Safety Platform for Emergency vACcines

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

Acute Encephalitis

Work Package: WP2 Standards and tools

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DEFINITIONS & ACRONYMS

ABLV	Australian Bat Lyssavirus
A/C	Acute / Convalescent
ADEM	Acute Disseminated Encephalomyelitis
AESI	Adverse Events of Special Interest
AFB	Acid Fast Bacilli
Ag	Antigen
ALT	Alanine Aminotransferase
AMPA-R	Alpha amino 3 hydroxy-5-methyl-4-isoxazolepropionic acid receptor
ANA	Antinuclear Antibody
AST	Aspartate Transaminase
BC	Brighton Collaboration
BKV	BK Virus
CBC	Complete Blood Count
CD	Case Definition
CEPI	Coalition for Epidemic Preparedness and Innovation
CMV	Cytomegalovirus
CNS	Central Nervous System
CSF	Cerebrospinal Fluid
CT	Computed Tomography
CTFV	Colorado Tick Fever Virus
CUI	Concept Unique Identifier
DPPX	Dipeptidyl peptidase like protein 6
EBV	Epstein Barr Virus
EEEV	Eastern Equine Encephalitis Virus
EEG	Electroencephalogram
ESR	Erythrocyte Sedimentation Rate
EV	Enterovirus
FTA-Abs	Fluorescent Treponemal Antibody Absorption (Syphilis, confirmatory test)
GABA-A-R	Gamma-aminobutyric acid receptor A
GABA-B-R	Gamma-aminobutryic acid receptor b
GAD	Glutamic Acid Decarboxylase
GlyR	Glycine receptor
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HHV6	Human Herpes Virus 6
HHV7	Human Herpes Virus 7
HLA	Human Leukocyte Antigen
HIV	Human Immunodeficiency Virus
HMPV	Human metapneumovirus
HSV-1	Herpes Simplex Virus Type 1
HSV-2	Herpes Simplex Virus Type 2
HZ	Herpes Zoster
ICD	International Classification of Diseases
ICU	Intensive Care Unit
IFA	Immunofluorescent Assay

IgG	Immunoglobulin G
INF	Influenza virus
JCV	John Cunningham Virus
JEV	Japanese Encephalitis Virus
KUNV	Kunjin Virus
L	Left
LaCV	La Crosse Virus
LCMV	Lymphocytic ChorioMeningitis Virus
LP	Lumbar Puncture
MedDRA	Medical Dictionary for Regulatory Activities
mGlu-R5	Metabotropic glutamate receptor 5
MHA	Microhemagglutination assay
MMR	Measles Mumps Rubella (vaccine)
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
MVEV	Murray Valley Encephalitis Virus
NA	Not Applicable
NMDAR	N-methyl-D-aspartate receptor
NMO	Neuromyelitis Optica
NP	Nasopharyngeal (swab sample)
PCR	Polymerase Chain Reaction
POW	Powassan Virus
R	Right
RF	Rheumatoid Factor
RMSF	Rocky Mountain Spotted Fever
RPR	Rapid Plasma Reagin (Syphilis screening test)
RT-PCR	Reverse transcriptase - Polymerase Chain Reaction
RV	Rotavirus
SLE	Systemic Lupus Erythematosus
SLEV	Saint Louis Encephalitis Virus
SPEAC	Safety Platform for Emergency vACcines
SSPE	Subacute sclerosing panencephalitis (Measles)
TB	Tuberculosis
TBEV	Tick-borne Encephalitis Virus
TOSV	Toscana Virus
TPHA	Treponema Pallidum Hemagglutinating Antibody (Syphilis confirmatory test)
UMLS	Unified Medical Language System
VDRL	Venereal Disease Research Laboratory (Syphilis screening test)
VEEV	Venezuelan Equine Encephalitis Virus
VGKC	Voltage-Gated Potassium (K) Channel Complex
VZV	Varicella Zoster Virus
WEEV	Western Equine Encephalitis Virus
WNV	West Nile 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 encephalitis.

2. Objective of this deliverable

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

3. Methods

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

- Encephalitis risk factors and background rates and risk factors: SO1-D2.4 Tier 1 AESI: Risk Factors and Background Rates
- Encephalitis Case definition key caveats for diagnosis, data analysis and presentation: SO1-D2.7 Guidance for CEPI Developers
- Encephalitis Diagnostic Codes: SO2-D2.3 Tier 1 AESI: ICD-9/10-CM and MedDRA Codes
- Encephalitis 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 used 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 appendices shown below.

1. Encephalitis Risk Factors
2. Encephalitis Background Rates
3. Encephalitis Case Definition key caveats for diagnosis, data analysis and presentation
4. Encephalitis Diagnostic Codes: ICD-9CM, ICD-10CM, MedDRA
5. Encephalitis Data Abstraction and Interpretation Form for Medical Chart Review
6. Encephalitis Tabular checklist for key case definition criteria and level of certainty algorithm
7. Encephalitis 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 encephalitis 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 encephalitis 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 encephalitis. 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 encephalitis is that it may present with features that indicate spinal cord involvement (myelitis) and also may be hard to distinguish from 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 in both the Developers' toolbox and Brighton collaboration website. The three guides can be used together for data collection and assessment of level of certainty as appropriate to the clinical presentation of illness.

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APPENDIX 1.
Encephalitis Risk Factors

1.1. Encephalitis Risk Factors

TABLE 1A. ENCEPHALITIS RISK FACTORS - GENERAL[1-11]

Age	Increased incidence in children especially <1 year; and elderly Increased risk of specific etiologies[4]: • **Neonate**: HSV-2, CMV, toxoplasmosis, congenital syphilis, Listeria monocytogenes, enterovirus, parechovirus • **Infant/Child:** HSV, VZV, enteroviruses, HHV6/7, *Mycoplasma pneumonia*e, EBV, parechovirus, Bartonella sp. • **>60 years:** Listeria monocytogenes, VZV, HZ, HSV
Gender	Increased risk of specific etiologies[4]: Female: anti-NMDAR encephalitis[7]
Genetics	HLA polymorphisms may be associated with increased risk of infection by herpesviruses and arboviruses [2]
Geography	Increased risk of specific etiologies (inhabitant / travel history)[2-6] – see Table 1B
Seasonal	Warmer months for insect spread encephalitides
Animal exposure	**Increased risk of specific etiologies[4]:** • **Monkeys/Bats/Dogs (endemic areas):** Rabies • **Cats:** *Bartonella hensellae* (Cat scratch disease) • **Horse:** Hendra virus, KUNV • **Rodents:** LCMV, *Leptospira sp.* • **Snails/other moluscs:** *Angiostrogylus cantonensis* • **Swine:** Nipah virus
Occupational	**Increased risk of specific etiologies[4]:** • **Animal husbandry, farming:** *Coxiella burnetii* (Q fever), leptospirosis • **Abbatoir workers:** *Coxiella burnetii* (Q fever) • **Lab workers – monkeys:** Herpes B virus
Comorbidity	**HIV infected individuals can have a variety of neurologic presentations. In addition, they and other immunocompromised individuals can be at risk of specific etiologies[4] :** • HHV-6, CMV, EBV, measles, VZV, LCMV, *Toxoplasma sp., Cryptococcus sp.*, JCV, BKV, *Bartonella sp.*
Recreational	**Increased risk of specific etiologies[4] :** • **Sexually transmitted:** HIV • **Fresh water:** *Naegleria fowleri*, Leptospirosis • **Soil/mud:** *Balamuthia mandrillis*
Vaccine	○ **Post vaccinial (smallpox vaccine) encephalitis[8]:** acute monophasic disorder with multifocal inflammatory and demyelinating lesions; observed onset from 1-23 days post smallpox vaccination. Most cases occurred within 7-14 days following vaccine and was thought to be caused by immune response as opposed to active infection. Incidence varied among countries possibly related to different strains: 2.9/million primary vaccinations in USA; 1.5-30/100,000 vaccinations in European countries. ○ **Institute of Medicine 2011[9] concluded evidence was:** • Strong for an association between live attenuated measles vaccine and measles inclusion body encephalitis in individuals with proven immunodeficiency.

	• Strong for encephalitis due to reactivation of Oka strain vaccine virus based on a single case in a 3-year-old female who had facial Herpes Zoster and mild encephalitis which onset 20 months after vaccination [9] • Inadequate to accept or reject a causal relationship between MMR, Influenza (inactivated), Hepatitis B, Diphtheria and Tetanus toxoid, acellular pertussis and meningococcal vaccines and encephalitis/encephalopathy. They noted that immune-mediated mechanisms included autoantibody, T cells and molecular mimicry. • Strong for disseminated VZV vaccine strain OKA infection with other organ involvement in individuals with demonstrated immunodeficiencies. The other organ involvement included pneumonia (5), hepatitis (3) and meningitis (1) but not encephalitis. o **Updated review[10] of evidence published since 2011 IOM report:** came to the same causality conclusions as IOM regarding encephalitis for similar range of vaccines. • **Risk window for encephalitis as a vaccine product related reaction** o **Post vaccinial encephalitis** – likely immune-mediated with onset most commonly 7-14 days post vaccine.[8] For this type, window would be similar to what is proposed for ADEM [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. o **Measles inclusion body encephalitis in immunocompromised host:** 4-9 months suggesting persistent infection following immunization with live attenuated measles virus[9] – which is contraindicated in such individuals. o **Disseminated VZV vaccine strain OKA infection with other organ involvement:** the time frame of observed cases was 10 days to 2 months following immunization suggesting active infection. [9] o **VZV reactivation associated with encephalitis (1 case) or meningitis (7 cases):** interval from immunization to reactivation and associated CNS involvement ranged from 19. Months to 8 years.[9]

TABLE 1B. Geographic distribution of pathogens causing encephalitis.[2-7] Bold font indicates higher prevalence relative to others. Limited circulation within continental area indicated with superscript.

Region	Range of Pathogens causing Encephalitis
Global – immune-competent hosts	Viral: Chikungunya, EBV, Enterovirus (Echo, Coxsackie, EV71), HSV-1, HSV-2, HHV-6, HHV-7, Influenza, Measles, Mumps, Rubella, VZV, WNV Bacteria: Listeria monocytogenes, Mycoplasma pneumoniae, TB
Global-immuno-compromised hosts	Viral: BKV, CMV*, EBV, HHV-6, HIV, JCV, LCMV, Measles, VZV Bacteria: Bartonella sp Fungal: Cryptoccocus sp. Parasitic: Toxoplasma sp.*
North America[2]	Viral: CTFV[US West], Dengue [US Florida,Texas,Hawaii,PuertoRico], EEEV[US East/Gulf Coasts], LACV[US E/Midwest], Powassan[NE US], SLEV[US all regions], WEEV[US West/Midwest], VEEV[US Florida, Texas, Gulf], Zika[US Texas, Florida, Puerto Rico] Bacteria -Tick-associated: Anaplasma sp (Anaplasmosis), Borrelia burgdorferi (Lyme disease – Neuroborreliosis); Ehrlichia sp (Ehrlichiosis); Rickettsia rickettsii (Rocky Mountain Spotted Fever), Fungal: Coccidioides sp. (Valley Fever) Parasitic: Babesiosis
South America	Viral: Dengue, EEEV, SLEV, VEEV, WEEV, Zika Parasitic: Trypanosomiasis
Europe	Viral: TBEV (Central and Eastern Europe, Russia), TOSV (Mediterranean Basin) Bacteria - Tick-associated: Anaplasma sp (Anaplasmosis), Borrelia burgdorferi (Lyme disease – Neuroborreliosis); Fungal: Coccidioides sp. (Valley Fever) Parasitic: Babesiosis
Africa	Viral: Dengue, Rabies, Zika Parasitic: Malaria, Trypanosomiasis
Asia	Viral: Dengue, Enterovirus 71(outbreaks), JEV, Nipah (especially Malaysia, Bangladesh, India), Rabies, Zika Parasitic: Malaria, Angiostrongylus cantonensis (Rat lungworm; eosinophilic meningitis)
Australia / Pacific	Viral: ABLV, Dengue, Hendra (primarily Australia), JEV, KUNV, MVEV, Nipah Parasitic: Angiostrongylus cantonensis (Rat lungworm; eosinophilic meningitis)

** As noted in table 1, congenital neonatal encephalitis can follow maternal infection with CMV or toxoplasma spp in the absence of immunocompromise.*

APPENDIX 2.
Encephalitis Background Rates

2.1 Encephalitis Background Rates

TABLE 1. ENCEPHALITIS BACKGROUND RATES [13-36]

Country [reference]	Study years	Population (age in years)	Incidence rate per 100,000 person years [95% confidence interval] (total cases)		
			All	Males	Females
AFRICA					
Nigeria [13]	1991-1993	16-56 17-42	2.3 (5) 'rabies' 0.9 (2) 'non-rabies'		
Libya [14]	1983-1984	17-36	1 (5)		
AMERICAs					
USA [15] (Minnesota)	1950-1981	<1 1-4 5-9 10-19 20-19 30-39 40-59 ≥60 **All ages**	22.5 (12) 15.2 (30) 30.2 (74) 6.3 (26) 4.2 (16) 4.5 (14) 1.8 (8) 3.2 (9) **7.42 [6.35-8.49] (189)**	17.8 (5) 16.9 (17) 36.6 (46) 5.9 (12) 4.4 (7) 4.5 (7) 2.8 (6) 6.0 (7) **8.6 [7.3-10.0] (107)**	27.7 (7) 13.5 (13) 23.4 (28) 6.6 (14) 4.1 (9) 4.5 (7) 0.9 (2) 1.2 (2) **6.3 [4.9-7.6] (82)**
USA [16] (National data)	1988-1987	<1 1-4 5-19 20-44 45-64 ≥65 **All ages**	13.7 [7.5-20.0] 5841 5.1 [2.1-8.0] (7684) 4.1 [2.2-5.5] (22182) 8.1 [6.9-9.4] (81817) 7.1 [5.8-8.5] (35292) 10.6 [8.5-12.8] (34348) **7.3 [5.6-8.1] (186804)**	**8.2[7.0-9.5](103083)**	**6.4[3.4-4.9](83721)**
USA [17] (California)	1990-1999	<1 1-4 5-19 20-44 45-64 ≥65 **All ages**	15.7 [14.7-16.8] (868) 4.1 [3.9-4.4] (973) 3.5 [3.3-3.6] (2350) 3.2 [3.1-3.3] (4157) 4.5 [4.4-4.7] (2707) 8.0 [7.7-8.3] (2752) **4.3 [4.2-4.4] (13807)**	4.2 [4.1-4.3] (6684)	4.5 [4.3-4.6] (7123)
USA [18] (National data)	1998-2010	<1 1-4 5-19 20-44 45-64 ≥65 **All ages**	11.93 (29) 2.75 (36) 1.31 (63) 2.02 (117) 5.37 (142) 4.83 (49) **3.14 (436)**	**3.14 (205)**	**3.14 (231)**
USA [19]	1998 - 2010	<1 1-4	11.1 [10.1-12.1] (5859) 4.7 [4.3-5.1] (9759)		

(National data)		5-19 20-44 45-64 ≥65 **All ages**	4.0 [3.7-4.2] (31814) 5.7 [5.5-5.8] (76650) 8.4 [8.1-8.6] (76-50) 13.2 [12.8-13.6] (63063) **6.9 [6.8-7.1] (263352)**	**6.6 [6.4-6.7] (123055)**	**7.2 [7.1-7.4] (139807)**
Canada [20] (National data)	1994-2008	<1 1-4 5-19 20-44 45-64 ≥65 **All ages**	10.31 [9.42-11.19] 4.08 [4.51-5.10] 3.24 [3.13-3.36] 3.47 [3.38-3.46] 4.93 [4.80-5.07] 13.59 [13.30-13.87] **5.16 [5.09-5.22] (24028)**	**5.28 [5.18-5.37]**	**5.57 [5.47-5.66]**
ASIA					
India [21]	2007	Adults	16		
Japan [22]	1984-1990	<1 1-<2 2-4 5-9 10-15 **All**	7.8 (32) 6.9 (29) 6.1 (79) 3.5 (83) 1.0 (33) **3.3 (256)**		
Japan [23]	1988-1992	Adults	0.90 (6)		
AUSTRALIA/OCEANIA					
Australia [24]	1999-2007	All ages	5.2 [4.2-6.7] (5926)	5.7	4.7
New Zealand[25]	2005-2009	>14	0.5 (37)		
EUROPE					
Sweden [26]	1970-79 1980-89 1990-99 2000-09	Children	7.7 (58) 6.4 (69) 8.7 (118) 7.9 (163)		
Finland [27,28]	1968-1987	1-1.9 2-<15 15 **All ages (0.1-<16)**	16.7 No data 1.0 **8.3**		
Finland [29]	1973-1987	<16	8.8 [6.7-10.1] (95)		
Finland [30]	1967-1991	≥15	1.4 (322)		
Finland [31]	1993-1994	<1 1-3 4-6 7-9 10-12	18.43 (17) 14.77 (57) 13.25 (39) 8.94 (26) 4.97 (15)		

		13-15 **All**	7.04 (21) **10.52 (175)**		
Finland [32]	1999-2003	≥16	2.2 (42)		
England [33]	1989-1998	All ages	1.5 (6414)		
Ireland [34]	2005-2008	All ages	2.49 [2.31-2.68] (418)		
Italy [35]	1999-2005	<1 1-14 15-64 ≥65 **All ages**	10.09 [9.04-11.06] (379) 7.04 [6.82-7] (3759) 5.0 [4.92-5.08] (13474) 7.97 [7.77-8.17] (5982) **5.88 [5.87-5.89] (23594)**	**6.43 [6.32-6.54] (12518)**	**5.35 [5.25-5.45] (11076)**
Slovenia [36]	1979-1991	1 mo to ≤15	6.7 [2.37-12.6] (170)		

APPENDIX 3

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

3.1. Encephalitis Case Definition[1] Key Caveats for Diagnosis, Data Analysis and Presentation

- Key elements of Case Definition (CD)
  - The key criteria needed to meet the encephalitis CD are presented in detail in the appendix 5 data abstraction and interpretation form and summarized in the appendix 7 pictorial algorithm. Characteristic brain biopsy findings of encephalitis 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 either encephalopathy or focal/multifocal neurologic signs along with evidence of brain inflammation (fever, CSF pleocytosis, characteristic CT/MRI/EEG findings in encephalitis) and absence of alternative diagnoses (meningitis, parameningeal processes such as brain abscess, traumatic brain injury, encephalopathy associated with: sepsis, toxin, metabolic abnormality, neurodegenerative disease, endocrine disorder and neoplastic disease).
  - As shown in tables 3A and 3B there are multiple infectious etiologies and non-infectious etiologies for acute encephalitis. Table 3B provides guidance on diagnostic investigation for many of these etiologies. It is understood that such testing is not available everywhere nor is it needed to meet the case definition for encephalitis. Where such testing may be helpful is in causality assessment of cases that follow vaccination.
  - Encephalitis may be accompanied by evidence of myelitis and there is a great deal of overlap between encephalitis and ADEM. There are separate companion guides for myelitis and ADEM available in both the Developers' toolbox and Brighton collaboration website, which should be consulted as noted below:
    - Myelitis: if there is evidence of myelopathy that accompanies encephalitis. If both reach the same level of certainty the case is one of encephalomyelitis. If both reach different levels of certainty specify separately for each…i.e., level 1 encephalitis (if there was a brain biopsy) and level 2 myelitis (no spinal cord biopsy but meets level 2 of the case definition).
    - ADEM: if there is evidence of demyelination in the brain or spinal cord. 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 encephalitis and level 3 ADEM should be reported as level 2 encephalitis; level 1 ADEM and level 2 encephalitis should be reported as level 1 ADEM.

- 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 here in appendix 5.
  - 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).
  - For investigating specific etiology for encephalitis, Table 3B summarizes what was recommended by the Brighton working group and adds some additional possibilities such as Henipaviruses. Further detail on diagnostic approach to acute encephalitis can be found in the articles by Tyler[2] and Britton et al[4].

- Data Collection Guidelines
  - Document all encephalitis case definition criteria that are met by each case. As an aid, the SPEAC data abstraction form can be used to record the data (see Appendix 5, Table 2) 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 all brain biopsy if done, CSF test results, brain CT and MRIs, EEG, EMG & Nerve Conduction studies, relevant autopsy findings if applicable, and all tests done for etiology of encephalitis 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 encephalitis. 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 CSF.
  - The published case definition[1] provides much more detail on recommended analysis when many cases are being analyzed.

TABLE 3A. Encephalitis: Clinical Pattern and associated range of infectious and non-infectious etiologies (adapted from Tyler[2] and Britton[4])

Location	Clinical Profile	EV	HSV	VZV	INF	EBV	Other viruses	Non-Viral pathogens	Non-infections Process
Generalized	Multifocal white matter lesions	Y	Y	Y	Y	Y	Adenovirus, HIV, HMPV, RV, SSPE, WNV	*Balamuthia mandrillaris, Bartonella sp., Mycoplasma pneumoniae*	MS, NMO, ADEM, CNS-lymphoma
	Intractable seizures	Y	Y			Y	Adenovirus, HHV6	*Mycoplasma pneumoniae*	Metabolic, toxic
	New onset psychosis	Y	Y	Y	Y		HCV, Rabies	*Bartonella,* prion disease	Autoimmune (e.g. SLE), psychiatric
	Diffuse cerebral edema	Y	Y	Y	Y		HMPV	*Mycoplasma pneumoniae*	
	Recurrent or chronic CNS inflammation	Y					HIV[4], JCV[4], BKV[4], SSPE[4]	*Mycoplasma pneumoniae,* Syphilis[4], Whipple's disease[4]	MS, vasculitis, other vascular process, autoimmune
	Seizures with rapid recovery	Y			Y	Y	Adenovirus	*Bartonella, Mycoplasma pneumoniae*	Metabolic, toxic, epilepsy
Focal	Temporal lobe	Y	Y	Y	Y	Y	HHV6	*Mycoplasma pneumoniae, Balamuthia, R. rickettsii* (RMSF), syphilis, fungal infection, prion disease	Tumor, vasculitis, autoimmune, paraneoplastic syndrome
	Cerebellar	Y				Y	Adenovirus, HCV, RV	*Mycoplasma pneumoniae*	Paraneoplastic syndrome, autoimmune, vascular, neoplasm
	Extrapyramidal movement disorders (thalamus/basal ganglia)	Y	Y	Y		Y	HHV6, Measles (SSPE) Respiratory viruses, WNV	TB, *S. pneumoniae, Mycoplasma pneumoniae*, prion disease	Autoimmune, paraneoplastic syndrome, neoplasm, metabolic, toxic, vascular
	Hydrocephalus	Y					Parainfluenza Adenovirus	Bacterial or Fungal infection, TB	Sinus thrombosis
Brainstem dysfunction[4]		Y					JEV, KUNV, MVEV, Nipah[2]	TB, *Listeria monocytogenes Burkholderia pseudomallei* Neuroborreliosis[4-CN palsies]	Paraneoplastic syndrome
Subacute behavioural / personality change[4]			Y				HIV, SSPE	Syphilis, Whipple's disease[4]	Autoimmune, paraneoplastic syndrome
Associated rash[4]		Y		Y			Dengue, HHV6, Measles	R. rickettsii (RMSF), *Neisseria meningitidis*	
Associated pneumonia[4]					Y		Nipah, Hendra	*Mycoplasma pneumoniae, Coxiella burnetii* (Q Fever)	

TABLE 3B. Etiologic specific tests for acute or post-infectious encephalomyelitis.

Adapted from what was published by the Working Group in the Appendix of the published case definition. Additions have been made based on more recent recommendations.[2-7] These are provided as information and not an exhaustive recommendation for testing. Regional variations should be considered (see Table 1B in Annex 1).

NOTE: *list specifically excludes bacterial agents primarily causing bacterial meningitis as it is assumed that these would be looked for routinely; also most fungal pathogens excluded because tend to present as a more prolonged chronic course; Not intended to be an exhaustive list.*

Tier 1(common worldwide etiologies)	Cerebrospinal fluid (CSF)	Blood / Serum as appropriate	Other
Bartonella hensellae (Cat-scratch disease)	PCR, serology, culture	PCR, acute/convalescent serology, culture	
Cytomegalovirus (CMV)	PCR, serology, culture	PCR, acute/convalescent serology, culture	
Cryptococcus neoformans*	PCR, antigen detection, India ink for yeast; culture, serology	acute/convalescent Serology	
Epstein Barr Virus (EBV)	PCR, serology, culture	PCR, acute/convalescent serology, culture	
Enteroviruses	PCR, serology, culture		Stool, rectal swab for culture
Human herpes virus 6 (HHV-6)	PCR, serology, culture	PCR, acute/convalescent serology, culture	
Human immunodeficiency virus (HIV)	PCR	PCR, Rapid antibody testing	
Herpes simplex virus 1 (HSV-1/HSV-2)	PCR (may be negative first 3 days[7], serology, culture	PCR, acute/convalescent serology, culture	
JC virus *	PCR		
Mycobacterium tuberculae	Acid-fast bacilli (AFB) stain, culture	AFB stain, culture	
Rabies	PCR, serology, culture, IFA		Brain biopsy – same as CSF tests Nuchal skin biopsy-PCR, IFA Saliva: PCR, IFA, culture
Treponema pallidum (TP) (Neurosyphilis) FTA-Abs: fluorescent treponemal antibody adsorbed MHA: microhemagglutination assay TPHA: TP hemagglutinating antibody	RPR, VDRL, culture, immunohistochemistry. Followed by confirmatory tests: (FTA-Abs, MHA-TP, TPHA) immunohistochemistry	RPR, VDRL; followed by confirmatory tests (same as for CSF), culture	
Trophyerma whippelli (Whipple's Disease)	PCR, serology	PCR, acute/convalescent serology	Intestinal or brain tissue: PCR
Varicella Zoster Virus (VZV)	PCR, serology, culture	PCR, acute/convalescent serology, culture	

Tier 2(common aetiologies but geographically restricted)	Cerebrospinal fluid (CSF)	Blood / Serum as appropriate	Other
Alphaviridae[a]	PCR serology	PCR, acute/convalescent serology	
Bunyaviridae[b]	PCR serology	PCR, acute/convalescent serology	
Flaviviridae[c]	PCR serology	PCR, acute/convalescent serology	
Borrelia burgdorferei (Lyme disease)	PCR serology		
Leptospira species	PCR serology, microagglutination testing	PCR, acute/convalescent serology, microagglutination testing	
Plasmodium species (Malaria)		Whole blood: smear	

* More common in immunosuppressed and HIV patients

[a] includes Eastern Equine (EEEV), Western Equine (WEEV), Venezuelan Equine (VEEV) Encephalitis Viruses;
[b] includes LaCrosse (LACV), Jamestown Canyon (JCV), Snowshoe hare, Cache Valley, another California serogroup viruses;
[c] includes St Louis (SLEV), West Nile (WNV), Japanese (JEV), Tick-Borne (TBEV), Murray Valley (MVEV) Encephalitis Viruses, Dengue, Zika and Roccio virus

Tier 3 (fewer common etiologies)	Cerebrospinal fluid (CSF)	Blood / Serum as appropriate	Other
Adenovirus			nasopharyngeal/throat swab: PCR, culture
Angiostrongylus cantonensis (Eosinophilic meningitis)	Parasite isolation, (presence of eosinophils in CSF suggestive)	Serology	Brain tissue: parasite isolation
Chlamydiae pneumoniae		PCR, acute/convalescent serology	
Ehrlichia chaffiensis	PCR, serology, culture	IFA for Antigen, acute/convalescent serology, whole blood PCR, culture	
Entamoeba histolytica	Microscopic identification of protozoa		Brain tissue, Fecal specimens/aspirate smears: identification of protozoa
Gnathostoma spinigerum (Gnathostomiasis)	Parasite isolation		Skin biopsy: parasite isolation
Henipavirus (Hendra, Nipah)[4]	PCR	PCR, acute/convalescent serology	PCR - respiratory, urine samples
Influenza A & B		Acute/convalescent serology	nasopharyngeal/throat swab: Antigen detection, PCR, culture
Measles	PCR, serology, culture	PCR, acute/convalescent serology, culture	

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Mumps	PCR, serology, culture	PCR, acute/convalescent serology, culture	
Mycoplasma pneumoniae	PCR, serology, culture	PCR, acute/convalescent serology, culture	
Parainfluenza			Nasopharyngeal/throat swab: Antigen detection, PCR, culture
Parvovirus B 19		PCR, acute/convalescent serology	
Primary amoebic meningoencephalitis (Naegleria fowleri, Acanthamoeba sp., Balamuthia mandrillaris)	Motile amoeba in fresh CSF or seen in stained CSF mounts; culture		
Rickettsia rickettsii (Rocky Mountain Spotted Fever)		acute/convalescent serology, antigen detection by immunofluorescence	Skin biopsy: antigen detection by immunofluorescence

The Brighton Working Group also noted additional tests that may be useful for investigating cause of acute encephalitis / ADEM (not available at all institutions):

- Serum:
    - Non-specific: CBC + diff, ESR, ALT, total protein, alkaline phosphatase, electrolytes, calcium, glucose, TSH, Vit B12, Folate, toxicology,
    - Auto-immune diseases: anti-nuclear antibody (ANA), Rheumatoid factor (RF), anti-double stranded DNA antibody, SS-A (Ro), SS-B (La), anti-cardiolipin antibody, angiotensin-converting enzyme, Lupus anticoagulant, serum protein electrophoresis
    - Autoimmune encephalitides: anti-NMDAR, anti-VGKC complex, anti-Hu, anti-Ma2, anti-GAD, anti-GABA-A-R, anti-GABA-B-R, anti AMPA-R, anti-GlyR, anti-DPPX, anti-mGlu-R5
- CSF: IgG index, IgG synthesis rate, oligoclonal bands, myelin basic protein, VDRL, RPR; anti-NMDAR, anti-VGKC complex.

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

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

TABLE 1. NARROW SEARCH TERMS FOR ENCEPHALITIS AND ENCEPHALOMYELITIS

UMLS Concept		Diagnostic Coding System Term and Codes			
CUI	Name	Term	MedDRA	ICD9CM	ICD10CM
C0014038	Encephalitis	Encephalitis	10014581		
		Encephalitis NOS	10014601		
C0751101	Post-vaccinal encephalitis	Encephalitis following immunization procedures	10014588 10056198		G04.02
		Encephalomyelitis, post immunization			G04.02
C0729577	Post-immunization encephalitis	Encephalitis post immunization	10014602 10054373		G04.02
C1719353	Encephalitis and encephalomyelitis following immunization procedures			323.51	G04.02
C1719358	Encephalitis, myelitis, and encephalomyelitis following immunization procedures			323.5	G04.02
C1719361	Postinfectious encephalitis, myelitis and encephalomyelitis			323.6	G04.01
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	

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

5.1. Encephalitis 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 encephalitis 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 encephalitis 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. Encephalitis may be accompanied by evidence of myelitis and there is extensive overlap between encephalitis and ADEM. There are separate companion guides for myelitis and ADEM available in both the Developers' toolbox and Brighton collaboration website, each with a similar Appendix 5 form for collecting relevant clinical data. 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 neurologic glossary of terms is available as well.

Seven 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. ENCEPHALITIS KEY CASE DEFINITION CRITERIA, LIKELY AND ACTUAL SOURCES OF INFORMATION

Criterion	Criterion category	Likely sources of information	Actual sources of information
A1	Brain histopathology	Surgical procedure(s) to obtain tissue samples Pathology/histopathology/autopsy reports;	
B	Encephalopathy – clinical evidence	Admitting history & physical; neurology and other consultation(s); discharge summary;	
C	Focal central nervous system (CNS) abnormal symptoms and signs		
E/F	Evidence for inflammation (fever, CSF pleocytosis, EEG and neuroimaging changes suggestive of inflammation)	Temperature chart; CSF laboratory results; CT scan/MRI finding(s)/report(s); other neuroimaging study report(s)	
X1	Exclusion criterion – alternative diagnosis for CNS abnormalities (neoplastic, vascular or metabolic disorder, infection, toxin)	Investigation/consultation for alternative diagnoses Discharge summary/diagnosis; Follow-up post discharge including hospital readmission; Neurology clinic visits;	

TABLE 2. ACUTE ENCEPHALITIS 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 terms 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-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	**B1 = UNKNOWN** IF **B1(a+b+c+d) = unknown** OR there is a combination of **No and unknown for B1(a + b + c + d)**
Glasgow Coma Score (if assessed during acute illness – see Tables 5A,B & C)	Best Eye Response: Best Verbal Response: Best Motor Response: Total Glasgow Coma Score:	Not a specific criterion but if known may help to complete section B2
Criterion B2 Accompanying encephalopathy – choose best answer for each of B2-a through B2-e	**B2-a.** Decreased or absent response to loud noise or painful stimuli: __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 = YES** IF **≥ 1 of B2(a-e) = Yes** **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 all of **(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 __1.Olfactory __2.Optic __3.Oculomotor __4.Trochlear __6.Abducens __5.Trigeminal __7.Facial __8.Vestibulocochlear __9.Glossopharyngeal __10.Vagus __11.Accessory __12.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(describe below)	
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) in the appropriate cell.	Strength / Normal / Weak(note worst grade out of 5 if known) / Not tested / Unknown Leg Arm	Use this space to provide more detai if needed for C1 – C8

C6 Sensory abnormalities
Specify location;

Location	Present (describe)	Not present	Not tested	Unknown

C7 Altered deep tendon reflexes
Specify sidedness (same as for C5)

Site	Absent	Decreased	Normal	Increased	Not tested	Unknown
Ankle						
Knee						
Biceps						
Triceps						
Other						

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
Criterion A1

A1. Spinal cord biopsy results: check all that apply below
1___acute inflammation of brain parenchyma
2___meningeal involvement in the inflammation
3___area(s) of demyelination (__multifocal. __focal. __diffuse)
4___normal histopathology
5___Other- describe:
6___Biopsy not done OR Biopsy done results unknown OR unknown if Biopsy done

A1 = YES IF **1 checked**
A1 = NO IF **4 or 6 checked**
***Caveat 1**: if only 2 and /or 5 checked will need expert help to assign criterion A1*
***Caveat 2**: if 3 checked should be assessed as possible ADEM*

E. Indicators of CNS inflammation
Criteria:
E1 - Fever

E2 - CSF pleocytosis

E1. Fever temperature ≥ 38.0C by any measured method (history of fever insufficient)
___YES (highest temp:) __NO __UNKNOWN (if no recorded measurement)

E1 = YES NO UNKNOWN

E2. Cerebrospinal fluid (CSF): ___Not collected ___Unknown if collected
___Collected – Provide results below (sample date dd/mon/yy: __/___/__)

CSF Parameter	Result	Not tested/no result
Opening/Closing pressure(mmHg)		
WBC count (cells/uL)		
WBC differential		
RBC count (cells/uL)		
Protein (mg/dl)		
Glucose (mg/dl)		

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:
  - E2 = NO IF ≤ 15 WBC/ul
  - E2 = YES IF >15 WBC/ul
- If age ≥ 2mo:
  - E2 = NO IF ≤ 5 WBC/ul

<table>
<tr>
<td></td>
<td>
<table>
<tr><td>Gram stain</td><td></td><td></td></tr>
<tr><td>Rapid antigen test</td><td></td><td></td></tr>
<tr><td>Culture</td><td></td><td></td></tr>
</table>
Other (describe)
</td>
<td>

- E2 = YES IF >5 WBC/ul

E2 = YES NO UNKNOWN
</td>
</tr>
<tr>
<td>E3 - EEG</td>
<td>
EEG ___Done*(check most appropriate result below) __Not Done __Unknown if done
___0. Results unavailable or uninterpretable
___1. Normal
___2. Changes consistent with encephalitis (includes but not limited to diffuse or multifocal nonspecific/non-physiologic background slowing. Seek expert help if unable to conclude if consistent with encephalitis).
___3. Inconsistent with encephalitis
</td>
<td>
E3 = YES IF 2 checked

E3 = NO IF 1 or 3 checked.

E3 = UNKNOWN IF 0 checked OR
EEG Not done OR Unknown if EEG done
</td>
</tr>
<tr>
<td>E4, F1
Neuroimaging

* NOTE: For all neuroimaging listed it is possible that more than one choice can be correct:
e.g. Head CT could have 1 + 4 checked;
Brain MRI could have 1+4 or 1+5 checked as well as 6. The rightmost column gives the key results to score the criteria for encephalitis</td>
<td>
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
<table>
<tr><th></th><th>Test</th><th>Results (check all applicable)*</th></tr>
<tr><td>E4</td><td>Head CT</td><td>__0. Not done or done but results unavailable/uninterpretable
__1. Acute inflammation OR consistent with encephalitis (include but not limited to: areas of hypodensity; contrast images showing meningeal & parenchymal enhancement or gyral enhancement)
__2. Normal
__3. Inconsistent with encephalitis
__4. Other (Describe)</td></tr>
<tr><td>F1</td><td>Brain MRI</td><td>__0. Not done or done but results unavailable/uninterpretable
__1. Acute inflammation or consistent with encephalitis
__2. Normal
__3. Inconsistent with encephalitis
__4. Diffuse or multifocal white matter lesions / demyelination
__5. Inconsistent with diagnosis of ADEM
__6. Other (describe)</td></tr>
</table>
</td>
<td>
E4 = YES IF E4 = 1
E4 = NO IF E4 = [2 OR 3]
E4 = UNKNOWN IF E4 = 0

F1 = YES IF F1 = [1 OR 4]
F1 = NO IF F1 = [2 OR 3]
F1 = UNKNOWN IF F1 = 0
Caveat 3: IF both Head CT and Brain MRI done and results differ, seek expert help to decide which most accurately reflects presence or absence of inflammation and/or demyelination consistent with encephalitis
Caveat4: if E4=4 or F1=6 seek expert help to interpret and assign the appropriate criterion values for E4 and F1
</td>
</tr>
<tr>
<td>X1. Exclusion criterion</td>
<td>
X1 Alternative diagnosis for illness? __Yes * __No __Unknown
*If yes describe (e.g., neoplasm, vascular disorder, toxic/metabolic encephalopathy)
</td>
<td>
X1 = MET NOT MET

X1 = MET IF X1 = Yes
X1 = NOT MET IF X1 = No or Unknown
</td>
</tr>
</table>

TABLE 3. BASED ON TABLE 2 DATA CIRCLE STATUS FOR EACH LISTED CRITERION BELOW AND RECORD FINAL DISPOSITION IN RIGHTMOST COLUMN

Diagnostic Criteria:					Additional decisions regarding diagnostic criteria	Final Criterion disposition
A. **Brain histopathology**	**A1**	Yes	No			**A1 =**
B. Encephalopathy	**B1**	Yes	No	Unknown	**B=YES** IF **B1+B2 both = Yes** **B=NO** IF **B1+B2 both = No.** Else **B = UNKNOWN**	**B =**
	B2	Yes	No	Unknown		
C. Focal/multifocal CNS abnormalities	**C**	Yes	No	Unknown		**C =**
E. Indicators of CNS inflammation:	**E1**	Yes	No	Unknown	**E = 0** IF **[E1+E2+E3+E4+F1] = No or unknown** **E = 1** IF **Yes to only 1 of [E1,E2,E3,E4 or F1]** **E = ³2** IF **Yes to ³2 of [E1, E2, E3, E4 or F1]**	**E =**
	E2	Yes	No	Unknown		
	E3	Yes	No	Unknown		
	E4	Yes	No	Unknown		
	F1	Yes	No	Unknown		
X. Exclusion Criterion	**X1**	Met	Not met			**X1 =**

TABLE 4. USING INFORMATION FROM TABLE 3, DETERMINE CORRECT LEVEL OF CERTAINTY(LOC) FOR ENCEPHALITIS BASED ON FORMULAE BELOW

LOC	
Level 1	**A1 = YES** ***(NOTE: X1 does not apply to Level 1)***
Level 2	**[B &/OR C] = YES AND E = ≥ 2 AND X1 = NOT MET**
Level 3	**[B &/OR C] = YES AND E = 1 AND X1 = NOT MET**
Level 4	**Reported as Encephalitis but insufficient evidence to meet any case definition level AND X1=NOT MET**
Level 5 (Not a case)	**[A1 & B & C = NO] OR [meets level 2 OR 3 but X1=MET]**

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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

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
Encephalitis Tabular Checklist for Key Case Definition Criteria and Level of Certainty Algorithm

6.1 Encephalitis 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 – 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 Acute inflammation of brain parenchyma	A1	Yes	No	Unknown		A1 =
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 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 =
E/F. Indicators of CNS inflammation:						
1. Fever ≥ 38.0° C	E1	Yes	No	Unknown	E=0 IF [E1+E2+E3+E4+F1] = NO OR UNKNOWN E=1 IF 1 of [E1,E2,E3,E4 or F1] = YES E=≥2 IF ≥ 2 of [E1,E2,E3,E4orF1]= YES	E =
2. CSF pleocytosis: IF < 2mos old: > 15WBC/uL; IF ≥ 2mos old: > 5 WBC/uL	E2	Yes	No	Unknown		
3. EEG findings consistent with encephalitis (diffuse/multifocal slowing)	E3	Yes	No	Unknown		
4. Brain CT(E4) shows acute inflammation +/or demyelination	E4	Yes	No	Unknown		
5. Brain MRI(F1) shows acute inflammation +/or demyelination	F1	Yes	No	Unknown		
X1. Exclusion Criterion: Alternative diagnosis for illness (cancer, vascular disorder, toxic or metabolic process)	X1	MET	NOT MET			X1 =

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

LOC	
Level 1	**A1 = YES *(NOTE: X1 does not apply to Level 1)***
Level 2	**[B &/OR C] = YES AND E = ≥ 2 AND X1 = NOT MET**
Level 3	**[B &/OR C] = YES AND E = 1 AND X1 = NOT MET**
Level 4	**Reported as Encephalitis but insufficient evidence to meet any case definition level AND X1=NOT MET**
Level 5 Not a case	**[A1 & B & C = NO] OR [meets level 2 OR 3 but X1=Met]**

[1] *Encephalitis may be hard to distinguish from ADEM (criteria B & C are identical for the two). If there is evidence of demyelination the case should be assessed for ADEM LOC as well. If case meets level 3 ADEM & encephalitis classify as level 3A. If there is myelopathy, assess LOC for myelitis also.*

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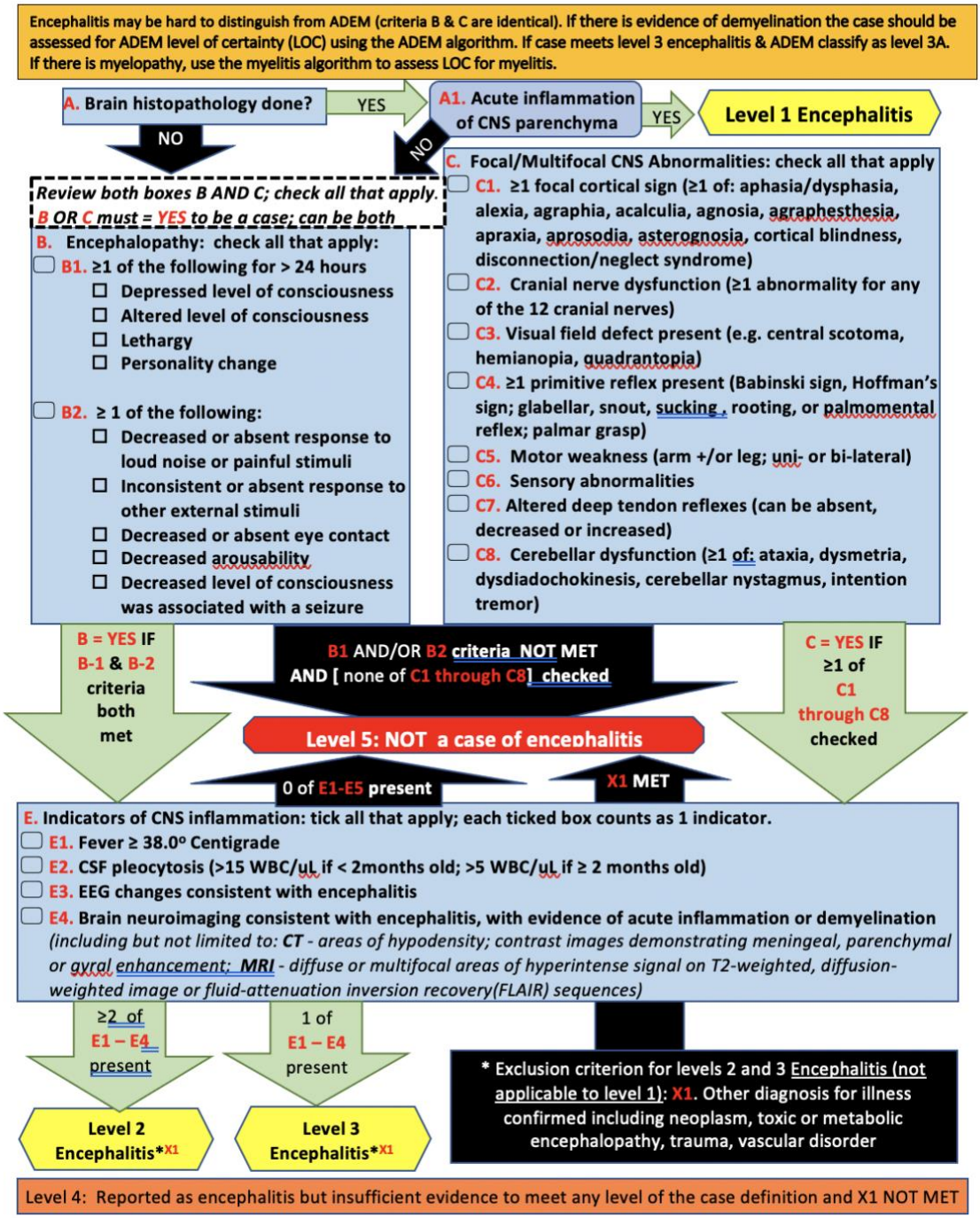
APPENDIX 7
Encephalitis Pictorial Level of Certainty Algorithm

7.1 Encephalitis Pictorial level of certainty algorithm

Use available clinical history, examination and laboratory investigation results to determine level of diagnostic certainty for Encephalitis. Consult companion guides for myelitis if myelopathy present and for ADEM if demyelination present are available in both the Developers' toolbox and Brighton collaboration website



APPENDIX 8.

Methodology: Brief Summary

8.1. Encephalitis 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 encephalitis 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 encephalitis.[2-11]

8.2. Encephalitis Background Incidence [12-36]

A systematic literature search to estimate the incidence of acute encephalitis in the population was conducted using the following search strategy:
("Encephalitis"[Mesh:noexp] OR "Encephalomyelitis"[Mesh:noexp] OR "encephalitis"[ti] OR "encephalomyelitis"[ti] OR "meningoencephalitis"[ti]) 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 encephalitis were

extracted. Encephalitis 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.[13-36] The spreadsheet with all extracted background incidence data is available on the Brighton Collaboration website.

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

The published Brighton case definition for encephalitis was reviewed and key aspects identified with particular relevance to real time assessment of encephalitis in the context of a clinical trial where it occurs as an AEFI. In addition, the guideline section of the published encephalitis case definition was reviewed, and key recommendations identified for data collection, analysis and presentation. Two publications used for risk factors that also provided updated details on diagnosis of encephalitis were used to update the recommendations.[2,4]

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. Encephalitis ICD-9/10-CM and MedDRA Codes [37-41]

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[37] 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.[38] 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.[39,40] A text-indexing engine Peregrine uses this dictionary to identify medical concepts in the case definition.[41]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 encephalitis Brighton case definitions for all Tier 1 AESI. The concepts identified for encephalitis were considered relevant for background incidence rate determination as well as to study hypotheses related to encephalitis as a vaccine-product related reaction. Most of the terms include encephalitis and acute disseminated encephalomyelitis since encephalitis 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 encephalitis[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 encephalitis 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.