties and activities
2 Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3 Moderate disability; requiring some help but able to walk without assistance
4 Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5 Severe disability; bedridden, incontinent and requiring constant nursing care and attention
6 Dead

TABLE 5. BARTHEL INDEX (MAHONEY FT, BARTHEL D. FUNCTIONAL EVALUATION: BARTHEL INDEX. MD STATE MED J 1965; 14:61-5) MAXIMUM SCORE = 100

Skill	0 pts	5pts	10pts	15pts
Feeding	Unable	Needs help cutting, spreading butter or needs modified diet	Independent	
Bathing	Dependent	Independent		
Grooming	Needs help with personal care	Independent face, hair, teeth, shaving		
Dressing	Dependent	Needs help but can do about half unaided	Independent (incl. buttons, zips, laces)	
Bowels	Incontinent or needs enemas	Occasional accident	Continent	
Bladder	Incontinent, catheterized or unable to manage alone	Occasional accident	Continent	
Toilet Use	Dependent	Needs some help but can do something alone	Independent (on and off, dressing, wiping)	
Transfers	Unable, no sitting balance	Major help (1-2 people, physical), can sit	Minor help (verbal or physical)	Independent
Mobility (on level surfaces)	Immobile or <50yds	Wheelchair independent, incl corners, >50yds	Walks with help of 1 person (verbal or physical) >50yds	Independent (but may use any aid – e.g. stick) >50yds
Stairs	Unable	Needs help (verbal, physical, carrying aid)	independent	

Notes: record what patient does – not what he or she could do; main aim is to establish degree of independence from any help; need for supervision renders patient not independent; performance should be established using best evidence – ie direct observation if possible but also can ask patient, friends/relatives, nurses; usually assessed over prior 24 hrs. – sometimes may need longer periods; middle categories imply that the patient supplies >50% of effort; use of aids to be independent is allowed

APPENDIX 6
Myelitis Tabular Checklist for Key Case Definition Criteria and Level of Certainty Algorithm

6.1 Myelitis Tabular Checklist for Key Case Definition Criteria and Level of Certainty Algorithm*

TABLE 1. STEP 1: USE AVAILABLE CLINICAL DATA TO ASSIGN VALUES FOR CRITERIA IN THE TABLE. YES' OR 'MET' MEANS CRITERION AS DESCRIBED IS DOCUMENTED TO BE PRESENT; 'NO' MEANS IT IS DOCUMENTED TO BE ABSENT; 'UNKNOWN' MEANS THERE WAS NO DOCUMENTATION OF CLINICAL FINDINGS OR A TEST WAS NOT DONE OR IT IS UNKNOWN IF THE TEST WAS DONE OR TEST RESULTS ARE UNAVAILABLE. 'NOT MET' CAN EQUAL 'NO' OR 'UNKNOWN' AS DEFINED ABOVE.

Diagnostic Criteria (Note: alphanumeric criterion codes match those in the data abstraction interpretation form and pictorial algorithm)		Circle the best answer for each criterion			Additional rules	Criterion Value
A3. **Spinal Cord histopathology** Acute spinal cord inflammation	A3	YES	NO	UNKNOWN	None	A3 =
D. **Myelopathy** ≥1 of: limb weakness with evidence of upper or lower motor neuron damage; sensory level; autonomic dysfunction (bowel, bladder, erectile)	D	YES	NO	UNKNOWN	None	D =
E. **Total indicators of CNS inflammation:**						
E1. **Fever** ≥ 38.0° C	E1	YES	NO	UNKNOWN	E=0 IF [E1+E2+E5 + F2] = NO or UNKNOWN E=1 IF only 1 of [E1, E2, E5, F2] = Yes E=≥2 IF ≥2 of [E1, E2, E5, F2] = Yes	E =
E2. **CSF pleocytosis:** IF < 2mos old: > 15WBC/uL; IF ≥ 2mos old: > 5 WBC/uL	E2	YES	NO	UNKNOWN		
E5/F2. **Spinal cord neuroimaging** shows acute inflammation or demyelination (E5 = CT ; F2 = MRI)	E5	YES	NO	UNKNOWN		
	F2	YES	NO	UNKNOWN		
X1. **Exclusion Criterion** Alternative diagnosis found for illness (cancer, vascular disorder, toxic or metabolic process, infectious process)	X1	MET	NOT MET		None	X1 =

THIS PROJECT HAS BEEN FUNDED IN WHOLE BY CEPI.

TABLE 2. STEP 2: APPLY CRITERION VALUES FROM CHECKLIST ABOVE TO FORMULAE BELOW TO DETERMINE LEVEL OF CERTAINTY (LOC)

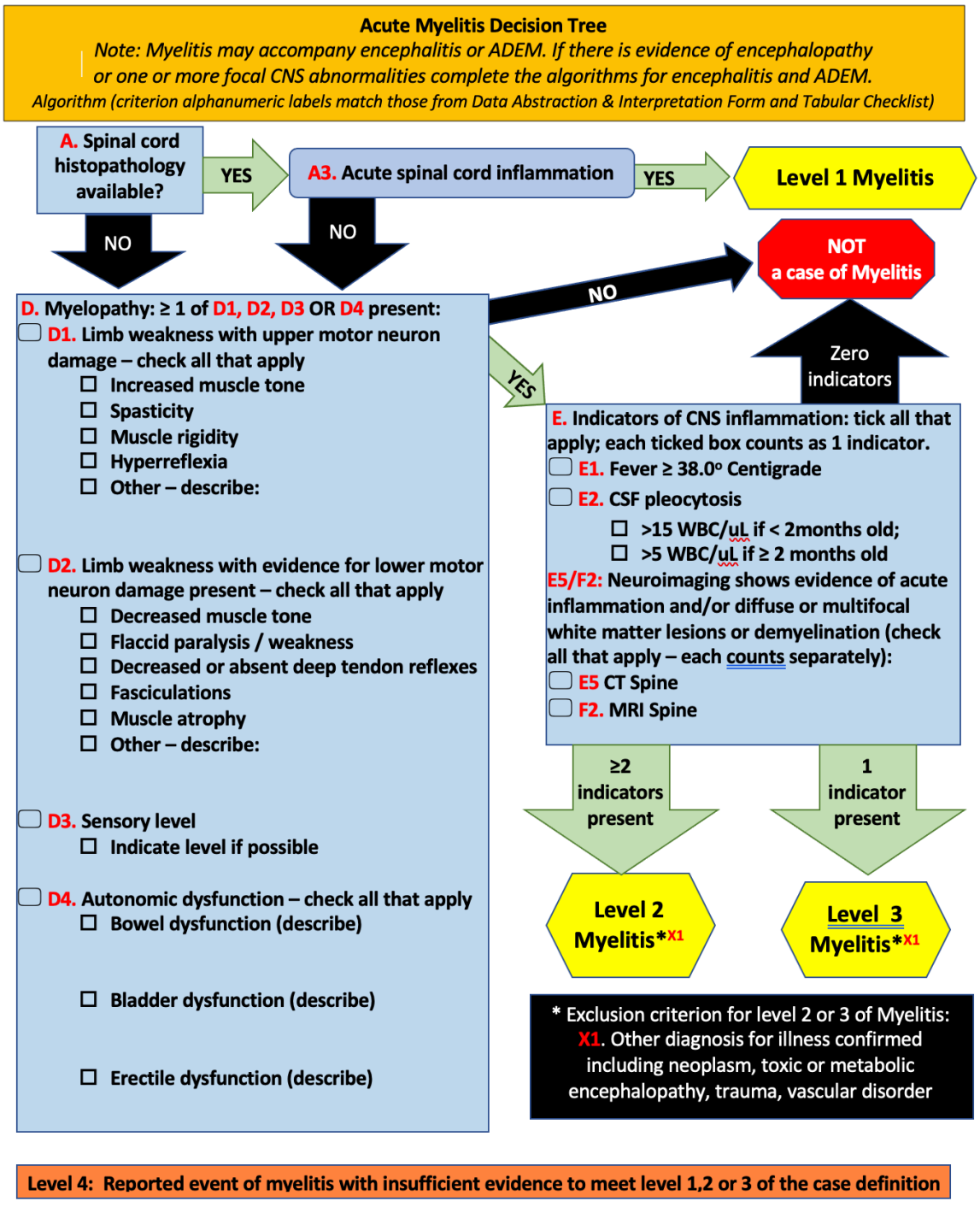
LOC	
Level 1	A3 = YES (NOTE: X1 does not apply to Level 1)
Level 2	D = YES AND E = ≥2 AND X1 = NOT MET
Level 3	D = YES AND E = 1 AND X1 = NOT MET
Level 4	Reported case of acute myelitis with insufficient evidence to meet the case definition
Level 5 (Not a case)	*D = NO AND/OR E = 0 AND/OR X1 = MET*

** Myelitis may accompany encephalitis and may be part of ADEM. If encephalopathy and/or focal or multifocal CNS signs are present LOC should be assessed for both encephalitis and ADEM using the appropriate tabular checklist or decision tree algorithms. LOCs may be different for each entity and if so should be noted separately (e.g. level 2 encephalitis, level 3 myelitis). However, if the case meets level 1 ADEM and level 2 or level 3 myelitis, the case should be classified as level 1 ADEM. The algorithms are contained in the separate Companion Guides for Encephalitis and Myelitis are available in both the Developers' toolbox and Brighton collaboration website*

APPENDIX 7
Myelitis Pictorial Level of Certainty Algorithm

7.1 Myelitis Pictorial level of certainty algorithm

Use available clinical history, examination and laboratory investigation results to determine level of diagnostic certainty.



APPENDIX 8.

Methodology: Brief Summary

8.1. Myelitis Risk Factors [1-9]

A risk factor is "an exposure, behavior, or attribute that, if present and active, clearly alters the occurrence of a particular disease compared with an otherwise similar group of people who lack the risk factor". According to James Last dictionary of epidemiology version 4, a risk factor is an aspect of personal behavior or lifestyle, an environmental exposure, or an inborn or inherited characteristic, that, on the basis of epidemiologic evidence, is known to be associated with health-related condition(s) considered important to prevent. The term risk factor is rather loosely used, with any of the following meanings:
1. An attribute or exposure that is associated with an increased probability of a specified outcome, such as the occurrence of a disease. Not necessarily a causal factor. A RISK MARKER.
2. An attribute or exposure that increases the probability of occurrence of disease or another specified outcome. A DETERMINANT.
3. A determinant that can be modified by intervention, thereby reducing the probability of occurrence of disease or other specified outcomes. To avoid confusion, it may be referred to as a modifiable risk factor.

Risk factors can include infection, medication, diet, surgical or medical procedure, environmental location, stress, toxins, trauma and vaccine. Attribute includes genetic makeup, age, gender, ethnicity, social status, occupation. Behavior includes smoking, drinking, other substance abuse, sexual practices, level of physical activity. A standard tabular format, as shown in the appendices was used to summarize the key known risk factors for each AESI. Risk factors are only included if there is evidence for an association with the AESI.

The published Brighton Case definition[1] for myelitis was reviewed for evidence related to associated risk factors. In addition, review articles published after the Brighton case definition were retrieved and reviewed in depth regarding known risk factors for acute myelitis.[2-8]

8.2. Myelitis Background Incidence [10-19]

A systematic literature search to estimate the incidence of acute myelitis in the population was conducted using the following search strategy:
("Myelitis, Transverse"[Mesh:noexp] OR "Myelitis"[ti]) AND ("Incidence"[Mesh:noexp] OR "incidence"[tiab]) AND English[lang] AND ("2000/01/01"[PDAT] : "3000/12/31"[PDAT]) AND ("Meta-Analysis"[Publication Type] NOT ("animals"[Mesh:noexp] NOT "humans"[Mesh:noexp]) NOT ("Coronavirus"[Mesh:noexp] OR "coronavirus"[ti] OR "nCoV"[ti] OR "COVID"[ti] OR "SARS-CoV-2"[ti]) NOT ("therapy"[ti] OR "therapies"[ti] OR "therapeutic"[ti] OR "treatment"[ti] OR "treatments"[ti] OR "drug"[ti] OR "drugs"[ti] OR trial[ti] OR "trials"[ti] OR "prevention"[ti] OR "prevent"[ti] OR "prevents"[ti] OR "surgery"[ti] OR "procedure"[ti] OR "procedures"[ti]).

Articles had to meet the following criteria:

1. Original research/meta-analysis
2. Population-based study (selecting the entire population or using probability-based sampling methods)
3. Reported an incidence estimate (or raw numbers that allowed the calculation of an estimate).

If multiple articles reported data from the same study population, the most comprehensive data were used. When studies reported on different data collection years or subgroups (sex, age), efforts to include all nonoverlapping data were made. Age, sex, study location, sources of ascertainment, and definitions/diagnostic criteria for myelitis were extracted. Myelitis incidence estimates, raw numbers, and confidence intervals (CIs) (when provided) were recorded along with any stratified results by age, sex, or year of data collection.

Articles were screened by a single medical reviewer (BL). Screened in articles were then reviewed independently by two reviewers and relevant data abstracted for inclusion in the background rate table.

The spreadsheet with all extracted background incidence data is available on the Brighton Collaboration website.

8.3. Myelitis Case Definition[1] key caveats for diagnosis, data analysis and presentation

The published Brighton case definition for myelitis was reviewed and key aspects identified with particular relevance to real time assessment of myelitis in the context of a clinical trial where it occurs as an AEFI. In addition, the guideline section of the published myelitis case definition was reviewed, and key recommendations identified for data collection, analysis and presentation.

For a more detailed description of methodology see SO1-D2.7 Guidance for CEPI Developers which is available in the CEPI Developers' Toolbox.

8.4. Myelitis ICD-9/10-CM and MedDRA Codes [20-24]

An initial set of codes were retrieved through the Codemapper tool that was developed in the IMI-ADVANCE project. Subsequently they were reviewed and classified into narrow or broad codes by the authors.

CodeMapper[20] builds upon information from the Metathesaurus of the Unified Medical Language System (UMLS). The Metathesaurus is a compendium of many medical vocabularies, which have been integrated by assigning equivalent codes and terms from different source vocabularies to the same concepts. Each concept in the UMLS is identified by a CUI. A CUI is a Concept Unique Identifier for a Metathesaurus concept to which strings with the same meaning are linked. The Metathesaurus contains more than one million concepts connected to codes from 201 vocabularies. Each concept is assigned to one or more of 127 semantic types, which define broad conceptual categories like Disease or syndrome, Finding, or Substance.[21] Codemapper was built on the version 2016AA of the UMLS. The automatic concept identification of CodeMapper is based on lexical information from the Metathesaurus. The lexical information of a concept consists of terms that can be used in free text to refer to that concept. We compiled a dictionary for the concepts in the semantic groups Anatomy, Chemicals & Drugs, Disorders, Genes & Molecular Sequences, Living Beings, Phenomena, Physiology, and Procedures of non-suppressible, English terms from several vocabularies including ICD-9 CM, ICD-10 CM, and MedDRA.[22,23] A text-indexing engine Peregrine uses this dictionary to identify medical concepts in the case definition.[24] Of note, while SPEAC focused on ICD-9/10-CM and MedDRA codes, the CodeMapper concepts shown in the table can be used to search for codes in other systems including SNOMED-CT, MeSH, ICPC-2 and Read-CTv3.

CodeMapper has three screens.

1. The first displays the free text entered by the user – in this case the Brighton case definition. Medical concepts are automatically identified in the text and highlighted inline.
2. The second displays the mapping as a table with one row for each medical concept, and one column for each targeted vocabulary. Each cell contains the names of the codes that are used to represent the medical concept of the row in the targeted vocabulary of the column. The codes are displayed when the names are hovered over with the mouse. Several user operations are available for revising the mapping. The user can remove concepts from the mapping, search and add concepts, or retrieve more general and more specific concepts. The retrieved concepts are shown in a list and can be selected by the user for inclusion in the mapping. The user can also add or remove vocabularies that should be targeted by the mapping. After every operation, the codes are automatically updated and displayed in the table.

3. The third shows a list of all operations that have been made, for later traceability of the mapping process. When the user saves the mapping, he has to provide a summary of the modifications, which is incorporated into the mapping history. The user can download the mapping as a spreadsheet file to incorporate the codes into extraction queries. The spreadsheet file comprises the original free-text case definition, the concepts of the mapping, the codes for the targeted vocabulary, and the full history of the mapping process.

Codemapping was conducted by MS. The output of the Codemapper concepts was reviewed by a medical expert (BL) familiar with the myelitis Brighton case definitions for all Tier 1 AESI. The concepts identified for myelitis were considered relevant for background incidence rate determination as well as to study hypotheses related to myelitis as a vaccine-product related reaction. Most of the terms include encephalitis and acute disseminated encephalomyelitis since myelitis may be part of these broader categories.

For a more detailed description of methodology see SO2-D2.3 Tier 1 AESI: ICD-9/10-CM and MedDRA Codes which is available in the CEPI Developers' Toolbox and at the Brighton Collaboration website

8.5. Data Abstraction & Interpretation Form, Tabular Checklist and Algorithms for Level of Certainty Determination

The Brighton Collaboration case definition for myelitis[1] was thoroughly and repeatedly reviewed by one individual (BL) to identify all clinical, laboratory and other criteria (e.g., temporal course of disease) used to define each and every case definition level of certainty.

The myelitis criteria were displayed in a tabular format to enable recording of all relevant clinical data (based on history, physical examination, laboratory investigation and temporal criteria as relevant to each case definition) needed to meet each criterion. A guide was developed for each criterion in the data abstraction table to ensure a standard approach to assigning a value to the criterion. For most criteria the following terms were used with the meaning as noted below:

- Yes: criterion was documented to be present (for some the term 'True' or 'Met' was used instead of 'Yes').
- No: criterion was documented to be absent (for some the term 'Not True' or 'Not met' was used instead of 'No').
- Unknown: criterion was not assessed, or not mentioned, or no results were available, so it was not possible to document it as either present or absent.

In some cases, lettered or numbered values were assigned to a given criterion. Rules to assign these values to the criterion were embedded within the data abstraction table or the tabular checklist depending on the specific tool, further described in results below.
Algorithms were developed for each level of diagnostic certainty based on the values of each criterion as described in the published case definition. Two types of algorithm were developed for each case definition. For one, formulae based on the logic in the case definition were put into tables with each row representing a level of certainty. For the second a more visual decision tree algorithm was developed. Both however, were based on the logic inherent in the published case definition.

For a more detailed description of methodology see Tabular checklist and Level of Certainty algorithms: SO2-D2.5.1.1-Tools for Tier 1 AESI Data Collection and Interpretation which is available in the CEPI Developers' Toolbox.