Safety Platform for Emergency vACcines

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

Generalized Convulsion

Work Package: WP2 Standards and tools

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DEFINITIONS & ACRONYMS

ADEM	Acute Disseminated Encephalomyelitis
AESI	Adverse Events of Special Interest
BC	Brighton Collaboration
CD	Case Definition
CEPI	Coalition for Epidemic Preparedness and Innovation
CNS	Central Nervous System
CUI	Concept Unique Identifier
DTaP	Diphtheria Tetanus acellular Pertussis (Vaccine)
EEG	Electroencephalogram
HIC	High Income Countries
ICD	International Classification of Diseases
IOM	Institute of Medicine
LMIC	Low- and Middle-Income Countries
MedDRA	Medical Dictionary for Regulatory Activities
MMR	Measles Mumps Rubella (Vaccine)
MMRV	Measles Mumps Rubella Varicella (Vaccine)
SPEAC	Safety Platform for Emergency Vaccines
Tdap	Tetanus diphtheria acellular pertussis (Vaccine)
UMLS	Unified Medical Language System

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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. Providing tabular summaries of risk factors and background rates for each AESI.
2. Guidance on AESI real time investigation, data collection, analysis and presentation.
3. Creating spreadsheet summaries of ICD9/10 and MedDRA codes for each AESI.
4. Creating 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 generalized convulsion.

2. Objective of this deliverable

To collate all SPEAC & BC tools, resources and guidance that have been developed for acute generalized convulsion.

3. Methods

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

- Generalized convulsion risk factors and background rates and risk factors: SO1-D2.4 Tier 1 AESI: Risk Factors and Background Rates
- Generalized convulsion Case definition key caveats for diagnosis, data analysis and presentation: SO1-D2.7 Guidance for CEPI Developers
- Generalized convulsion Diagnostic Codes: SO2-D2.3 Tier 1 AESI: ICD-9/10-CM and MedDRA Codes
- Generalized convulsion 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. Generalized convulsion Risk Factors
2. Generalized convulsion Background Rates
3. Generalized convulsion Case Definition key caveats for diagnosis, data analysis and presentation
4. Generalized convulsion Diagnostic Codes: ICD-9CM, ICD-10CM, MedDRA
5. Generalized convulsion Data Abstraction and Interpretation Form for Medical Chart Review
6. Generalized convulsion Tabular checklist for key case definition criteria and level of certainty algorithm
7. Generalized convulsion 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 generalized convulsion 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 generalized convulsion 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 generalized convulsion. This standard, harmonized approach will facilitate signal detection and assessment as well as the capacity to combine data across trials for meta-analyses.

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APPENDIX 1.
Generalized Convulsion Risk Factors

1.1. Generalized Convulsion

TABLE 1. RISK FACTORS [1-10]

The data in the table covers both febrile seizures and epilepsy since a seizure following immunization could be the first manifestation of epilepsy, and not be linked to immunization other than temporally.

Age	Incidence of epilepsy higher in youngest and oldest age groups.[5] (see appendix 2, Background Rates)
	• Febrile seizure[3]: defined as a seizure occurring in childhood after one month of age associated with a febrile illness not caused by an infection of the central nervous system, without previous neonatal seizures or a previous unprovoked seizure and not meeting criteria for other symptomatic seizure
	  ○ Most common from 6 months to 6 years of age with peak incidence at 18 months
	  ○ Cumulative incidence: 2-5% in US/Europe; 6-9% in Japan; 14% India/Guam
	  ○ After initial episode, 1/3 of children have a recurrence – 75% within 1 year

Gender	Incidence and prevalence of epilepsy slightly higher in men than in women[5]
Genetics	• Epilepsy: family history of a close family member (parents/sibling) with epilepsy • Febrile seizure: parent or sibling with a past history of febrile seizure[3] • Familial epilepsy syndromes include those with 'febrile seizures +' meaning febrile seizures that persist beyond the age of 6 years. These include mutations in sodium cannel genes such as Dravet syndrome (severe myoclonic epilepsy of infancy) which can start as prolonged seizures triggered by fever and which can be temporally associated with immunization. Immunization may trigger the seizure but does not cause the mutation which underlies the seizure disorder.
Geography	• Incidence and prevalence of epilepsy is higher in Low-Middle Income countries (LMIC) versus High Income countries (HIC).[5] (see Appendix 2, Background Rates)

Vaccine	• No evidence that vaccines cause epilepsy
	• Vaccines associated with an increased risk of febrile seizure in <6 years old [8]:
	  ○ MMR: 26.4/1000 person years 7-10 days after vaccination
	  ○ MMRV: 86.4/1000 person years 7-10 days after vaccination
	  ○ Influenza, pneumococcal conjugate vaccines
	  ▪ Given separately: very small risk of febrile seizure: 5/100,000 doses
	  ▪ Given together: increases risk of febrile seizure to 17.5/100,000 doses
	• Institute of Medicine 2011[9] concluded the evidence was strong for a link between MMR and febrile seizures. They found the evidence for febrile seizure following VZV, influenza, Hepatitis B, DTaP, Tdap and influenza vaccines inadequate to accept or reject a causal relationship.
	• Updated review of evidence published since 2011 IOM report for a range of vaccines had similar conclusion to IOM regarding no evidence to accept/reject a link between vaccines and epilepsy. With respect to febrile seizure, they reported that vaccines that induce fever in infants and young children (e.g., MMR, influenza, Pneumococcal conjugate vaccines) can very rarely cause febrile seizures [10]
	• Risk window for convulsion as a vaccine product related reaction relates to the period of reactogenicity when fever may occur

	○ Inactivated or subunit vaccines – usually within the first few days after vaccination ○ Live attenuated vaccines – relates to the incubation period. As noted above the evidence strongly supports an association with MMR and the most typical time for onset is 7 – 10 days after vaccination.
Other factors	• History of a 1st unprovoked seizure is associated with an increased risk of recurrence[5] ○ 36-37% within 1 year; 43-45% by 2 years • Vascular disease (hypertension, past history of stroke, diabetes) autoimmune diseases in children associated with 5-fold higher risk of epilepsy • first onset of seizures in an adult usually due to identifiable cause including trauma, CNS infection, CNS space-occupying lesion, cerebrovascular accident, metabolic disorder or drugs

TABLE 2. COMPARISON OF TYPICAL FEATURES OF EPILEPSY AND FEBRILE SEIZURE

	Epilepsy[5]	Febrile Seizure[3]
Definition	Disease of the brain characterized by an enduring predisposition to generate seizures. Also impacted by the neurobiologic, cognitive, psychological and social consequences of seizure recurrences. For population-based studies defined as ³2 unprovoked seizures occurring ³24 hours apart.	A seizure occurring in childhood after one month of age associated with a febrile illness not caused by an infection of the central nervous system, without previous neonatal seizures or a previous unprovoked seizure and not meeting criteria for other symptomatic seizure
Main type of seizure	May be focal or generalized.	○ most are generalised tonic-clonic ○ 30-35% have ≥ 1 complex feature ○ focal onset ○ duration >10 minutes ○ multiple seizures during same febrile episode
Prevalence	Lifetime: 7.6/1000 population (95%CI 6.17-9.38) Point prevalence active epilepsy: 6.38/1000 (95% CI 5.57-7.30)	○ 1 in 30 individuals overall ○ 1 in 5 if one sibling affected ○ 1 in 3 if both parents & a sibling affected
Main Risk factors	○ family history of epilepsy ○ complex febrile seizures ○ neurodevelopmental impairment	○ age <6 years ○ Parent or sibling with history of febrile seizure
Risk of recurrence	After first unprovoked seizure: ○ 36-37% at 1 year ○ 43-45% at 2 years Time frame for recurrence ○ about 50% occur within 6 months	In up to 1/3 of children with an initial febrile seizure Time frame: 75% within one year Risk factors for recurrence (80% in children with all vs 4% with none): ○ first episode before 18 months of age ○ history of febrile seizure in 1st degree relative (parent, sibling) ○ seizure associated with fever <39C ○ seizure onset after <1 hour of fever ○ multiple seizures during same febrile illness ○ day nursery attendance
Remission	About 50%	

Mortality	Sudden unexpected death in epilepsy (SUDEP): 1.2/1000 person years among individuals with epilepsy (95%CI 0.9-1.5) – varies by age: ○ <16years: 1.1 (95%CI 0.5-2.3) ○ >50years: 1.3 (95%CI 0.9-1.8) SUDEP risk factors: ○ generalized tonic-clonic seizures ○ nocturnal seizures ○ persistence of seizures	
Global Burden	2016 estimate: 46 million people with 80% residing in LMIC	

APPENDIX 2.
Generalized convulsion Background Rates

2.1 Generalized Convulsion Background Rates

TABLE 1. GENERALIZED CONVULSION BACKGROUND RATES [11-43] The rates in the table include combined incidence of febrile convulsions as well as first onset epilepsy.

Country reference	Study years	Population (age in years)	Incidence rate per 100,000 person years [95% confidence interval] (total cases)		
			All	Males	Females
AFRICA					
Egypt [11]	2010	All ages	1.52 [0.53-2.51] (75)		
Ethiopia [12]	Not provided (3.5 yr Period overall)	0-9 10-19 20-29 3-=39 40-49 50-59 60-69 ≥ 70 **All ages**	94 (68) 74 (42) 73 (16) 38 (9) -- (0) 9.4 (1) 24 (2) 16 (1) **64 (139)**	103 (37) 77 (23) 115 (10) 39 (4) -- (0) 19 (1) 23 (1) -- (0) **72 (76)**	86 (31) 71 (19) 46 (6) 38 (5) -- (0) -- (0) 25 (1) 30 (1) **57 (63)**
Kenya [13]	2003-2007	≥ 6	37.6 [32.7-43.3] (193) 77.0 [67.7-87.4] #		
Tanzania [14]	1979-1988	0-9 10-19 20-29 30-39 40-49 50-59 ≥ 60 All ages	80.1 (48) 111.7 (46) 57.2 (13) 14.4 (6) 35.2 (4) 22.0 (2) 39.7 (3) **73.3 (122)**		
Tanzania [15]	1999-2003	All ages	81.1 [65-101] (29)		
Uganda [16]	1991-1995	2-23 *	156 (40)		
AMERICAs					
USA [17]	2003-2005	65-69 70-74 75-79 80-84 ≥85 **≥ 65**	0.98 2.2 2.8 3.4 3.7 **2.4 (186)**	**2.3**	2.4
USA [18]	1988-1994	<5 5-14	93.5 (53) 79.7 (87)	76.0 (22) 84.7 (47)	111.7 (31) 74.5 (40)

		15-24 25-34 35-44 45-54 55-64 65-74 75+ **0-64**	59.6 (45) 23.3 (28) 20.0 (24) 24.8 (18) 36.5 (14) 64.0 (5) 99.2 (1) **50.9 (269)**	76.3 (23) 22.5 (10) 16.4 (8) 25.3 (8) 33.4 (6) 72.6 (3) -- (0)	48.5 (22) 23.9 (18) 22.4 (16) 24.3 (10) 39.2 (8) 54.3 (2) 182.8 (1)
USA [19] (New York)	2003-2005	<1 1-4 5-9 10-14 15-24 25-34 35-44 45-54 55-64 65-74 75-84 ≥ 85 **All ages ***	134.4 [51.1–217.7] 50.4 [24.9–75.9] 41.5 [21.8–61.3] 30.7 [13.3–48.1] 39.8 [26.4–53.1] 13.1 [5.7–20.5] 21.3 [11.4–31.1] 31.5 [18.0–44.9] 35.3 [17.4–53.2] 45.3 [20.7–69.9] 144.7 [88.0–201.5] 235.5 [123.6–347.5] **41.1 [35.4-46.8] (209)**	104.7 [2.1–207.3] 65.4 [24.9–106.0] 52.7 [21.6–83.9] 45.8 [15.9–75.6] 50.0 [29.1–70.9] 15.5 [4.0–27.0] 26.8 [11.0–42.7] 39.0 [16.9–61.1] 42.7 [13.1–72.3] 43.8 [5.4–82.2] 212.6 [92.3–332.9] 108.3 [–41.8–258.5] **46.6 [378-55.4] (113)**	165.7 [33.1–298.3] 34.5 [4.3–64.8] 29.9 [6.0–53.8] 15.5 [–2.0–32.9] 28.9 [12.6–45.3] 10.8 [1.3–20.2] 16 [4.2–27.9] 25 [8.7–41.3] 29.5 [7.6–51.3] 46.2 [14.2–78.3] 111.8 [51.0–172.6] 279.2 [137.9–420.5] **35.9 (28.7-43.1) (96)**
USA [20] (Minnesota, Olmsted Country)	1980-2004	1-4	65.3 (122)	77.7 (75)	52.0 (47)
Canada [21]	1986-2001	29 days to 15.5 years	63 (648)		
Martinique [22]	1994-1995	1-9 10-19 20-29 30-39 40-49 50-59 60-69 ≥ 70 **All ages**	94 (59) 63 (36) 38 (24) 50 (33) 52.5 (24) 89.7 (30) 146.6 (41) 224 (62) **80.5 (309)**	111.5 (35) 78.6 (23) 45.5 (14) 74.8 (24) 79 (17) 151.6 (24) 192.5 (25) 33 1 (37) **331 (199)**	76.6 (24) 46.6 (13) 31 (10) 26.6 (9) 28.9 (7) 34 (6) 106.7 (16) 151.5 (25) **55.4 (110)**
Honduras [23]	1996-1997		92.7 [18.5-166.9] (6)		
Chile [24]	1984-1988	0-14 15-29 30-44 45-59 > 59 **All ages**	124.4 (43) 144.8 (29) 81.0 (29) 103.9 (10) -- (0) **113.0 (102)**	151.6 (24) 147.5 (15) 85.1 (11) 97.9 (6) -- (0) **125.3 (56)**	101.4 (19) 142.1 (14) 76.5 (9) 114.4 (4) -- (0) **100.9 (46)**

Ecuador [25] (Andean region)	1986-1987	0-9 10-19 20-29 30-39 40-49 50-59 60-69 70-98 **All ages**	174.4 (35) 268.3 (49) 180.3 (17) 55.9 (4) 255.9 (16) 141.2 (7) 126.0 (4) 177.6 (5) 190.0 (137)		
ASIA					
India [26]	1990-1991	<10 10-<20 20-<30 30-<40 40-<50 50-<60 60-<70 70-<80 ≥ 80 **All ages**	74.5 (11) 46.9 (7) 62.8 (7) 32.2 (3) -- (0) 74.2 (3) -- (0) 91.9 (1) -- (0) **49.3 (32)**	90.9 (7) 37.8 (3) 54.3 (3) 43.3 (2) -- (0) 47.1 (1) -- (0) 195.3 (1) -- (0) 50.7 (17)	56.6 (4) 57.3 (4) 71.1 (4) 21.3 (1) -- (0) 104.2 (2) -- (0) -- (0) -- (0) **47.4 (15)**
India [27]	2003-2008	0-4 5-9 10-14 15-19 20-24 25-29 30-34 35-39 40-44 45-49 50-54 55-59 60-64 65-69 70-74 75-79 80-84 ≥85 **All ages ***	63.35 10.41 24.72 46.85 11.96 8.35 4.64 9.12 16.47 16.47 17.47 21.25 66.26 45.25 35.81 37.17 205.65 160.64 **27.27 [21.03-34.80] (66)**	59.17 0 39.90 44.17 14.75 16.19 0 17.71 30.53 19.59 16.03 38.87 65.22 60.42 69.08 0 307.69 0 30.54 [21.06-42.83]	68.17 21.52 8.51 49.87 8.68 0 9.62 0 0 24.98 19.19 0 67.34 30.12 0 84.75 103.09 296.3 23.34 [16.18-35.71]
EUROPE					
Denmark [28]	1995-2002	All ages	83.3 (33)		
Denmark [29]	1979-1983	60-64 65-69 70-74 75-79	63 (20) 83 (26) 101 (31) 90 (22)		

		≥80 **≥60**	47 (13) **77 (112)**		
Estonia [30]	1994-1996	20-29 30-39 40-49 50-59 60-69 70-79 ≥80 **All ages**	20.6 [8.4-32.8] (11) 32.8 [15.6-50.0] (14) 29.3 [12.0-46.6] (11) 41.2 [20.4-62.0] (15) 56.0 [30.1-81.9] (18) 39.9 [10.3-69.5](7) 55.1 (6.8-103.4] (5) **35.4 [27.7-43.1] (81)**	32.6 [11.3–53.9] (9) 49.2 [18.7–79.7] (10) 35.2 [7.1–63.3] (6) 57.4 [19.9–94.9] (9) 109.1 [52.0–166.2] (14) 91.8 [11.3–172.3] (5) 92.0 [0.0–219.5] (2) **54.4 [40.0–68.8] (55)**	7.7 [0.0–18.4] (2) 17.9 [0.3–35.5] (4) 24.5 [3.1–45.9] (5) 28.9 [5.8–52.0] (6) 20.7 [0.4–41.0] (4) 16.5 [0.0–39.4](2) 43.5 [0.0–92.7](3) **20.4 [12.6–28.2](26)**
Estonia [31]	1973-1974	<1 1-4 5-9 10-15 **0-15**	95.7 (3) 139.9 (17) 52.1 (9) 71.0 (14) **82.3 (43)**		
Finland [32]	1960-1979	16-19 20-29 30-39 40-49 50-59 60-69 ≥ 70 **All ages ***	27 (25) 16 (36) 22 (32) 23 (36) 32 (46) 26 (31) 29 (23) **24 [16-32] (230)**	31 (14) 22 (24) 24 (19) 26 (23) 46 (29) 42 (22) 50 (14) **32 [20-44] (145)**	22 (11) 10 (12) 19 (13) 20 (13) 20 (17) 15 (9) 18 (9) **17 [9-25] (85)**
Germany [33]	1999-2000	<1 1-<5 5-<10 10-<15 **<15 ***	145.8 [47.4-340.1] (5) 62.1 [29.8-114.2] (10) 49.7 [23.8-91.3] (10) 55.9 (27.9-100.0) (11) **60.3 (36)**		
Iceland [34]	1995-1999	<1 1-4 5-9 10-14 15-24 25-34 35-44 45-54 55-64 65-74 75-84 ≥85 **All ages** **All ages ***	130.2 (18) 54.0 (31) 65.8 (48) 56.0 (37) 71.2 (98) 36.1 (48) 31.9 (42) 34.4 (35) 48.3 (32) 70.5 (41) 168.5 (55) 151.9 (16) **56.8 [51.8-61.8] (501)** **55.2**	127.6 (9) 47.6 (14) 77.3 (29) 62.4 (21) 64.1 (45) 31.5 (21) 32.8 (22) 38.4 (20) 45.8 (15) 86.3 (24) 186.3 (26) 238.3 (9) **57.7 (255)** **57.3**	132.9 (9) 60.8 (17) 53.6 (19) 49.5 (16) 78.5 (53) 40.8 (27) 30.8 (20) 30.2 (15) 50.7 (17) 55.9 (17) 155.1 (29) 103.6 (7) **55.9 (246)** **53.7**
Italy [35]	1996-2005	<1 1-4 5-9 20-24	109.4 [69.4-164.1] (23) 58.9 [43.9-78.5] (51) 67.76 [53.4-84.7] (76) 33.8 [23.9-52.1] (38)	77.8 [35.6-147.8] (9) 62.5 [41.5-90.6] (28) 74.27 [53.5-100.2] (42) 32.9 [19.8-61.1] (19)	134.1 [73.2-225.3] (14) 55 [35.2- 81.9] (23) 64.9 [45.0-90.9] (34) 34.9 [21.0-54.4] (19)

		<1-14 **<1-14 ***	**57.1 [49.3-65.9) (188)** **58.1 [49.7-66.4]**	**57.5 [46.7–70.1] (98)**	**56.6 [45.5–69.6] (90)**
Netherlands [36]	1998-2000	14-24 35-44 45-64 ≥ 65 **All ages**	59.7 (26) 25.3 (29) 51.4 (55) 119.7 (64) **54.6 (174)**	**58.3 (90)**	**51.2 (84)**
Sweden [37] (Stockholm)	2001-2004	<1 1-4 5-9 10-14 15-19 20-24 25-29 30-34 35-39 40-44 45-49 50-54 55-59 60-64 65-69 70-74 75-79 80-84 ≥ 85 **All ages**	77.1 [53.8–100.4] (42) 51.7 [42.4–61.0] (119) 77.7 [64.4–91.0] (131) 49.4 [39.2–59.6] (90) 41.2 [31.1–51.3] (64) 30.0 [21.6–38.4] (49) 16.1 [10.8–21.5] (35) 14.5 [9.7–19.3] (35) 13.9 [9.2–18.7] (33) 19.1 [13.1–25.1] (39) 16.1 [10.4–21.9] (30) 25.4 [18.2–32.7] 47) 28.0 [20.7–35.2] (57) 40.2 [30.1–50.3] (61) 41.2 [29.0–53.3] (44) 38.8 [25.9–51.6] (35) 55.4 [39.6–71.2] (47) 33.3 [20.0–46.6] (24) 53.1 [35.0–71.2] (33) **33.9 [31.8–36.0] (1015)**	66.3 [39.8–92.9] (24) 40.0 [30.4–49.7] (66) 71.6 [53.8–89.4] (62) 56.9 [41.6–72.2] (53) 54.1 [37.9–70.2] (43) 36.9 [23.7–50.0] (30) 17.8 [9.8–25.8] (19) 18.2 [10.6–25.8] (22) 14.1 [7.4–20.9] (17) 24.0 [14.6–33.4] (25) 15.9 [7.9–24.0] (15) 33.0 [21.2–44.8] (30) 26.1 [16.1–36.1] (26) 47.9 [32.3–63.6] (36) 53.0 [33.0–73.0] (27) 47.5 [26.2–68.9] (19) 69.4 [41.6–97.1] (24) 41.2 [16.8–65.5] (11) 96.9 [50.8–142.9] (17) **37.1 [34.1–40.2] (566)**	98.3 [52.9–143.7] (18) 81.1 [59.3–102.9] (53) 84.1 [64.3–103.9] (69) 41.6 [28.2–55.0] (37) 27.7 [15.8–39.5] (21) 23.2 [12.8–33.7] (19) 14.5 [7.4–21.6] (16) 10.8 [4.9–16.7] (13) 13.7 [7.0–20.4] (16) 14.0 [6.7–21.4] (14) 16.4 [8.1–24.6] (15) 18.1 [9.5–26.7] (17) 29.8 [19.3–40.3] (31) 32.6 [19.8–45.4] (25) 30.4 [16.0–44.9] (17) 31.8 [16.2–47.3] (16) 45.8 [27.1–64.5] (23) 28.7 [13.1–44.3] (13) 35.9 [18.3–53.5] (16) **30.5 [27.7–33.3] (449)**
Sweden [38]	1990-1992	<16	53 (79)		
Sweden [39]	1992-1994	17-29 30-39 40-49 50-59 60-69 70-79 ≥ 80 **≥ 17**	34 (26) 23 (12) 41 (22) 47 (18) 70 (22) 153 (39) 173 (21) **56 [41-70] (160)**	29 (11) 11 (3) 44 (12) 47 (9) 108 (16) 177 (20) 158 (7) **55 (78)**	40 (15) 36 (9) 38 (10) 47 (9) 36 (6) 133 (19) 182 (14) **56 (82)**
Sweden [40]	2000	1 month to 16 years	40.0		
Switzerland [41]	1990-1991	0-9 10-19 20-29 30-39 40-49 50-59 60-69	70.8 (28) 66.6 (28) 66.7 (40) 45.1 (28) 55.1 (34) 57.8 (28) 96 (33)	74 (15) 93.8 (20) 75.5 (22) 71.8 (22) 91 (27) 63 (15) 115 (18)	67 (13) 38.7 (8) 58.4 (18) 19.1 (6) 21.9 (7) 52.9 (13) 80 (15)

		70-79 ≥80 **All ages ***	106.4 (23) 207.7 (31) **69.4 (273)**	142 (12) 258.4 (11) **88.4 (162)**	83.8 (11) 187.4 (20) **52.1 (111)**
UK [42]	2005	0-4 5-9 10-19 20-29 30-39 40-49 50-59 60-69 70-79 80-89 **All ages** **All ages ***	57.0 [42.9-74.2] (55) 40.6 [29.9-53.8] (48) 36.4 [29.4-44.6] (93) 43.3 [35.4-52.5] (105) 44.9 [37.7-53.1] (137) 34.3 [28.1-41.5] (106) 43.1 [35.7-51.7] (116) 56.5 [46.6-67.8] (115) 95.8[80.6-113.0] (140) 126.2[102.6-153.7] 99 **50.1[47.1-53.3](1014)** **48**		
UK [43]	1995-1996	0–4 5–9 10–14 15–19 20–24 25–29 30–34 35–39 40–44 45–49 50–54 55–59 60–64 65–69 70–74 75–79 80–84 85–89 **All ages**	86 46 94 52 33 19 24 54 18 50 50 31 34 37 142 50 32 29 **46 [36-60]**		

**Age-adjusted incidence; # Adjusted for loss to follow-up and sensitivity of survey methodology*

TABLE 2.2 Incidence of Status Epilepticus [44-49]

Country [reference]	Study years	Population (age in years)	Incidence rate per 100,000 person years [95% confidence interval] (total cases)		
			All	Males	Females
USA [44] (Minnesota)	1965-1984	<1 1-4 5-9 10-14 15-19 20-29 30-39 40-49 50-59 60-69 70-79 ≥80 **All ages ***	135.2 (28) 35.3 (26) 12.2 (12) 3.7 (3) 6.5 (6) 2.8 (6) 4.7 (7) 6.5 (7) 10.9 (10) 29.5 (21) 88.3 (45) 98.9 (28) **18.3 [15.9-21.1] (199)**	**23.2 [18.9-28.4]**	**13.1 [10.5-16.3]**
USA [45] (Virginia)	1989-1991	≥ 31 days	41 (166)		
USA [46] (California)	1991-1998	0-4 5-19 20-54 55-74 ≥75 **All ages**	7.52 2.57 4.58 11.93 22.32 **6.18 (15601)**	**6.38 (8051)**	**5.98 (7550)**
Germany [47]	1997-1999	18-59 ≥ 60 **≥ 18 ***	4.2 54.2 **17.1**	**26.1**	**13.7**
Switzerland [48]	1997-1998	0-4 5-14 15-29 30-44 45-59 60-74 ≥75 **All ages**	38.7 [27–50.4] (42) 10.9 [16.3–5.4] (22) 4.4 [2.2–6.6] (15) 3.9 [2.0–5.7] (16) 7.8 [4.8–10.8] (26) 15.1 [10–20.3] (33) 15.5 [8.3–22.7] (18) **9.9 [8.4–11.4] (172)**		
UK [49]	2002-2004	<1 1-4 5-15 **All ages**	50.7 (42) 29.2 (94) 5.0 (31) **13.3 [12.6-14.0] (176)**	56.6 (24) 31.2 (51) 4.9 (20) **14.0 [13.0-15.0] (95)**	44.5 (18) 27.1 (43) 5.1 (20) **12.5 [11.5-13.4] (81)**

**Age-adjusted incidence*

APPENDIX 3

Generalized Convulsion Case Definition Key Caveats for Diagnosis, Data Analysis and Presentation

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

- Key elements of Case Definition (CD)
  - There are three levels of certainty based on observed or history of loss of consciousness and presence and type of generalized motor manifestations.
  - Fever is not part of the case definition but should be documented since febrile seizures are the most common seizure disorder in infants and children and the most common type of non-epileptic seizure observed following immunization.

- Duration of Surveillance for Generalized Convulsion
  - Most cases of febrile convulsion occur during the timeframe that local and systemic reactogenicity is monitored – usually 7 days. However, for live attenuated vaccines surveillance should continue through the expected incubation period of the vaccine agent. Peak occurrence of seizures following live attenuated measles vaccines is 7 – 10 days following immunization.
  - For any seizure still present on the last day of scheduled follow-up, the period should be extended until recovery or a final outcome is reached.

- Recommendations for real time assessment (and see figure 1)
  - A witnessed loss of consciousness is required for level 1 and efforts should be made to document this at the time of first awareness of the event occurrence and to include details of type of witness and contact information (parent/other caregiver, healthcare personnel, other – describe).
  - Seizure is part of the criteria for both encephalitis and acute disseminated encephalomyelitis (ADEM) and could be a presenting feature of aseptic meningitis. Accordingly, these should all be considered and if possibilities would require further investigation. There are separate companion guides for each of these entities available in both the Developers' toolbox and Brighton collaboration website

- Data Collection Guidelines
  - For trials involving children baseline assessment should include history of premature birth, developmental stage at time of immunization, any past or family history of febrile seizure.
  - Ensure collection of information about specific predisposing conditions for generalized convulsion including drug withdrawal, hypoxia, head trauma, CNS infection, neoplasm and metabolic causes (e.g., uremia, hypoglycemia, electrolyte disorders).
  - Provide detailed clinical description of convulsion including temperature and postictal drowsiness.
  - Describe concurrent signs, symptoms and diseases
  - Describe any concurrently administered medications
  - Include EEG/laboratory examinations, surgical and/or pathological findings and diagnoses.

- Data Analysis Guidelines
  - Determine time to onset as number of subjects with seizure occurring within hourly intervals for the first 24 hours following immunization (e.g., ≤ 1, >1-2, >2-3 etc.) and then in 24-hour intervals (e.g., >24-48, >48-72 etc.). The study population denominators should be specified for each time point along with % having a seizure.
  - Duration of seizure should be analyzed in increments of minutes as: 0 - <1, 1-5, 6-10, 10-15, 16-30, 31-45, 46-60 etc. in 15-minute intervals.
  - If generalized convulsion occurs intermittently base the analysis on the value corresponding to the longest seizure.
  - The prevalence and incidence of cases should be presented and for each case definition level of certainty the numerator/denominator should be presented for febrile, afebrile, unknown fever episodes.

APPENDIX 4

Generalized Convulsion Diagnostic Codes: ICD-9/10-CM and MedDRA

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

TABLE 1. NARROW SEARCH TERMS FOR GENERALIZED CONVULSION

UMLS		Diagnostic Coding System Term and Codes			
CUI	Name	Term	MedDRA	ICD9CM	ICD10CM
C0234533	Generalized seizures	Convulsions generalised	10010916 10010917		
		Generalized convulsion	10018079		
C0036572	Seizures	Convulsions	10010914	780.3	
		Unspecified convulsions			R56.9
		Convulsion	10010904		
		Convulsion (NOS)	10010906		
		Convulsions (NOS)	10010922		
		Seizure	10039906	780.39	
		Seizures	10039910	780.39	
		Fit	10016731		
		Fits NOS	10016735		
		Fitting	10039910		
C0856799	Classic fit	Classic fit	10009234		
C0234975	Convulsions aggravated	Convulsions aggravated	10010915		
		Convulsions NOS aggravated	10010923		
C0751494	Convulsive seizures	Convulsive seizure	10010926		
		Seizure(s) (convulsive) NOS			R56.9
C0495698	Convulsions, not elsewhere classified				R56.9
C0751056	Non-epileptic convulsion	Fit (non-epileptic)	10016733		
C0490011	Other convulsions	Other convulsions		780.39	
C0270846	Epileptic drop attack	Atonic seizures	10003628		
		Drop seizures	10071377		
C0014544	Epilepsy	Epileptic fit	10015051		
		Epileptic seizure	10015052		
C0494475	Tonic-clonic seizures	Grand mal seizure	1008663		
		Grand mal seizure NOS			G40.4
		Grand mal fit	10018662		
		Grand mal epileptic fit	10018661		
		Seizure grand mal	10039909		
		Generalised tonic-clonic seizure	10018100		
		Generalised tonic-clonic seizures	10018101		
C0234535	Seizures, Clonic	Clonic seizures	10009340		

		Clonic convulsion	10053398		
C0270844	Seizures, Tonic	Tonic convulsion	10043994		
		Tonic seizure	10043996		
		Tonic seizures	10043997		
C3263970	Epileptic seizures related to external causes				G40.5
	Epileptic seizures related to external causes, NOS				G40.509
C0009952	Febrile convulsions	Febrile convulsions	10016284		R56.0
		Febrile convulsions(simple) unspecified		780.31	
		Febrile convulsion NOS			R56.00
		Convulsion febrile	10010908		
		Febrile convulsion seizure	10016285		
		Febrile seizure	10016290		
		Febrile fits	10016287		
		Fever convulsions	10016560		
		Pyrexial fit	10037670		
C0149886	Seizure, Febrile, Simple			780.31	R56.00
C0751057	Seizure, Febrile, Complex			780.32	R56.01
C0311335	Grand Mal Status Epilepticus	Grand mal status (epileptic)	10018664	345.3	
		Status epilepticus grand mal	10041963		
		Convulsive status epilepticus	10057955		
C0270823	Petit mal status	Petit mal status (epileptic)	10034760	345.2	
		Status epilepticus petit mal	10041964		
C0863106	Afebrile seizure	Afebrile seizure	1001436		
		Afebrile convulsion	1001435		
C0159020	Convulsions in the newborn	Convulsions in newborn	10010919	779.0	P90
		Convulsion neonatal	10010911		
		Convulsions in newborn	10010921		
		Neonatal convulsion	10028932		
		Neonatal seizures	10061197		
		Neonatal fit	10028939		

TABLE 2. ADDITIONAL TERMS FOR BACKGROUND RATE DETERMINATION FOR GENERALIZED CONVULSION

UMLS		Diagnostic Coding System Term and Codes			
CUI	Name	Term	MedDRA	ICD9CM	ICD10CM
C0014544	Epilepsy	Epilepsy, unspecified	10015046	345.9	G40.9
		Epilepsy NOS	10015042		G40.909
		Epilepsy	10015037		
		Epileptic fit	10015051		
		Epileptic seizure	10015052		
C0311334	Generalized convulsive epilepsy		10018109 10073920	345.1	
C0154709	Generalized convulsive epilepsy, without mention of intractable epilepsy		10018111	345.10	
C0017332	Generalized nonconvulsive seizure disorder	Generalized non-convulsive epilepsy	10018090 10018119 10057704	345.0	
C0270850	Idiopathic generalized epilepsy		10071081 10071096		G40.3
C3263996	Juvenile myoclonic epilepsy (impulsive petit mal)				G40.B
C0477370	Other generalised epilepsy and epileptic syndromes (NOS)				G40.4 G40.40
C3263972	Other epilepsy and recurrent seizures				G40.8
C1718409	Other forms of epilepsy and recurrent seizures			345.8	
C0220669	Familial benign neonatal epilepsy	Benign familial neonatal convulsions	10067866		

APPENDIX 5
Generalized convulsion Data Abstraction and Interpretation Form for Medical Chart Review

5.1. Generalized convulsion 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 generalized convulsion 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 generalized convulsion 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. A neurologic glossary of terms is available as well.

Four tables are included in the form.

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

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

Criterion	Criterion category	Likely sources of information	Actual sources of information
A	Loss of consciousness	• Outpatient clinic / emergency room record(s) • Neurology / Infectious Disease / other consultation notes • Hospital admitting history & physical exam; discharge summary; • ICU admission notes • Follow-up clinic records	
B	Motor manifestations of seizure		

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

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

1.Data Category	2.Results *(NOTE: glossary of neuruologic 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		
A. Loss of consciousness	Check the statement that most closely reflects the case history: __1. There was a witnessed sudden loss of consciousness (Describe the witness) __2. There was a history of loss of consciousness but either it was not witnessed or it was unknown whether or not it was witnessed. __3. It was not possible to determine from the clinical history whether or not there was a loss of consciousness. __4. There was no loss of consciousness.	**A -1 = YES** IF **1 is checked** **A -1 = NO or UNKNOWN** IF **2, 3 or 4 are checked** **A-2 = YES** IF **2 is checked** **A-2 = UNKNOWN'** IF **3 is checked** **A-2 = NO** IF **4 is checked**
B. Motor manifestations of seizure	1. Did the event include motor manifestations? __Yes* __No __Not documented *If yes, check all that apply below ___a) generalized motor manifestations ___b) tonic movements ___c) clonic movements ___d) tonic-clonic movements ___e) atonic motor manifestation[1] ___f) other – describe:	**B-1 & B-2 = UNKNOWN** IF 1 = Not documented **ELSE:** **B-1 = YES** IF **(a) & ³ 1 of (b,c,d, e) checked** **B-1 = NO** IF **(a) not checked and/or none of (b,c,d or e) checked** **B-2 = YES** IF **(a+f) checked AND B-1 =NO or Unknown** **B-2 = 'NO'** IF **(a) and/or (f) not checked**

[1] *Can't count 'atonic motor manifestation' as part of seizure manifestations if hypotonic hyporesponsive episode, myoclonic jerks or syncope*

TABLE 3. Based on information recorded in Table 2 above, circle record the final status for each criterion.

Criterion	Criterion description	Criterion Value as Recorded in Table 2		
A1	Witnessed Loss of Consciousness	YES	NO OR UNKNOWN	
A2	History of Loss of Consciousness	YES	NO	UNKNOWN
B1	Generalized tonic, clonic, tonic-clonic or atonic motor manifestations	YES	NO	UNKNOWN
B2	Generalized other motor movements that don't meet criteria for B1.	YES	NO	UNKNOWN

TABLE 4. Based on the values for the Criteria in table 3 above, circle the corresponding value in the table below to determine the level of certainty.

Level of Diagnostic Certainty	Diagnostic criteria – from Table 2
1	A-1 = YES AND B-1 = YES
2	A1 = NO/UNKNOWN AND A-2 = YES AND B-1 = YES
3	A-1 =[NO OR UNKNOWN] AND A-2 = YES AND B-1 = NO AND B-2 = YES OR A-1 = YES AND B1 = NO AND B-2 = YES
4	Reported generalized convulsive seizure with insufficient evidence to meet the case definition [A1 = NO/UNKNOWN AND A-2 = UNKNOWN] AND/OR [B1= NO/UNKNOWN AND B-2 = UNKNOWN]
5	Not a case: [A1 = NO/UNKNOWN AND A-2 = NO] AND/OR [B1= NO/UNKNOWN AND B-2 = No]

APPENDIX 6

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

6.1 Generalized convulsion 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 A AND B

Clinical Criteria	Results	BCCD Criterion Rules
Criterion A. Loss of consciousness	Indicate which of the following best fits the situation: __1. A sudden loss of consciousness was witnessed. If checked, who was/were the witness(es): __2. History of unconsciousness but not witnessed. If checked, who gave the information: __3. Unable to establish either 1 or 2 above __4. Established that there was no loss of consciousness during the episode	**A-1='YES'** IF 1 is checked **A-1='NO or UNKNOWN'** IF 2, 3 or 4 checked **A-2='YES'** IF 2 is checked **A-2='UNKNOWN'** IF 3 is checked **A-2='NO'** IF 4 is checked
Criterion B. Motor manifestations of seizure	1. Did the event include motor manifestations? ___Yes* ___No ___Unknown *If yes, check all that apply below ___a) generalized motor manifestations ___b) tonic movements ___c) clonic movements ___d) tonic-clonic movements ___e) atonic motor manifestation ___f) other – describe:	**B-1 and B2 = 'UNKNOWN'** IF 1 = Unknown **B-1 = YES** IF (a) AND ³ 1 of (b, c, d or e) checked **B-1 = NO** IF (a) is not checked and/or none of (b, c, d or e) are checked **B-2 = YES** IF (a+f) checked AND **B-1 = 'NO' or 'Unknown'** **B-2 = NO** IF (a) and/or (f) not checked

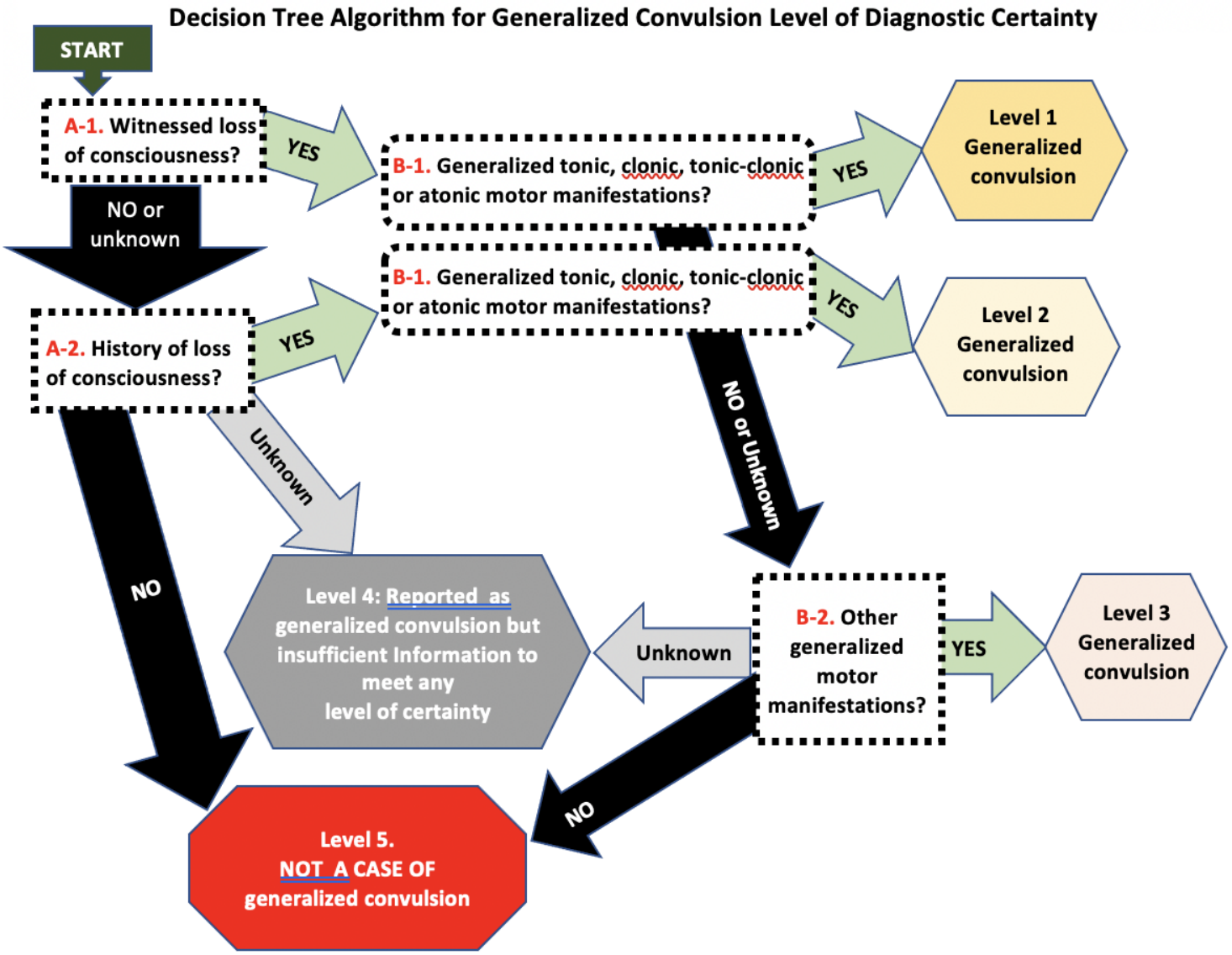
TABLE 2. STEP 2: APPLY CRITERION VALUES FROM CHECKLIST ABOVE TO FORMULAE BELOW TO DETERMINE LEVEL OF CERTAINTY (LOC)

LOC	
Level 1	**A-1 = YES AND B-1 = YES**
Level 2	**A1 = NO/UNKNOWN AND A-2 = YES AND B-1 = YES**
Level 3	**[A-1 =[NO OR UNKNOWN] AND A-2 = YES AND B-1 = NO AND B-2 = YES] OR. [A-1 = YES AND B1 = NO AND B-2 = YES]**
Level 4	**Reported generalized convulsive seizure with insufficient evidence to meet the case definition**
Level 5 (Not a case)	**[A1 = NO/UNKNOWN AND A-2 = NO] AND/OR [B1= NO/UNKNOWN AND B-2 = No]**

APPENDIX 7
Generalized convulsion Pictorial Level of Certainty Algorithm

7.1 Generalized convulsion Pictorial level of certainty algorithm.

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



APPENDIX 8.

Methodology: Brief Summary

8.1. Generalized convulsion Risk Factors [1-10]

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 generalized convulsion 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 generalized convulsion.[2-10]

8.2. Generalized convulsion Background Incidence [11-49]

A systematic literature search to estimate the incidence of acute generalized convulsion in the population was conducted using the following search strategy:
("Seizures"[Mesh:noexp] OR "Seizures, Febrile"[Mesh:noexp] OR "Epilepsy"[Mesh:noexp] OR "Seizure"[ti] OR "Seizures"[ti] OR "Convulsion"[ti] OR "Convulsions"[ti] OR "Epilepsy"[ti] OR "Epilepsies"[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 generalized convulsion were extracted. Generalized convulsion 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. Generalized convulsion Case Definition[1] key caveats for diagnosis, data analysis and presentation

The published Brighton case definition for generalized convulsion was reviewed and key aspects identified with particular relevance to real time assessment of generalized convulsion in the context of a clinical trial where it occurs as an AEFI. In addition, the guideline section of the published generalized convulsion 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. Generalized convulsion ICD-9/10-CM and MedDRA Codes [50-54]

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[50] 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.[51] 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.[52,53] A text-indexing engine Peregrine uses this dictionary to identify medical concepts in the case definition.[54] 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 generalized convulsion Brighton case definitions for all Tier 1 AESI. The concepts identified for generalized convulsion were considered relevant for background incidence rate determination as well as to study hypotheses related to generalized convulsion 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 generalized convulsion[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 generalized convulsion 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.