Safety Platform for Emergency vACcines

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

Acute Disseminated Encephalomyelitis (ADEM)

Work Package: WP2 Standards and tools

V1.0 – February 11th, 2021

Authors: Barbara Law

Nature: Report | Diss. level: Public

TABLE OF CONTENTS

THIS PROJECT HAS BEEN FUNDED IN WHOLE BY CEPI.

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	February 11th 2021
Status	Draft ☐ Final ☑	Old due date:	Version	*1.0*
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	Marc Gurwith	E-mail: @cepi.net
Reviewer 2		E-mail: @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 ADEM 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 Acute Disseminated Encephalomyelitis (ADEM) in several settings including as an adverse event following immunization.
Key words	ADEM, 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	30 January 2021	V0.1	Barbara Law Marta Rojo Villaescusa	First draft
SO2-D2.5.2.1 Transform Tier 1 AESI Tools	7 February 2021	V0.1	Marc Gurwith	Review
SO2-D2.5.2.1 Transform Tier 1 AESI Tools	11 February 2021	V1.0	Barbara Law	Consolidation

THIS PROJECT HAS BEEN FUNDED IN WHOLE BY CEPI.

DEFINITIONS & ACRONYMS

ADEM	Acute Disseminated Encephalomyelitis
AESI	Adverse Events of Special Interest
AIDS	Acquired Immunodeficiency Syndrome
BC	Brighton Collaboration
CD	Case Definition
CEPI	Coalition for Epidemic Preparedness and Innovation
CM	Clinical Modification (Relates to numbered versions of ICD codes)
CMV	Cytomegalovirus
CNS	Central Nervous System
CT	Computed Tomography
CUI	Concept Unique Identifier
DTaP	Diptheria Tetanus acellular Pertussis (vaccine)
EBV	Epstein Barr Virus
EEG	Electroencephalogram
EMG	Electromyogram
HHV-6	Human Herpes Virus type 6
HIV	Human Immunodeficiency Virus
HPV	Human Papilloma Virus
HSV	Herpes Simplex Virus
ICD	International Classification of Diseases
ICU	Intensive Care Unit
L	Left
MedDRA	Medical Dictionary for Regulatory Activities
MMR	Measles Mumps Rubella (Vaccine)
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
NA	Not Applicable
R	Right
SPEAC	Safety Platform for Emergency Vaccines
spp	*species* (relates to bacteria/fungi where species isn't names)
Tdap	Tetanus diptheria acellular pertussis (Vaccine)
UMLS	Unified Medical Language System
VZV	Varicella Zoster Virus

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 ADEM.

2. Objective of this deliverable

To collate SPEAC & BC tools, resources and guidance that have been developed for ADEM.

3. Methods

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

- ADEM risk factors and background rates and risk factors: SO1-D2.4 Tier 1 AESI: Risk Factors and Background Rates
- ADEM Case definition key caveats for diagnosis, data analysis and presentation: SO1-D2.7 Guidance for CEPI Developers
- ADEM Diagnostic Codes: SO2-D2.3 Tier 1 AESI: ICD-9/10-CM and MedDRA Codes
- ADEM 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. ADEM Risk Factors
2. ADEM Background Rates
3. ADEM Case Definition key caveats for diagnosis, data analysis and presentation
4. ADEM Diagnostic Codes: ICD-9CM, ICD-10CM, MedDRA
5. ADEM Data Abstraction and Interpretation Form for Medical Chart Review
6. ADEM Tabular checklist for key case definition criteria and level of certainty algorithm
7. ADEM 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 ADEM 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 ADEM 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 ADEM. 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 ADEM is that it may present with features that indicate central nervous system involvement including encephalitis or myelitis. 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. Cole J, Evans E, Mwangi M. Acute disseminated encephalomyelitis in children: an updated review based on current diagnostic criteria. Pediatric Neurology 2019; https://doi.org/10.1016/j.pediatrneurol.2019.06.017
3. Pohl D, Alper G, Van Haren K et al. Acute disseminated encephalomyelitis: updates on an inflammatory CNS syndrome. Neurology 2016; 87 (Suppl2): S38-S45.
4. Pellegrino P, Radice S, Clementi E. Geoepidemiology of acute disseminated encephalomyelitis. Epidemiology 2014; 25(6): 928-929.
5. Menge T, Kieseier BC, Nessler S et al. Acute disseminated encephalomyelitis: an acute hit against the brain. Curr Opin Neurol 2007; 20:247-254.
6. Tenembaum SN. Acute disseminated encephalomyelitis. Handbook of Clinical Neurology 2013; 112:1253-1262.
7. Hemachudha T, Griffin DE, Giffles D et al. Myelin basic protein as an encephalitogen in encephalomyelitis and neuritis following rabies vaccination. NEJM 1987; 316:369-374.
8. IOM (Institute of Medicine). 2011. Adverse effects of vaccines: Evidence and Causality. Washington, DC: The national Academies Press.
9. 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.
10. Baxter R, Lewis E, Goddard K et al. Acute demyelinating events following vaccines: a case-centered analysis. Clin Infect Dis 2016; 63(11): 145601462.
11. 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.
12. Leake JAD, Albani S, Kao AS et al. Acute disseminated encephalomyelitis in childhood: epidemiologic, clinical and laboratory features. Pediatr Infect Dis J 2004; 23: 756 – 764 10.1097/01.inf.0000133048.75452.dd
13. Banwell B, Kennedy J, Sadovnick D et al. Incidence of acquired demyelination of the CNS in Canadian children. Neurology 2009; 72: 232 – 239 https://doi.org/10.1212/01.wnl.0000339482.84392.bd
14. Torisu H, Kira R, Ishizaki Y et al. Clinical study of childhood acute disseminated encephalomyelitis, multiple sclerosis, and acute transverse myelitis in Fukuoka Prefecture, Japan. Brain Dev 2010; 32: 454 – 462 10.1016/j.braindev.2009.10.006
15. Xiong CH, Yan Y, Liao Z, et al. Epidemiological characteristics of acute disseminated encephalomyelitis in Nanchang, China: a retrospective study. BMC Public Health 2014;14:111.
16. Pavone P, Pettoello-Mantovano M, Pira AL, Giardino I, Pulvirenti A, Giugno R, et al. Acute Disseminated Encephalomyelitis: A Long-Term Prospective Study and Meta-Analysis. Neuropediatrics 2010;41(06):246–55.
17. Pohl D, Hennemuth I, von Kries R, Hanefeld F. Paediatric multiple sclerosis and acute disseminated encephalomyelitis in Germany: results of a nationwide survey. Eur J Pediatr 2007;166:405–12.
18. 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.
19. 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

20. 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.
21. Rogers F. Medical subject headings. Bull Med Libr Assoc, 1963. 51(1): 114-6. PMID: 13982385; PMCID: PMC197951.
22. 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.
23. 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.
ADEM Risk Factors

1.1. ADEM Risk Factors

TABLE 1. ADEM RISK FACTORS [1-11]

Age	Historically, highest incidence has been in children with onset typically in the first decade of life [2,3,5]
Gender	Some evidence for a slightly higher incidence in boys than girls but not a uniform finding.
Geography	Incidence noted to increase as distance from equator increases [4]

Infection	• 55-86% of pediatric ADEM cases have preceding symptoms of systemic viral illness[2,3,5,6]
	  ○ Known association following vaccine preventable infections: about 1/1000 wild type measles or varicella; 1/5000 rubella[1]
	  ○ Also noted to follow EBV, CMV, HSV, Hepatitis A, Enterovirus, HHV-6, HIV, Influenza, Dengue, West Nile Virus[1-3,5,6]
	• Has also been noted to follow bacterial (*Mycoplasma pneumoniae, Campylobacter jejuni, Chlamydia pneumoniae, Borrelia burgdorferi, Legionella pneumoniae, Leptospira spp*, beta-hemolytic Group-A Streptococcus) and parasitic (Malaria, Toxoplasmosis) infections [1-3,5,6]

Vaccine	• Only proven association with vaccine is with the now unavailable Semple rabies vaccine derived from sheep or mouse brains [1,7]
	• Institute of Medicine reviewed evidence for a 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.[8]
	• An updated review of evidence published since the 2011 IOM report for the same vaccines had a similar conclusion to IOM regarding no evidence to accept/reject causality[9]
	• A recent US Vaccine safety data link study found a possible association of ADEM following Tdap vaccine, but the excess risk was no more than 1.16 cases/million vaccine doses administered[10]
	• Risk window for ADEM as a vaccine product related reaction[11]
	  ○ Inactivated or subunit vaccines: 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
	  ○ 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.

APPENDIX 2.
ADEM Background Rates

2.1 ADEM Background Rates

TABLE 1. ADEM BACKGROUND RATES[12-18]

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 (California)[12]	1991-2000	0-4 5-9 **All (<20)**	0.6 0.8 **0.4 (42)**		
Canada (Nationwide) [13]	2004-2007	<18	0.2 [0.15-0.3] (49)		
ASIA					
Japan (Fukuoka Prefecture)[14]	1998-2003	<15	0.64 (26)		
China (Nanching)[15]	2008-2010	0-4 5-9 10-14 15-19 20-29 30-39 40-49 50-59 ≥60 **All ages**	0.28 (3) 0.75 (8) 0.40 (5) 0.27 (3) 0.30 (5) 0.08 (2) 0.25 (6) 0.26 (5) 0.55 (10) **0.31 (47)**	**0.31 (24)**	**0.32 (23)**
	2009	All ages	0.28 (14)	0.27 (7)	0.30 0(7)
	2010	All ages	0.34 (17)	0.23 (6)	0.46 (11)
EUROPE					
Italy (Catania)[16]	1992-2009	<10	1.1 (17)		
Germany (nationwide)[17]	1997-1999	<10 10-15 **All <16**	0.09 0.03 0.07 (28)		
European ADVANCE (Accelerated Development of Vaccine benefit-risk Collaboration in Europe) Project[18]					
All country data combined	2003-2014	0-1 2-4 5-14 15-24 25-44 45-64 ≥65 **All ages**	2.86 [2.43-3.37] 2.71 [2.35-3.13] 1.79 [1.63-1.97] 3.10 [2.90-3.32] 6.99 [6.79-7.21] 6.31 [6.11-6.52] 5.34 [5.11-5.58] **5.25 [5.15-5.34]**	4.31[4.19-4.44]	6.19[6.00-6.29]
Denmark		0-1	4.5 [3.6-5.6]		

(Aarhus University Hospital and Staten Serum Institute)	2003-2014 for all	2-4 5-14 15-24 25-44 45-64 ≥65 **All ages**	3.8 [3.1-4.6] 2.0 [1.8-2.4] 2.5 [2.3-2.8] 6.7 [6.3-7.0] 7.1 [6.7-7.5] 6.4 [5.9-6.8] **5.4 [5.2-5.5] (3866)**		
Italy (Agenzia regionale di sanità)		0-1 2-4 5-14 15-24 25-44 45-64 ≥65 **All ages**	5.8 [5.14-9.06] 5.8 [4.54-7.53] 4.2 [3.58-4.96] 12.1 [10.99-13.31] 20.2 [19.37-21.01] 15.0 [14.26-15.68] 8.6 [8.02-9.21] **13.5 [13.11-13.82] (5521)**		
Italy (Val Padana)		0-1 2-4 5-14 15-24 25-44 45-64 ≥65 **All ages**	1.4 [0.20-10.17] 4.8 [2.01-11.57] 2.8 [1.50-5.18] 10.1 [7.23-14.17] 22.9 [20.18-25.97] 14.4 [12.33-16.84] 8.6 [6.86-10.73] **13.4 [12.35-14.65] (527)**		
Italy (Pedianet)		0-1 2-4 5-14 **All 0-14**	1.2 [0.17-8.76] 1.0 [0.14-6.86] 1.9 [0.73-5.15] **2.1 [1.93-2.26] (6)**		
Spain (Base de Datos para la Ivestigación Farmacoepidemiológica en Atención Primaria)		0-1 2-4 5-14 15-24 25-44 45-64 ≥65 **All ages**	1.3 [0.67-2.49) 0.2 [0.06-0.90] 0.7 [0.47-1.14] 0.8 [0.56-1.06] 1.2 [1.01-1.45] 2.2 [1.87-2.58] 6.8 [6.02-7.59] **2.1 [1.93-2.26] (619)**		
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**	0.8 [0.25-2.45] 1.2 [0.55-2.73] 1.3 [0.83-1.95] 1.6 [1.06-2.28] 3.1 [2.57-3.66] 2.9 [2.42-3.50] 2.5 [1.97-3.23] **2.4 [2.19-2.70] (353)**		
UK		0-1 2-4 5-14 15-24	0.6 [0.28-1.11] 1.2 [0.79-1.79] 0.7 [0.52-093] 1.0 [0.76-1.25]		

(The Health Improvement Network)		25-44 45-64 ≥65 **All ages**	1.1 [0.96-1.29] 1.2 [1.08-1.43] 0.9 [0.77-1.16] **1.0 [0.96-1.13] (601)**		

APPENDIX 3

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

3.1. ADEM 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 signs, brain imaging with MRI and duration of follow-up for recurrence or relapse. ADEM is a diagnosis of exclusion and the CD identifies 4 separate exclusionary criteria based on alternative diagnoses, acute infectious etiologies for the disease (as opposed to an infectious illness several weeks prior to onset of ADEM which is consistent with the diagnosis), histopathologic or neuroradiologic imaging findings that are considered incompatible with ADEM and/or a temporal course that has relapse or recurrence of illness 3 months or longer after the acute presentation. The table below provides a listing of the differential diagnoses that would exclude ADEM as a consideration.
  - ADEM may be accompanied by evidence of myelitis. If so, consult the companion guide for myelitis in order to assess the corresponding level of certainty.
  - There is a great deal of overlap between ADEM and encephalitis and all cases with encephalopathy should be assessed against both case definitions (see the separate companion guide for encephalitis). A level 3A of certainty can be used to specify cases where there are insufficient data to allow distinction between Level 3 encephalitis 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 ADEM and level 3 encephalitis should be reported as level 2 ADEM.

TABLE 3.1 Differential Diagnoses of ADEM (all considered exclusionary to ADEM as a case; not an exhaustive list)[2,3,5,6]

Underlying Process	Possible causes

Infection	• Acute meningoencephalitis: viral, bacterial, parasitic (see Encephalitis Companion Guide for etiologic possibilities)
	• CMV subacute encephalitis
	• HIV associated encephalopathy
	  ○ Primary HIV disease
	  ○ Opportunistic neurologic infection in AIDS patients
	  ○ Progressive multifocal leukoencephalopathy
	• Subacute sclerosing panencephalitis

Other central nervous system demyelinating disorders	• Multiple sclerosis • Marburg disease (acute variant of Multiple sclerosis) • Neuromyelitis Optica • Acute demyelinating brainstem encephalitis • Acute demyelinating cerebellitis • Neurosarcoidosis • Neurologic Behcet's disease
Autoimmune encephalitides	• Anti NMDA receptor encephalitis
Central nervous system vasculitic disorders	• Systemic vasculitis with neurologic involvement (e.g., Systemic lupus erythematosus) • Anti-phospholipid antibody syndrome • Primary isolated central nervous system angiitis

	• Moyamoya disease • Carotid artery dissection
Central nervous system malignancy	• Gliomatosis cerebri • Primary CNS lymphoma • Histiocytosis
Toxic, Nutritional or Metabolic Disorders	• Carbon monoxide poisoning • Vitamin B12 deficiency • Folate deficiency • Mercury poisoning • Organic acidurias • Mitochondrial encephalopathy with lactic acidosis and stroke like episodes • Inherited leukodystrophies • Radiation induced leukoencephalopathy • Grave's disease • Hashimoto encephalopathy
Other	Posterior reversible leukoencephalopathy

- Recommendations for real time assessment
  - Neurologic consultation should be obtained when possible, as early as possible in the illness course.
    In addition to notes summarizing the neurologic exam findings, neurologic status should be measured using Glasgow Coma Scale/Pediatric Coma Score, Mini-Mental State Examination, Barthel Index, Modified Rankin Functional Score. (All can be found in the Brighton published CD[1] and are reproduced in Appendix 5 at the end of the data abstraction and interpretation form.
  - Follow-up should be for a minimum of 3 months from the time of clinical nadir, but a longer duration is recommended since it may enable identification of alternate illnesses, primarily multiple sclerosis, or neuromyelitis optica, should there be a recurrence or relapse of illness after 3 months.
  - 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).
  - Recent ADEM review publications provide recommendations for investigation and summarize clinical, laboratory and radiologic features that may point to one of many entities in the differential diagnosis, especially MS.[2,3] However, there are no absolute features that rule in ADEM and as noted, it is a diagnosis of exclusion.

- Data Collection Guidelines
  - Document all ADEM case definition criteria that are met by each case. As an aid, the data abstraction form in appendix 5 can be used to record the data including:
    - Neurologic symptoms/signs plus all relevant (to the case definition criteria) laboratory results including neuroimaging and/or histopathologic features (include test dates). Relevant results include brain biopsy, brain CT and MRIs, EEG, EMG & Nerve Conduction studies, relevant autopsy findings if applicable, and all tests done for illness etiology or exclusionary criteria for alternate causes.
    - Identify the initial neurologic findings that enabled the first fulfilment of case definition criteria including start and end dates.
    - Characterize the temporal nature of the onset of encephalopathy as either acute (evolving over minutes-hours to hours-days) or subacute (evolving over hours-days to days-weeks).

- Identify the level of consciousness at the clinical nadir.
- Document any concurrent signs, symptoms and diseases other than the event described.
- Document the neurologic/functional outcome and disposition at last observation.

- Data Analysis Guidelines
  - When there is one or a few cases, individual case summaries or case reports represent the ideal method of assessment for each case of ADEM. Include specification of the following intervals:
    - Days from immunization to onset of prodromal symptoms
    - Days from immunization to onset of neurologic signs
    - Days from onset of neurologic signs to clinical nadir
    - Days with a Glasgow Coma Scale score <10.
    - Days between onset of neurologic signs and each collection of CSFs.

The published case definition [1] provides much more detail on recommended analysis

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

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

TABLE 1. NARROW SEARCH TERMS ACUTE DISSEMINATED ENCEPHALOMYELITIS (ADEM)

UMLS Concept		Diagnostic Coding System Term and Codes			
CUI	Name	Term	MedDRA	ICD9CM	ICD10CM
C0014059	Encephalomyelitis, Acute Disseminated	Acute disseminated encephalomyelitis	10000709		
C1719722	Infectious acute disseminated encephalomyelitis (ADEM)			323.61	
C2875015	Acute disseminated encephalitis and encephalomyelitis, unspecified Acute disseminated demyelination, unspecified			 341.9	G04.00 G04.81 G04.90 G36.9
C3263956	Postinfectious acute disseminated encephalitis and encephalomyelitis (postinfectious ADEM)				G04.01
C3263957	Postimmunization acute disseminated encephalitis, myelitis and encephalomyelitis				G04.02

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

5.1. ADEM 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 ADEM 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 ADEM 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. ADEM may be difficult to distinguish from encephalitis and may be accompanied by myelitis. Separate companion guides are available in both the Developers' toolbox and Brighton collaboration website and should be used for assessing such cases. 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 term 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.
- Tables 5 A, B & C: Glasgow Coma Scoring for Adults and Children
- Tables 6 A & B: Mini-mental state examination.
- Tables 7 A & B: Disease outcome overall severity (Modified Rankin Scale) and functional outcome (Barthel index)

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

Criterion	Criterion category	Likely sources of information	Actual sources of information
A	Brain histopathology	Surgical procedure(s) to obtain tissue samples; laboratory results – specifically pathology/histopathology reports; post-mortem findings	
B	Encephalopathy	Admitting history&physical; neurologic consultation(s); other consultation(s); discharge summary;	
C	Focal neurologic symptoms/signs		
F	MRI	MRI findings, report(s)	

G	Temporal pattern of illness	Progress reports in chart, repeat neurologic assessments to determine date of clinical nadir (worst clinical status); date of admission to ICU, need for mechanical ventilation, death.	
X	Exclusion criteria (follow-up, investigation for infectious etiologies / alternative diagnosis	Follow-up post discharge: neurologic or other clinic visits; illness recurrence; hospital readmission, new diagnoses. Investigations/specialty consultations for acute infectious diseases as well as alternative diagnoses (neoplasm, vascular disorder, toxic/metabolic encephalopathy); Discharge summary; Discharge diagnosis;	

TABLE 2. ACUTE ADEM 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 BCCD criterion value based on the formulae in column 3.

1.Data Category	2.Results (NOTE: glossary of neurologic term is available as a separate document.)	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
Clinical Criteria		
B. Level of consciousness (LOC)		
Criterion B1 Encephalopathy	B1-a. Depressed LOC for >24 hours: Yes No Unknown	B1 = YES IF ≥ 1 of B1(a,b,c OR d) = Yes B1 = NO IF B1(a + b + c + d) = No B1 = UNKNOWN IF B1(a+b+c+d) = unknown OR there is a combination of No and unknown for B1(a + b + c + d)
	B1-b. Altered LOC for > 24 hours: Yes No Unknown	
	B1-c. Lethargy for > 24 hours: Yes No Unknown	
	B1-d. Personality change for > 24 hours: Yes No Unknown	
Glasgow Coma Score (if assessed during acute illness – see appendix)	Best Eye Response:	Not a specific criterion but if known may help to complete section B2
	Best Verbal Response:	
	Best Motor Response:	
	Total Glasgow Coma Score:	
Criterion B2	B2-a. Decreased or absent response to loud noise or painful stimuli:	B2 = YES IF ≥ 1 of B2(a-e) = Yes

Accompanying encephalopathy – choose best answer for each of B2-a through B2-e	__Yes __No __Unknown __Not tested B2-b. Inconsistent or absent response to other external stimuli: __Yes __No __Unknown __Not tested B2-c. Decreased or absent eye contact: __Yes __No __Unknown __Not tested B2-d. Decreased arousability: __ Yes __No __Unknown__Not tested B2-e. LOC was associated with a seizure? __Yes __No __Unknown	B2 = NO IF B2[a + b + c + d + e] = No B2 = UNKNOWN IF B2[a + b + c + d + e] = Not tested or unknown OR there is a mixture of No and Not tested /unknown

C. Focal or Multifocal CNS Abnormalities (Criterion C)

C1 Focal cortical signs (see glossary for definitions)	**Focal cortical signs**: __Yes(specify below) __No __Not tested __Unknown ___Aphasia/Dysphasia ___Alexia ___Agraphia ___Acalculia ___Agnosia ___Agraphesthesia ___Apraxia ___Aprosodia ___Astereognosia ___Cortical blindness ___Disconnection/neglect syndrome	**C = YES** IF **≥ 1 of (C1,C2,C3,C4,C5,C6,C7 OR C8) = Yes** **C = NO** IF **(C1+C2+C3+C4+C5+C6+C7+C8) = No** **C = UNKNOWN** IF **(C1+C2+C3+C4+C5+C6+C7+C8) = Not tested or Unknown OR is a combination of No or Not tested/Unknown**
C2 Cranial nerves	**Cranial nerve dysfunction:** __Yes(specify below) __No __Not tested__Unknown __I.Olfactory __II.Optic __III.Oculomotor __IV.Trochlear __V.Trigeminal __VI.Abducens __VII.Facial __VIII.Vestibulocochlear __IX.Glossopharyngeal __X.Vagus __XI.Accessory __XII.Hypogloxssal	
C3 Visual fields Specify sidedness (same as C5 below)	**Visual field defect**: __Yes(specify below) __No __ Not tested __Unknown __central scotoma (R L) __hemianopia (R L) ___quadrantopia (R L) Other:	
C4 Primitive reflexes	**Primitive reflex present:** __Yes(specify below) __No __Not tested __unknown __Babinski __Glabellar __Snout __Sucking __Other:	
C5 Motor weakness Specify sidedness as right(R), left (L), or both(R+L)	Strength | Normal | Weak (specify worst grade[1] if known) | Not tested | Unknown Leg Arm	**Use this space to provide 'other details' as appropriate for C1-C8.**
C6 Sensory abnormalities Specify sidedness (same as for C5)	Present (describe) | Not present | Not tested | Unknown Leg Arm	

C7 Altered deep tendon reflexes Specify sidedness (same as for C5) If 'Other' describe below table	<table><tr><th>Site</th><th>Absent</th><th>Decreased</th><th>Normal</th><th>Increased</th><th>Not tested</th><th>Unknown</th></tr><tr><td>Ankle</td><td></td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>Knee</td><td></td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>Biceps</td><td></td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>Triceps</td><td></td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>Other</td><td></td><td></td><td></td><td></td><td></td><td></td></tr></table>	
C8 Cerebellar dysfunction	**Cerebellar dysfunction:** __Yes (specify below) __No __Not tested __Unknown ___Ataxia (___incoordination___postural instability ___broad stance gait) ___Dysmetria ___dysdiadochokinesis ___Cerebellar nystagmus ___Intention tremor ___Other (describe)	
Laboratory Criteria		
Brain Histopathology Criteria A2 AND exclusion criterion X2 (only complete this section if done and results are available) *NOTE: A1 is the criterion relevant to encephalitis and A3 to myelitis – both fully defined in the relevant companion guides.*	**A2.** Brain biopsy results: check all that apply below 1___acute inflammation of brain parenchyma 2___meningeal involvement in the inflammation 3___diffuse areas of demyelination 4___multifocal areas of demyelination 5___focal area of demyelination 6___histopathology is inconsistent with diagnosis of ADEM 7___normal histopathology 8___other: Describe	**A2 = NO** if biopsy not done, done but results unavailable OR unknown if done **A2 = YES** IF **3 OR 4 OR 5 checked** **A2 = NO** IF **7 checked** **X2 = MET** IF **6 checked** *Caveat 1: if only 2 and /or 8 checked will need expert help to assign criterion A2* *Caveat 2: if 1 and/or 2 checked assess case for acute encephalitis as well.*
F. Demyelination Criterion F1 And Exclusion criterion X2	**F1. Brain MRI results** __0. Not done or done but results unavailable/uninterpretable __1. Normal __2. Diffuse or multifocal white matter lesions / demyelination on T2-weighted, diffusion-weighted (DWI) or fluid-attenuated inversion recovery (FLAIR) sequences.	**F = YES** IF **F1 = 2** **F = NO IF F1 = 1** **F = UNKNOWN** IF **F1 = 0**

	(± gadolinium enhancement on T1 sequences) __3. Inconsistent with diagnosis of ADEM __4. Other (describe)	**X2 = Met** IF **F1= 3**
Temporal and Other Exclusionary Criteria		
Criterion G **Exclusion criterion X3** ***NOTE: Symptomatic nadir represents the worst point of the clinical illness***	**G1**. If known, date of symptomatic nadir: (dd/mon/yy) __/___/__ If exact date unspecified estimate date based on hospital course (e.g. if admitted to ICU use date of that admission as the nadir). Estimated nadir: dd/mon/yy): -__/___/__. Provide rationale below:	**G = YES** IF **G3 = ≥ 3months** **G = NO** IF **G2 = No OR unknown** **OR if G3 = <3months OR unknown**
	G2. Has there been 1 or more follow up assessments? *Yes No Unknown *If yes date of last follow up for illness: (dd/mon/yy): __ / ___ /__	**X3 = MET** IF G4 = Yes **X3 = NOT MET** IF G4 = No
	G3. Interval from symptomatic nadir to last known follow-up: ____<3 months ____≥ 3months ____unknown	
	G4. Was there a relapse of illness ≥ 3 months past the symptomatic nadir? __Yes* __No ___Unknown *If Yes date of relapse: (dd/mon/yy): __/___/__	
X. Alternate diagnosis for illness		
Exclusion criteria **X1 and X4**	**X1** Alternative diagnosis for illness? __Yes * __No __Unknown *If yes describe below (could be neoplasm, vascular disorder, infection, toxic/metabolic encephalopathy)	**X1 = MET** IF **= Yes** **X1 = NOT MET** IF **= No or Unknown**
	X4 Is there evidence for an acute CNS infectious process (i.e. concurrent with the disease event as opposed to preceding it)? __Yes* __No __Unknown *If yes describe:	**X4 = MET** IF **= Yes** **X4 = NOT MET** IF **= No or Unknown**

TABLE 3. Based on information recorded in Table 2 above, circle status for each of the listed criteria below and fill in final disposition column

I. Diagnostic Criteria: Use the information gathered in the data abstraction form and the instructions in column 3 'BCCD' criteria to choose the status for each lettered criterion below					**Additional decisions regarding diagnostic criteria**	**Final Criterion disposition**
A. Brain / Spinal Cord histopathology	**A2**	Yes	No			**A2 =**
B. Encephalopathy	**B1**	Yes	No	Unknown	**B = YES** IF **B1 AND B2 both = 'Yes'; B = NO** IF **B1 AND B2 both = 'No';** Else **B = 'UNKNOWN'**	**B =**
	B2	Yes	No	Unknown		
C. Focal/multifocal CNS abnormalities	**C**	Yes	No	Unknown		**C =**
F. Demyelination on MRI	**F**	Yes	No	Unknown		**F =**
G. ≥ 3 months Follow-up	**G**	Yes	No	Unknown		**G =**
X. Exclusion Criteria	**X1**	Met	Not met			**X1 =**
	X2	Met	Not met			**X2 =**
	X3	Met	Not met			**X3 =**
	X4	Met	Not met			**X4 =**

TABLE 4. Apply Criterion values from checklist above to formulae below to determine level of certainty (LOC)

LOC		
Level 1 (2 ways to meet Level1)	Either I. OR ii. meets level 1	**I. A2=YES AND [X1-X4] = NOT MET OR UNKNOWN** **II. [B &/OR C]=YES AND F=YES AND G=YES AND [X1-X4] = NOT MET**
Level 2	**[B &/OR C]=YES AND F=YES AND G=[NO OR UNKNOWN] AND [X1-X4] = NOT MET**	
Level 3	**[B &/OR C]=YES AND F=[NO OR UNKNOWN] AND [X1-X4] = NOT MET**	
Level 4	**Reported as ADEM but insufficient evidence to meet any level of the case definition level AND [X1-4]=NOT MET**	
Level 5 - Not a case	**[B & C=No] OR [meets level 1 OR 2 OR 3 but any of X1, X2, X3 OR X4 = MET]**	

[1] ADEM may be difficult to distinguish from encephalitis and the criteria B and C are identical for the two entities plus demyelination on brain MRI doesn't rule out encephalitis. ADEM may also have a myelitis component. With encephalopathy or focal/multifocal CNS findings complete the encephalitis data abstraction form to assess the LOC for encephalitis; and with myelopathy use the abstraction form for myelitis and assess the LOC. If case meets both level 3 ADEM and encephalitis classify as level 3A. In cases where level 1 of ADEM is met and level 2 or 3 of encephalitis and/or myelitis are met, classify the case as level 1 ADEM.

5.2 Supplemental material[1]

5.2.1 Glasgow coma score

TABLE 5A. GLASGOW COMA SCORE – ADULT (From CD[1] appendix; source Teasdale G, Jennett B. Assessment of coma and impaired consciousness. Lancet 1974)

Score	Best Eye Response (E)	Best Verbal Response (V)	Best Motor Response (M)
6			__Obeys commands
5		__Oriented	__Localising pain
4	__Eyes open spontaneously	__Confused	__Withdrawal from pain
3	__Eye opening to verbal command	__Inappropriate words	__Flexion to pain
2	__Eye opening to painful stimulus	__Incomprehensible sounds	__Extension to pain
1	__No eye opening	__No verbal response	__No motor response
Score	___E + ____V + ____M = ____total Glasgow Coma Score (GCS)		

TABLE 5B. PEDIATRIC COMA SCALE (from CD appendix; source Simpson D, Reilly P. Paediatric Coma Scale, Lancet 1982; 2:450)

Score	Eyes Open	Best Verbal Response	Best Motor Response
5		Orientated	Obeys command
4	Spontaneously	Words	Localizes pain
3	o speech	Vocal sounds	Flexion to pain
2	To pain	Cries	Extension to pain
1	None	None	None
Score	___E + ____V + ____M = ____total Glasgow Coma Score (GCS)		

TABLE 5C. Best achievable normal scores for age: (13+ = mild brain injury; 9-12=moderate; <=8=severe

	Best verbal response	Best motor response	Normal aggregate score
0-6mos	Cry = 2	Flexion to pain = 3	9
6-12mos	Vocal sound = 3	Locates pain = 4	11
12-24 mos	Words = 4	Locates pain = 4	12
2-5 yrs	Words = 4	Obeys command = 5	13
>5 yrs	Orientated = 5	Obeys command = 5	14
Adult	Orientated=5	Obeys command=6	15

5.2.2 Mental State Examination

TABLE 6A. MINI-MENTAL STATE EXAMINATION (From CD[1] appendix; Source: Folstein M, Folstein S. McHugh P. Mini-mental state – a practical method for grading the cognitive state of patients for the clinician. J Psychiatric Res 1975; 12:189-98.)

Ability	Task	Points assigned	Maximum points
Orientation	Identify current: Year, Season, Date, Day of week, Month, Town or city, County or district, State or Province, Hospital or Clinic, specific floor of hospital or clinic.	1 point for each correct response	10
Registration (up to 3 points)	1. Examiner names 3 objects, spoken distinctly and with brief pause (e.g. apple, table, penny) 2. Patient repeats all three 3. Examiner repeats process until all 3 objects named correctly; record how many trials needed to learn the 3 objects	1 point for each correct response in step 2	3
Attention and Calculation	Examiner asks patient to spell WORLD backwards;	1 point for each correct letter until first error (e.g. DLORW scores 2)	5
Recall	Examiner asks patient to recite the 3 objects learned in the Registration section	1 point for each	3
Language	1. Examiner shows 2 objects and asks patient to name them (e.g. pencil, watch) 2. Examiner says a short sentence and asks patient to repeat (e.g. "No ifs ands or buts") 3. Examiner asks patient to follow a three-stage command: (e.g. "take a paper in your right hand, fold it in half, put in on the floor") 4. Examiner gives patient a sheet to read and obey containing: 'Close your eyes, write a sentence, copy the design (picture of 2 overlapped pentagons)	1. 1 point each 2. 1 point 3. 1 point each 4. 1 point each	1. 2 2. 1 3. 3 4. 3
All			30

TABLE 6B. Interpretation of score: Normal = 24 and higher; but can adjust per education/age norms

Education	18-69 years	70-79 years	>79 years
4th grade	22-25	21-22	19-20
8th grade	26-27	25	23-25
High School	28-29	27	25-26
College	29	28	27

THIS PROJECT HAS BEEN FUNDED IN WHOLE BY CEPI.

5.2.3 Disease outcome measures

TABLE 7A. MODIFIED RANKIN SCALE (FROM CD[1] APPENDIX; SOURCE: RANKIN J. CEREBRAL VASCULAR ACCIDENTS IN PATIENTS OVER THE AGE OF 60: PROGNOSIS. SCOTT MED J 1957; 2:200-215)

Score	Status
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 7B. BARTHEL INDEX FOR FUNCTIONAL OUTCOME (FROM CD[1] APPENDIX; SOURCE: 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 (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+off/dressing/ wiping)	
Transfers	Unable, no sitting balance	Major help (1-2 people, physical), can sit	Minor help (verbal / 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 (may use aid) >50 yds
Stairs	Unable	Needs help (verbal, physical, carrying aid)	independent	

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

6.1 ADEM 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.

I. Diagnostic Criteria: (Note – the alphanumeric criterion codes match those in the data abstraction and interpretation form and the pictorial algorithm for level of certainty)					Additional rules to assign Criterion value	Criterion Value
A. Brain histopathology diffuse, multifocal of focal areas of demyelination	A2*	YES	NO	UNKNOWN		A2 =
B. Encephalopathy (LOC = level of consciousness)						
>24hrs of ≥1 of: depressed LOC; altered LOC; lethargy; personality change	B1	YES	NO	UNKNOWN	B=YES IF [B1 & B2] = 'YES'; B=NO IF [B1 OR B2] = 'NO'; Else B = 'UNKNOWN'	B =
≥1 of: decreased or absent response to loud noise or painful stimuli; absent or inconsistent response to other external stimuli; decreased or absent eye contact; decreased arousability; decreased LOC was associated with a seizure	B2	YES	NO	UNKNOWN		
C. Focal/multifocal CNS abnormalities ≥1 of: focal cortical sign; cranial nerve dysfunction; visual field defect; primitive reflex; motor weakness; sensory abnormality; cerebellar dysfunction; altered deep tendon reflexes.	C	YES	NO	UNKNOWN		C =
F1. MRI shows diffuse, multifocal or focal white matter lesions/demyelination	F1	YES	NO	UNKNOWN		F1 =
G. ≥ 3 months Follow-up past the symptomatic nadir (worst point)	G	YES	NO	UNKNOWN		G =
X. Exclusion Criteria						
1. Alternative diagnosis for illness (cancer, vascular disorder, toxic or metabolic process, infectious process)	X1	MET	NOT MET			X1 =
2. Brain histopathology &/OR MRI inconsistent with diagnosis of ADEM	X2	MET	NOT MET			X2 =
3. Illness relapse occurred 3 months or more after the symptomatic nadir	X3	MET	NOT MET			X3 =
4. There is evidence for an acute concurrent infectious process	X4	MET	NOT MET			X4 =

* A2 is the histopathologic finding relevant to ADEM. A1 relates to encephalitis and A3 to myelitis – these are fully characterized in the corresponding case definition companion guides.

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 **(2 ways to meet Level1)**	Either I. OR ii. meets level 1	**III. A2=YES AND [X1-X4] = NOT MET OR UNKNOWN** **IV. [B &/OR C]=YES AND F=YES AND G=YES AND [X1-X4] = NOT MET**
Level 2	**[B &/OR C]=YES AND F=YES AND G=[NO OR UNKNOWN] AND [X1-X4] = NOT MET**	
Level 3	**[B &/OR C]=YES AND F=[NO OR UNKNOWN] AND [X1-X4] = NOT MET**	
Level 4	**Reported as ADEM but insufficient evidence to meet any level of the case definition level AND [X1-4]=NOT MET**	
Level 5 - Not a case	**[B & C=No] OR [meets level 1 OR 2 OR 3 but any of X1, X2, X3 OR X4 = MET]**	

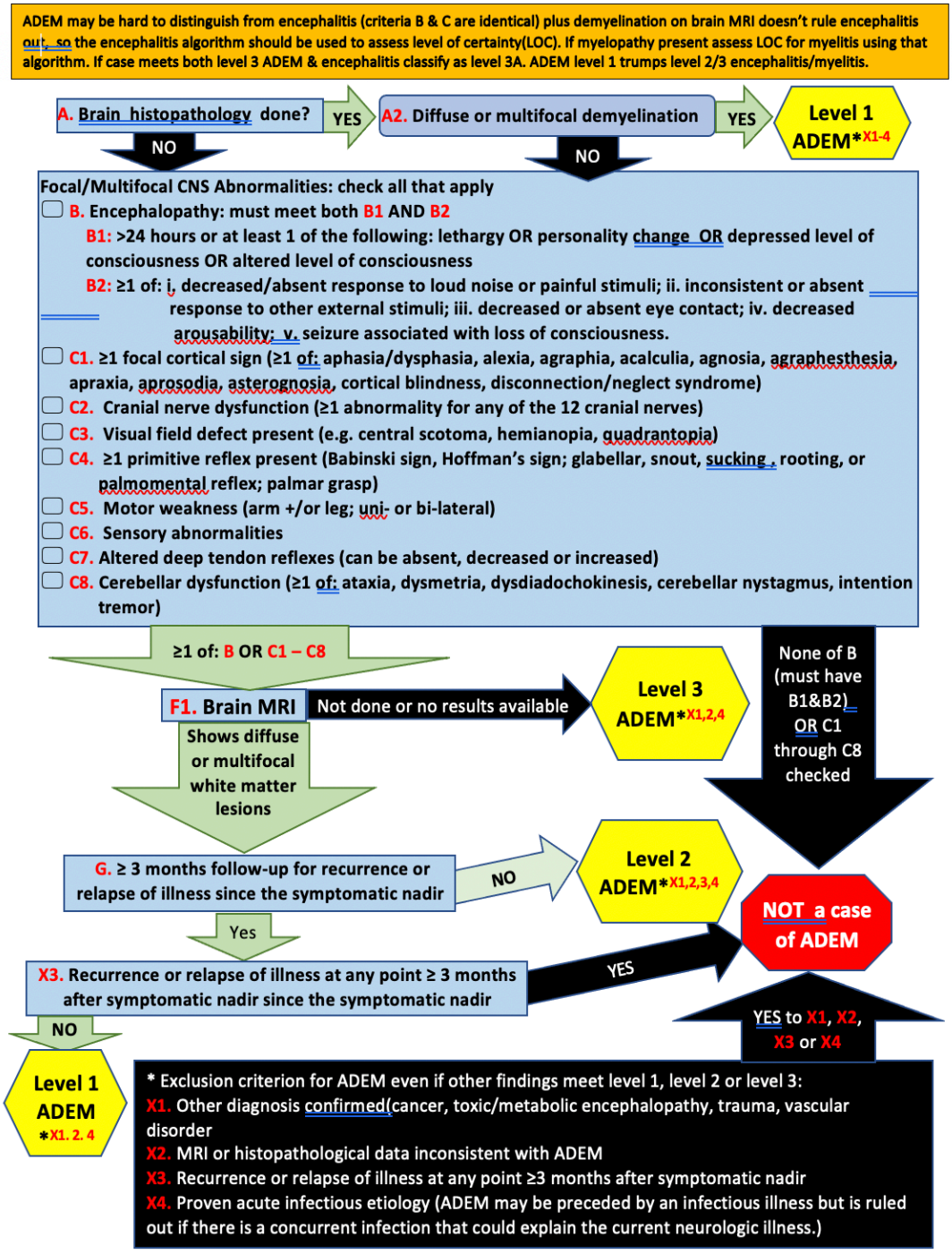
[1] ADEM may be difficult to distinguish from encephalitis and the criteria B and C are identical for the two entities plus demyelination on brain MRI doesn't rule out encephalitis. ADEM may also have a myelitis component. With encephalopathy or focal/multifocal CNS findings assess the LOC for encephalitis; and with myelopathy assess the LOC for myelitis. If case meets both level 3 ADEM and encephalitis classify as level 3A. In cases where level 1 of ADEM is met and level 2 or 3 of encephalitis and/or myelitis are met, classify the case as level 1 ADEM. Companion Guides with similar algorithms specific to encephalitis and myelitis are available.

THIS PROJECT HAS BEEN FUNDED IN WHOLE BY CEPI.

APPENDIX 7
ADEM Pictorial Level of Certainty Algorithm

7.1 ADEM Pictorial level of certainty algorithm

Use available clinical history, examination and laboratory investigation results to determine level of diagnostic certainty for ADEM. Companion Guides with similar algorithms specific to encephalitis and myelitis are available.



APPENDIX 8.

Methodology: Brief Summary

8.1. ADEM Risk Factors [1-11]

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 ADEM 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 ADEM.[2-11]

8.2. ADEM Background Incidence[12-18]

A systematic literature search to estimate the incidence of acute ADEM in the population was conducted using the following search strategy:

("Encephalomyelitis, Acute Disseminated"[Mesh:noexp] OR "acute disseminated encephalomyelitis"[ti] OR "acute disseminated encephalomyelitides"[ti] OR "ADEM"[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 ADEM were extracted. ADEM 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. ADEM Case Definition[1] key caveats for diagnosis, data analysis and presentation

The published Brighton case definition for ADEM was reviewed and key aspects identified with particular relevance to real time assessment of ADEM in the context of a clinical trial where it occurs as an AEFI. In addition, the guideline section of the published ADEM 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. ADEM ICD-9/10-CM and MedDRA Codes[19-23]

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[19]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.[20] 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.[21,22] A text-indexing engine Peregrine uses this dictionary to identify medical concepts in the case definition.[23] 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 ADEM Brighton case definitions for all Tier 1 AESI. The concepts identified for ADEM were considered relevant for background incidence rate determination as well as to study hypotheses related to ADEM as a vaccine-product related reaction.

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 ADEM[1] was thoroughly and repeatedly reviewed by one individual (Barbara Law) 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 ADEM 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.[1]

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.