Safety Platform for Emergency vACcines

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

Aseptic Meningitis

Work Package: WP2 Standards and tools

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DEFINITIONS & ACRONYMS

AESI	Adverse Events of Special Interest
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
CRP	C-Reactive Protein
CSF	Cerebrospinal Fluid
CUI	Concept Unique Identifier
EBV	Epstein Barr Virus
HIV	Human Immunodeficiency Virus
HLMIC	High, Low, Middle Income Countries
HHV-6	Human Herpes Virus 6
HSV-1	Herpes Simplex Virus Type 1
HSV-2	Herpes Simplex Virus Type 2
ICD	International Classification of Diseases
IOM	Institute of Medicine
LCMV	Lymphocytic Choriomeningitis Virus
LP	Lumbar Puncture
MedDRA	Medical Dictionary for Regulatory Activities
MMR	Measles Mumps Rubella (vaccine)
PCR	Polymerase Chain Reaction
RBC	Red Blood Cell
SPEAC	Safety Platform for Emergency Vaccines
spp	Species (in context where pathogen genus but not species named)
TB	Tuberculosis
UMLS	Unified Medical Language System
VZV	Varicella Zoster Virus
WBC	White Blood Cell
WHO	World Health Organization

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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 aseptic meningitis.

2. Objective of this deliverable

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

3. Methods

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

- Aseptic meningitis risk factors and background rates and risk factors: SO1-D2.4 Tier 1 AESI: Risk Factors and Background Rates
- Aseptic meningitis Case definition key caveats for diagnosis, data analysis and presentation: SO1-D2.7 Guidance for CEPI Developers
- Aseptic meningitis Diagnostic Codes: SO2-D2.3 Tier 1 AESI: ICD-9/10-CM and MedDRA Codes
- Aseptic meningitis 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. Aseptic meningitis Risk Factors
2. Aseptic meningitis Background Rates
3. Aseptic meningitis Case Definition key caveats for diagnosis, data analysis and presentation
4. Aseptic meningitis Diagnostic Codes: ICD-9CM, ICD-10CM, MedDRA
5. Aseptic meningitis Data Abstraction and Interpretation Form for Medical Chart Review
6. Aseptic meningitis Tabular checklist for key case definition criteria and level of certainty algorithm
7. Aseptic meningitis Pictorial level of certainty algorithm
8. Summary of methods for creation of each tool. Some of the documents with a detailed methodology will be available at the Brighton Collaboration website and this will be indicated in appendix

5. Recommendations & discussion

This guide brings together many resources and tools related to the AESI of aseptic meningitis 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 aseptic meningitis 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 aseptic meningitis. This standard, harmonized approach will facilitate signal detection and assessment as well as the capacity to combine data across trials for meta-analyses.

6. References

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APPENDIX 1.
Aseptic meningitis Risk Factors

1.1. Aseptic meningitis Risk Factors

TABLE 1. ASEPTIC MENINGITIS RISK FACTORS [1-9]

Age[1-5]	• Premature infants • Adults ≥60
Season[1-5]	Infectious Causes • Enteroviruses cause 85-95% of cases and have a May-October prevalence in temperate climates but occur throughout the year in tropical climates • Mosquito spread arboviruses more common in the rainy season in tropical climates or in spring – summer – early fall in temperate climates
Comorbidity[4]	• Persistent enteroviral viral infection in those with congenital hypo- or agammaglobulinemia
Infection	• As noted above, enteroviruses cause by far the vast majority of aseptic meningitis cases. See appendix 3, Table 3.1 for a list of the other, less common etiologies as well as the differential diagnoses to be considered for aseptic meningitis.

Vaccine	• The Institute of Medicine (IOM) evaluated mechanistic and epidemiologic evidence for meningitis following MMR and Varicella Zoster vaccines used in the US and concluded the following: [6,7]
	  ○ the evidence was inadequate to accept or reject a causal relationship between Jeryl-Lynn or Rubini mumps containing vaccine and meningitis
	  ○ the evidence from a single case supported a causal association between VZV vaccine and disseminated Oka VZV with subsequent meningitis in a child with demonstrated immunodeficiency.
	  ○ The evidence from multiple cases of meningitis associated with reactivation of VZV vaccine strain virus strongly supports a causal relationship between vaccination and later meningitis (months to years after immunization) in the context of vaccine strain reactivation. Several cases occurred in the absence of immunocompromise.
	• An updated review of evidence published since the 2011 IOM report for the same vaccines had a similar conclusion to IOM regarding MMR and VZV with no new associations involving other vaccines routinely given in the USA.[8]
	• A global pharmacovigilance study with participants from H and LMIC countries spanning all 6 WHO regions assessed the risk of aseptic meningitis following mumps containing vaccines[9]:
	  ○ Adjusted overall relative incidence 10.8 [95% CI 4.0-29.2]. The risk following Leningrad-Zagreb mumps strains was significantly increased: 10.8 [1.3-87.4]. Estimates for other mumps virus strains (S79, Urabe Am9, RIT 4385/Jeryl-Lynn) couldn't be assessed. The highest IRR was in Iran: 20.3 (4.8-85.2) and applied to Hosino/Leningrad-Zagreb/UrabeAm9 with inability to distinguish between the strains.
	• Risk interval of 8-35 days for aseptic meningitis following mumps containing vaccines[9]

APPENDIX 2.
Aseptic meningitis Background Rates

2.1 Aseptic meningitis Background Rates

TABLE 1. ASEPTIC MENINGITIS BACKGROUND RATES [10-14]

Country [reference]	Study years	Population (age in years)	Incidence rate per 100,000 person years [95% confidence interval] (total cases)		
			All	Males	Females
AFRICA					
Libya[10]	1983-1984	15-36	3.4 (17)		
AMERICAs					
USA (Minnesota)[11]	1950-1959	All ages (adjusted rate)	11.4 [8.6-14.3]		
	1960-1967	All ages (adjusted rate)	8.5 [6.4-10.6		
	1970-1975	All ages (adjusted rate)	9.5 [6.9-12.0]		
	1976-1981	<1 1-4 5-9 ≥10 **All ages** (adjusted rate)	No data 27.7 16.7 11.7 **17.8 [14.3-21.3]**		
EUROPE					
England[12] Nationwide (confirmed viral meningitis)	1999-2003	≥16	2.73 [2.13-3.44] (1389)		
England [12] Northwest (confirmed viral meningitis)			1.27 [0.99-1.60] (71)		
Finland[13]	1999-2003	16-84	7.6 (144)		
Finland[14]	1980	All ages	26.7 (128)		

APPENDIX 3

Aseptic meningitis Case Definition Key Caveats for Diagnosis, Data Analysis and Presentation

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

- Key elements of Case Definition (CD)
  - Only 2 levels of diagnostic certainty
  - Lumbar puncture for CSF examination is critical to meeting the case definition, with WBC pleocytosis and results of a gram stain being more important than culture results (See Figure 1 below). The working group did not incorporate other CSF measurable parameters into the CD for reasons as noted[1]:
    - CSF glucose/protein: low diagnostic accuracy for distinguishing bacterial from non-bacterial meningitis in the setting of having a negative gram stain.
    - CSF lactate / CRP: not available in all settings.
    - Polymorphonuclear cell differential count: may be present early in the course of viral meningitis and thus not useful as a criterion to rule out aseptic meningitis
    - Latex agglutination results not included because of low diagnostic accuracy
    - PCR not included because of false positive results that may arise due to contamination and false negative results due to inhibitors of amplification reaction that may be present in the sample.
  - CSF criteria are part of the case definition for encephalitis. **For cases with other diagnostic features of encephalitis (altered level of consciousness, focal neurologic abnormalities) the WG recommends that the case be assessed as encephalitis, not aseptic meningitis.** A companion guide for encephalitis is available and should be used in such cases. Further if a case meets a level of certainty for both encephalitis and aseptic meningitis, it should be reported as encephalitis.

- Duration of Surveillance
  - All reports of aseptic meningitis should be collected regardless of the time elapsed between vaccination and the adverse event. If not feasible study periods during which safety data are being collected should be clearly defined.

- Recommendations for real time assessment
  - A lumbar puncture (LP) for collection and examination of cerebrospinal fluid (CSF) is absolutely required to meet any level of the case definition. At a minimum, there needs to be a white blood cell (WBC) count and a gram stain.
  - Ensure that the date and time of CSF collection and first dose of antibiotic therapy are documented
  - CSF investigation for possible causes of meningitis (see Table 3.1 below for possible, albeit not all, etiologies)
    - For live attenuated vaccine platforms: PCR or culture as appropriate for the vaccine/vector strain
    - For trial sites in target disease endemic areas: test as appropriate for the wild type strain
    - Depending on laboratory capacity, CSF should be sent for viral, fungal, protozoan and parasitic pathogens known to be common to the geographic area (by stain techniques, culture, PCR as appropriate)
    - CSF should also be tested for typical meningeal bacterial pathogens as appropriate for age
  - Blood should be collected for serologic studies (preferably as paired acute & convalescent samples)
  - For each trial site a list of the common local causes of viral meningitis should be compiled and feasibility for investigation determined. Variation in etiology by age should also be determined.

- Peripheral blood may contaminate the CSF if the lumbar puncture is traumatic. The case definition provides guidelines for interpretation based on peripheral blood WBC and RBC counts as follows:
  - Visual threshold for blood contamination of CSF is 400 RBC/uL.[1]
  - If there is a traumatic LP, CSF pleocytosis is defined as one of the following:
    - If blood WBC and RBC counts are known:
      - Calculate predicted CSF WBC: CSF RBC X (Blood WBC/Blood RBC)
      - CSF pleocytosis exists if the ratio of observed CSF WBC: predicted CSF WBC >1:1
    - If blood WBC and RBC counts are not known:
      - CSF pleocytosis exists if ratio of CSF WBC: CSF RBC is >1:500

TABLE 1. DIFFERENTIAL DIAGNOSIS OF ASEPTIC MENINGITIS [1-5]

Process	Subgroup	Specific Etiology or Diagnosis

Meningeal infection	Viral	• Enteroviruses 85-95% of cases
		  ○ Echovirus 30 and Coxsackie A1 the most common
		  ○ Also Echo subtypes 6, 7, 9, 11, 16, 18, 25 and 71
		  ○ Also Coxsackie subtypes A9, B1, B2, B3, B4
		• Vaccine preventable viruses that caused meningitis relatively frequently prior to widespread immunization
		  ○ Mumps, Poliovirus, Measles
		• Herpesviruses – range from 0.5-3% of cases
		  ○ HSV-1, HSV-2, HHV-6, CMV, EBV, VZV
		• HIV
		• Other common viruses that can rarely cause meningitis
		  ○ Influenza, Parainfluenza, Rotavirus,
		• Parvovirus B19
		• Arboviruses – rare but more common in certain geographic areas
		  ○ Flaviviruses (e.g. St Louis encephalitis, West Nile, Jamestown Canyon, snowshoe hare)
		  ○ Bunyaviruses (e.g. La Crosse)
		  ○ Alphaviruses
		  ○ Reoviruses
		  ○ Tick-borne encephalitis virus
		• Lymphocytic choriomeningitis virus (LCMV)
		• Human parechovirus
		• Live attenuated vaccine strain viruses known to cause meningitis
		  ○ Mumps' vaccine strains especially Urabe (1/2041 doses), Leningrad-Zagreb, Hoshino strains: 5.5-38-fold higher risk than other strains, with onset 2-7 weeks after immunization. Extremely low risk with commonly used Jeryl-Lynn vaccine strain - <1/1.8 million doses

	Bacterial	• Partially treated bacterial meningitis – classic pathogens – *Streptococcus pneumoniae, Haemophilus influenzae, Neisseria menigitidis, Listeria monocytogenes* • Bacterial pathogens that don't grow on commonly used culture media to rule out the classic bacterial pathogens noted above:

		○ *Mycobacterium tuberculosis* ○ *Treponema pallidum* (syphilis) ○ *Borrelia burgdorferi* (Lyme disease) ○ *Mycoplasma spp* ○ *Chlamydia spp* ○ *Rickettsia spp* ○ *Bartonella henselae* (cat scratch disease) ○ *Leptospira spp* ○ *Brucella spp*
	Parasitic	• Toxoplasmosis • Malaria • *Acanthamoeba spp*
	Fungal	• *Cryptococcus spp*
Parameningeal infection		• Sinusitis, Otitis, Mastoiditis • Abscess – brain, spinal cord, vertebral body • Vertebral or skull osteomyelitis • Cysts
Malignancy		• Meningeal carcinomatosis • Leptomeningeal metastasis from primary tumors especially leukemias, lymphomas
Autoimmune or immune-mediated Vasculitis		• Systemic lupus erythematosus • Sarcoidosis • Kawasaki disease • Sjögren's syndrome • Multisystem Inflammatory Syndrome (COVID-19)
Drugs		• Non-steroidal anti-inflammatory drugs (NSAIDs) • Intravenous immunoglobulins

- Data Collection Guidelines
  - document date and time of onset of signs and symptoms suggestive of meningitis
  - CSF: document date and time of 1st simple; CSF WBC and RBC count; CSF gram stain and culture results including if not performed; document all investigations for possible microbial pathogens
  - Document details of antibiotic therapy including timing of first dose relative to obtaining CSF sample
  - Document date and time of recovery and presence of any sequelae including fatal outcome.
- Data Analysis Guidelines
  - In addition to classifying cases by level of certainty, where possible also classify as:
    - Confirmed vaccine associated etiology
    - Probable vaccine associated etiology
    - Possible vaccine associated etiology
    - Unknown etiology
    - Non-vaccine-associated etiology
  - The interval between immunization and onset of aseptic meningitis should be analyzed in predefined increments such as 1st week (0-7 days), 2nd week (8-14 days) etc. up to >10 weeks (>71 days).
  - If few cases are reported the respective values of time to event should be presented individually.

APPENDIX 4

Aseptic Meningitis Diagnostic Codes: ICD-9/10-CM and MedDRA

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

TABLE 1. CONCEPTS AND CODES FOR ASEPTIC MENINGITIS

UMLS Concept		Diagnostic Coding System Term and Codes			
CUI	Name	Term	MedDRA	ICD9CM	ICD10CM
C0025290	Aseptic meningitis	Aseptic meningitis	10003458		G03.0
		Meningitis aseptic	10027201		
C0154651	Non-pyogenic meningitis	Non-pyogenic meningitis	10029669	322.0	
		Non-pyogenic meningitis	10057724		G03.0
C0025297	Viral meningitis	Viral meningitis	10047469		A87
		Viral meningitis, unspecified	10046236		A87.9
		Meningitis viral	10027260		
		Meningitis viral NOS	10027262		
C0153092	Mumps meningitis	Mumps meningitis	10028263	072.1	B26.1
		Mumps virus meningitis	10028273		
		Meningitis mumps	10027250		
		Meningitis due to mumps virus	10027220		
C0276430	Enterovirus meningitis	Enteroviral meningitis			A87.0
		Meningitis due to enterovirus	10027213	047	
		Meningitis due to enterovirus, other	10027214		
		Meningitis due to another enterovirus	10027222		
		Meningitis due to enterovirus, unspecified	10027215		
		Meningitis due to unspecified enterovirus	10027229		
C0276431	Coxsackie meningitis	Meningitis due to coxsackie virus	10027211	047.0	
		Coxsackie aseptic meningitis	10011253		
		Meningitis coxsackie viral	10027208		
C0338388	Echovirus meningitis	Echovirus meningitis			A87.0
		Meningitis due to echo virus	10027212	047.1	
		Meningitis echo viral	10027231		
C0029843	Other specified viral meningitis		10032945	047.8	
C0025297	Viral meningitis	Unspecified viral meningitis		047.9	
C0868783	Meningitis due to viruses not elsewhere classified			321.2	
C2887055	Aseptic leptospiral meningitis	Aseptic meningitis in leptospirosis			A27.81

No broad codes identified

APPENDIX 5
Aseptic meningitis Data Abstraction and Interpretation Form for Medical Chart Review

5.1. Aseptic meningitis Data Abstraction and Interpretation Form for Medical Chart Review

Instructions are provided with each table. The focus is on the specific data needed to meet and/or exclude myelitis based on the Brighton case definition.[1] This form will be most applicable to situations where a hospital/other institutional chart is available and used retrospectively to gather the information needed to validate that a case coded as aseptic meningitis 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. If symptoms/signs of encephalopathy or focal cortical signs accompany meningitis manifestations the case should be assessed as encephalitis for which a separate companion guide is available both in the Developers' toolbox and Brighton collaboration website. A neurologic glossary of terms is available as a separate document.

Four tables are included in the form.

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

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

Criterion	Criterion category	Likely sources of information	Actual sources of information
A	Clinical evidence of acute meningitis	Emergency room assessment Admitting history and physical Consultations (especially infectious disease, neurology)	
B	CSF pleocytosis	Laboratory results – Emergency room records and inpatient. records	
C	CSF gram stain		
D	CSF culture		
	CSF antigen / PCR tests		
E	Antibiotic therapy	Emergency room treatment records Admitting orders Pharmacy / therapeutic records	

TABLE 2. ACUTE ASEPTIC MENINGITIS DATA ABSTRACTION FORM

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

<table>
<tr><th>1.Data Category</th><th>2.Results (Note: Glossary of neurologic terms available as a separate document)</th><th>3.BCCD Criteria Value Determination</th></tr>
<tr><td>Patient age</td><td>___ ≤ 2 months old ___ > 2months old ___unknown
Specify age if known: _____</td><td>(needed for assessing CSF pleocytosi)</td></tr>
<tr><td>Illness onset</td><td>a) Date of first symptom(s) onset: (dd/mon/yy): __ / ___ /__
b) Hospital admission? ___Yes ___No ___Uncertain
If yes date of admission: (dd/mon/yy): __ / ___ /__</td><td>NA</td></tr>
<tr><td>Diagnosis</td><td>Admitting diagnosis:
Discharge diagnosis:</td><td></td></tr>
<tr><td>Criterion A Clinical evidence of acute meningitis</td><td>For each of the following symptoms/signs check what best applies to the acute illness:
<table>
<tr><th>Symptom/Sign</th><th>Present</th><th>Absent</th><th>Not Assessed</th><th>Unknown</th></tr>
<tr><td>1. Temp ≥ 38°C</td><td></td><td></td><td></td><td></td></tr>
<tr><td>2. Headache</td><td></td><td></td><td></td><td></td></tr>
<tr><td>3. Vomiting</td><td></td><td></td><td></td><td></td></tr>
<tr><td>4. Bulging fontanelle</td><td></td><td></td><td></td><td></td></tr>
<tr><td>5. Stiff neck</td><td></td><td></td><td></td><td></td></tr>
<tr><td>6. Kernig’s sign</td><td></td><td></td><td></td><td></td></tr>
<tr><td>7. Brudzinski’s sign</td><td></td><td></td><td></td><td></td></tr>
<tr><td>8. Other</td><td></td><td></td><td></td><td></td></tr>
</table></td><td>A = YES IF ≥ 1 of A1-A8 = Present
A = NO IF ALL of A1-A7=Absent and no other clinical evidence of acute meningitis (A8)
Else A = UNKNOWN</td></tr>
<tr><td>Criteria B, C, D</td><td>Lumbar puncture (LP): ___DONE* ___NOT DONE ___Unknown if DONE
* Date & time of LP: _____</td><td>B = UNKNOWN IF LP not done OR not known if LP done OR if no results for CSF WBC count</td></tr>
</table>

<table>
<tr>
<td>Cerebrospinal fluid (CSF) examination</td>
<td>Record all available results in table below:
<table>
<tr><th>CSF Parameter</th><th>Result</th><th>Not tested/no result</th></tr>
<tr><td>Opening pressure(mmHg)</td><td></td><td></td></tr>
<tr><td>Closing pressure(mmHg)</td><td></td><td></td></tr>
<tr><td>WBC (cells/uL)(Criterion B)</td><td></td><td></td></tr>
<tr><td>WBC differential</td><td></td><td></td></tr>
<tr><td>RBC count (cells/uL)</td><td></td><td></td></tr>
<tr><td>Protein (mg/dl)</td><td></td><td></td></tr>
<tr><td>Glucose (mg/dl)</td><td></td><td></td></tr>
<tr><td>Gram stain (Criterion C)</td><td></td><td></td></tr>
<tr><td>Rapid antigen test</td><td></td><td></td></tr>
<tr><td>PCR test</td><td></td><td></td></tr>
<tr><td>Bacterial Culture (Criterion D)</td><td></td><td></td></tr>
<tr><td>Viral/TB/fungal culture</td><td></td><td></td></tr>
<tr><td>Other(Describe)</td><td></td><td></td></tr>
</table>
NOTE: RBCs in CSF indicate traumatic LP (unless other reason such as head trauma/CNS bleed). Can use two alternate methods to define pleocytosis:
a. If peripheral blood CBC done near or at same time as LP calculate predicted CSF WBC and presence of CSF pleocytosis using the formulae below:
• predicted CSF WBC = CSF RBC X (blood WBC / blood RBC).
• CSF pleocytosis present if observed CSF WBC: predicted CSF WBC > 1 : 1
b. If no peripheral blood CBC available: ratio of CSF WBC:CSF RBC >1:500 = pleocytosis</td>
<td>If CSF WBC results available then:
• If age < 2 months:
• B = NO IF ≤15 WBC/ul
• B = YES IF >15 WBC/ul
• If age ≥ 2mo:
• B = NO IF ≤5 WBC/ul
• B = YES IF >5 WBC/ul then

C = C1 IF No organisms seen on gram stain
C = C2 IF Gram positive OR Gram negative organisms seen on gram stain
C = C3 IF Gram stain: Not done OR Done but results unavailable OR Not known if done

D = D1 IF CSF bacterial culture negative
D = D2 IF CSF bacterial culture positive
D = D3 IF CSF bacterial culture not done
D = D4 IF CSF bacterial culture done but results unavailable OR uninterpretable OR unknown if culture done</td>
</tr>
<tr>
<td>Criterion E Antibiotic therapy</td>
<td>Check the option that applies to treatment with antibiotic(s):
___1. Not given OR not started until after CSF collected for bacterial culture
___2. Started before CSF collected for bacterial culture
___3. Details of antibiotic therapy relative to timing of CSF collection for culture unknown OR unavailable OR uncertain</td>
<td>Criterion E = 1,2 or 3 as checked</td>
</tr>
</table>

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

Clinical Criteria	Criterion Values
A. Clinical evidence of acute meningitis	__YES __NO __UNKNOWN
B. CSF pleocytosis	__YES __NO __UNKNOWN
C. CSF gram stain	__C1 __C2 __C3
D. CSF culture	__D1 __D2 __D3 __D4
E. Antibiotic therapy	__E1 __E2 __E3

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

LOC	
Level 1	A=YES AND B=YES AND C=C1 AND D=D1 AND E=E1
Level 2	A=YES AND B=YES AND C=C1 AND EITHER: [D=D3] OR [D=D1 AND E={E2 OR E3}]
Level 3	Not applicable
Level 4	Reported as a case of aseptic meningitis but (A OR B) = UNKNOWN or C=C3 or D=D4
Level 5 (Not a case)	(A &/OR B) = NO OR C=C2 OR D=D2

NOTE: *Recovery of TB, fungus, virus, parasite, spirochete or other (e.g. amoeba seen in wet prep) is not relevant to criteria to satisfy case definition, although all are considered causes of 'aseptic meningitis' because none are isolated on routine culture which includes media designed to recover the typical bacterial pathogens: H. influenza, S. pneumoniae, N. meningitides, Listeria monocytogenes, Group B streptococcus, Gram negative bacterial pathogens like E. coli; Recovery of these organisms do speak to causality of aseptic meningitis following immunization and thus are key data to gather if known. NOTE: If vaccine virus species identified in CSF (tissue culture, PCR and sequence or restriction fragment – length polymorphism (RFLP) analysis) then causal association between vaccine virus and aseptic meningitis confirmed (e.g., mumps Urabe strain, VZV vaccine strain).*

Caveats: *re applying aseptic meningitis or encephalitis case definition: Meningitis may accompany encephalitis. If any of the criteria for encephalitis are present (altered level of consciousness, multifocal of focal central nervous system signs, symptoms etc.) the case should be assessed using the encephalitis data abstraction and interpretation form in the encephalitis companion guide which can be found in the Developers' toolbox and Brighton collaboration website*

APPENDIX 6

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

6.1 Aseptic meningitis 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. PRESENT MEANS IT WAS DOCUMENTED AS PRESENT; ABSENT MEANS IT WAS DOCUMENTED TO BE ABSENT; NOT ASSESSED MEANS IT WAS DOCUMENTED THAT THE CRITERION WAS NOT ASSESSED; UNKNOWN MEANS THERE WAS NO DOCUMENTATION REGARDING THE CRITERION.

A. Clinical evidence of acute meningitis: For each listed symptoms/signs A1-7 check which option best applies.					**A = YES IF ≥ 1 of A1-7 = Yes OR A8 is considered valid clinical evidence of acute meningitis** **A = NO IF All of A1-A7 = Absent and there is no other valid clinical evidence of acute meningitis** **Else A = UNKNOWN**
1. Fever ≥ 38.0°	Present	Absent	Not Assessed	Unknown	
2. Headache	Present	Absent	Not Assessed	Unknown	
3. Vomiting	Present	Absent	Not Assessed	Unknown	
4. Bulging fontanelle	Present	Absent	Not Assessed	Unknown	
5. Stiff neck	Present	Absent	Not Assessed	Unknown	
6. Kernig's sign	Present	Absent	Not Assessed	Unknown	
7. Brudzinski's sign	Present	Absent	Not Assessed	Unknown	
8. Other (describe)					**CRITERION VALUES:** **A =**

B. CSF pleocytosis	**B=YES** IF:	__Age <2mos old &>15WBC/uL __Age ≥2mos old & > 5 WBC/uL	**B=NO** IF	__Age <2mos old & ≤15WBC/uL __Age ≥2mos old & ≤ 5 WBC/uL	**B=Unknown** IF: LP or CSF WBC not done or unknown if done **B =**
C. CSF gram stain	**__C1** no organisms seen	**__C2** Gram (+)/Gram (-) organisms seen	**__C3** not done or results unknown		**C =**
D. CSF bacterial culture	**__D1** CSF Bacterial culture negative **__D2** CSF Bacterial culture positive. Describe:		**__D3** CSF Bacterial culture not done **__D4** CSF bacterial culture done but results unavailable OR uninterpretable; OR unknown if culture done		**D =**
E. Antibiotic Therapy	**__E1** No antibiotic given, OR not started until after CSF collected for bacterial culture. **__E2** Antibiotic(s) started before CSF collected for bacterial culture. **__E3** Details of antibiotic therapy relative to timing of CSF collection for bacterial culture unknown/uncertain/ unavailable.				**E =**

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

LOC (No level 3)	
Level 1	A=YES AND B=YES AND C=C1 AND D=D1 AND E=E1
Level 2	A=YES AND B=YES AND C=C1 AND EITHER: [D=D3] OR [D=D1 AND E={E2 OR E3}]
Level 4	Reported as a case of aseptic meningitis but (A OR B) = UNKNOWN or C=C3 or D=D4
Level 5 (not a case)	(A &/OR B) = NO OR C=C2 OR D=D2

Meningitis may accompany encephalitis. If altered level of consciousness, multifocal or focal neurologic signs present, assess case should using encephalitis paradigm (see separate encepahlitis companion guide in the Developers' toolbox and Brighton collaboration website)

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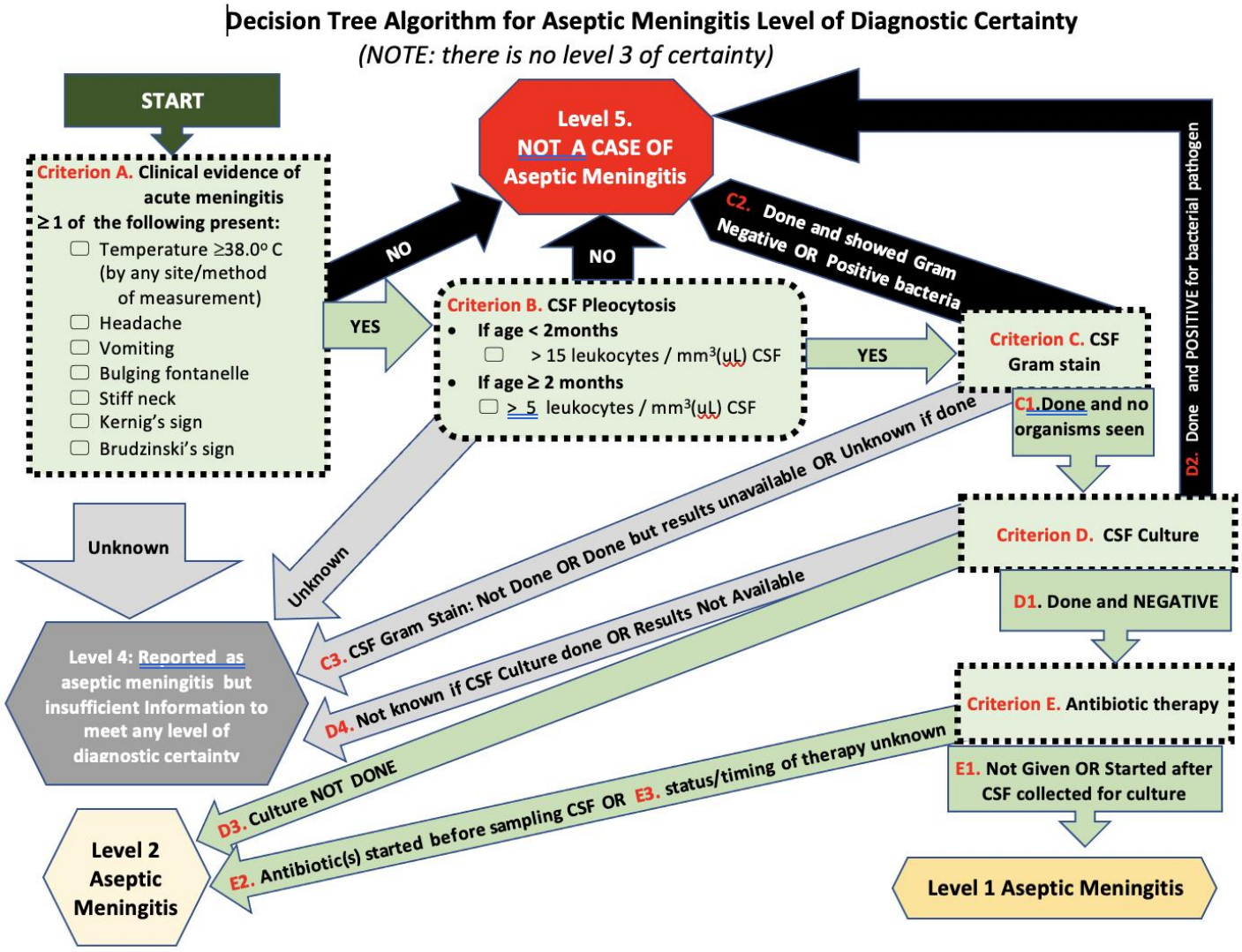
APPENDIX 7

Aseptic meningitis Pictorial Level of Certainty Algorithm

7.1 Aseptic meningitis Pictorial level of certainty algorithm

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



APPENDIX 8.

Methodology: Brief Summary

8.1. Aseptic meningitis Risk Factors [1-9]

A risk factor is "an exposure, behavior, or attribute that, if present and active, clearly alters the occurrence of a particular disease compared with an otherwise similar group of people who lack the risk factor". According to James Last dictionary of epidemiology version 4, a risk factor is an aspect of personal behavior or lifestyle, an environmental exposure, or an inborn or inherited characteristic, that, on the basis of epidemiologic evidence, is known to be associated with health-related condition(s) considered important to prevent. The term risk factor is rather loosely used, with any of the following meanings:

1. An attribute or exposure that is associated with an increased probability of a specified outcome, such as the occurrence of a disease. Not necessarily a causal factor. A RISK MARKER.
2. An attribute or exposure that increases the probability of occurrence of disease or another specified outcome. A DETERMINANT.
3. A determinant that can be modified by intervention, thereby reducing the probability of occurrence of disease or other specified outcomes. To avoid confusion, it may be referred to as a modifiable risk factor.

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

The published Brighton Case definition[1] for aseptic meningitis 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 aseptic meningitis.[2-9]

8.2. Aseptic meningitis Background Incidence [10-14]

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

(("Meningitis, Aseptic"[Mesh:noexp] OR "Meningitis, Viral"[Mesh:noexp]) OR (("meningitis"[ti] OR "meningitides"[ti] OR "pachymeningitis"[ti] OR "pachymeningitides"[ti] OR "meningomyelitis"[ti]) AND ("aseptic"[ti] OR "viral"[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 aseptic meningitis were extracted. Aseptic meningitis 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. Aseptic meningitis Case Definition[1] key caveats for diagnosis, data analysis and presentation

The published Brighton case definition for aseptic meningitis was reviewed and key aspects identified with particular relevance to real time assessment of aseptic meningitis in the context of a clinical trial where it occurs as an AEFI. In addition, the guideline section of the published aseptic meningitis 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. Aseptic meningitis ICD-9/10-CM and MedDRA Codes [15-19]

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[15] 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.[16] 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.[17,18] text-indexing engine Peregrine uses this dictionary to identify medical concepts in the case definition.[19] 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 aseptic meningitis Brighton case definitions for all Tier 1 AESI. The concepts identified for aseptic meningitis were considered relevant for background incidence rate determination as well as to study hypotheses related to aseptic meningitis 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 aseptic meningitis[1] was thoroughly and repeatedly reviewed by one individual (BL) to identify all clinical, laboratory and other criteria (e.g., temporal course of disease) used to define each and every case definition level of certainty.
The aseptic meningitis 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.