



CEPI | Brighton Collaboration

Generalized convulsive seizure Companion Guide - Updated

V2.0 – January 26, 2026

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Nature: Report

DOI: [10.5281/zenodo.18377124](https://doi.org/10.5281/zenodo.18377124)

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DOCUMENT INFORMATION

Project acronym	SPEAC	Full project title	Safety Platform for Emergency Vaccines
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Title	AESI Case Definition Companion Guide – Generalised convulsive seizure update
Title	Standards and tools

Status	Draft <input type="checkbox"/> Final <input checked="" type="checkbox"/>	Version	[2.0]
Nature	Report <input checked="" type="checkbox"/> Toolbox <input type="checkbox"/> List <input type="checkbox"/> Template <input type="checkbox"/> Guidance <input type="checkbox"/> Handbook <input type="checkbox"/> Questionnaire <input type="checkbox"/>		
Dissemination Level	Public <input checked="" type="checkbox"/> Confidential <input type="checkbox"/>		

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Description of the deliverable	This deliverable updates the previous Companion Guide for Generalized Convulsive Seizure (SO2 D2.5.2.1, Feb 15, 2021) as follows: Generalized convulsion changed to Generalized convulsive seizure throughout the guide to be consistent with the published case definition title; SNOMED-CT codes added; MedDRA codes put into separate table and list both Preferred and Lower Level Terms (PT, LLT). Background incidence and Risk Factor sections updated and expanded section added with methods for incidence studies and evidence for vaccine association with generalized convulsive seizure; data abstraction and interpretation form along with algorithms for assessing level of diagnostic certainty amended to harmonize with those available online as part of digital transformation including a glossary of terms. In addition, the order of appendices has been aligned with that used for all companion guides developed since 2022. This guide can be used by stakeholders to assess the occurrence of generalized convulsive seizure in several settings including as an adverse event following immunization.
Key words	Generalized convulsive seizure, Brighton case definition, risk factors, background rates, ICD-9-CM, ICD-10-CM, MedDRA, SNOMEDCT, case definition level of certainty.

DOCUMENT HISTORY

NAME OF DOCUMENT	DATE	VERSION	CONTRIBUTOR(S)	DESCRIPTION
SPEAC 1.0 SO2-D2.5.2.1 AESI Case Definition Companion Guide for Tier 1	February 14 th , 2021	V1.0	Barbara Law Marta Rojo Villaescusa	First version of Generalised convulsive seizure Companion Guide published
SPEAC 2.0 D2.4.1	October 13 th , 2025	V1.1	Hammad Ali Barbara Law	Updated version of the Generalised convulsive seizure Companion Guide sent for review
SPEAC 2.0 D2.4.1	November 29 th , 2025	V1.1	Wan-Ting Huang Esperança Sevene	Review
SPEAC 2.0 D2.4.1	December 4 th , 2025	V1.3	Hammad Ali	Response to reviewers comments and submission of the document for final approval
SPEAC 2.0 D2.4.1	January 4 th , 2026	V1.3	Miriam Sturkenboom	Review and approval
SPEAC 2.0 D2.4.1	January 13 th , 2026	V1.3	Robert Chen	Review and approval
SPEAC 2.0 D2.4.1	January 26 th , 2026	V2.0	Barbara Law Hammad Ali Marta Rojo Vilaescusa Miriam Sturkenboom Ariel Zadok Wan-Ting Huang Matthew Z. Dudley	<p>Change order of appendices: 1 = Code terms (was 4) 2 = Background incidence (was 2) 3 = Risk factors (was 1) 4 = Caveats and guidance for real time investigation (was 3) 5 = Data abstraction form and algorithms for levels of certainty (was 5, 6 and 7)</p> <p>Renumber references to match the new order of appendices Add SNOMED-CT codes. Separate code table into two: one for ICD and SNOMEDCT codes for electronic health data studies and one for MedDRA for pharmacovigilance. New material added to Background incidence and Risk Factors based on scoping literature review. Update data collection forms and LOC algorithms to the latest versions developed as part of digital transformation</p>

DEFINITIONS & ACRONYMS

ABC	Automated Brighton Classification
ADEM	Acute Disseminated Encephalomyelitis
AESI	Adverse Events of Special Interest
aP	Acellular pertussis
BC	Brighton Collaboration
CACNA	Gene
CD	Case Definition
CEPI	Coalition for Epidemic Preparedness and Innovation
CIOMS	Council for International Organizations of Medical Sciences
CLCN	Gene
CMs	Cavernous malformations
CNS	Central Nervous System
CPA	Cerebral proliferative angiopathy
CUI	Concept Unique Identifier
DTaP	Diphtheria, tetanus, and acellular pertussis
DTaP-IPV	Diphtheria, tetanus, acellular pertussis, inactivated poliovirus
DTaP-IPV-Hep B-PRP-T	Diphtheria, tetanus, acellular pertussis, inactivated poliovirus, hepatitis B, and Haemophilus influenzae type b combination vaccine
DTaP-IPV-Hib	Diphtheria, tetanus, acellular pertussis, inactivated poliovirus, and Haemophilus influenzae type b combination vaccine
DTaP-IPV-Hib-HBV	Diphtheria, tetanus, acellular pertussis, inactivated poliovirus, hepatitis B, and Haemophilus influenzae type b combination vaccine
DTPa	Diphtheria, tetanus, acellular pertussis
DTP-HB-Hib	Diphtheria, tetanus, pertussis, Hepatitis B, and Haemophilus influenzae type b
DTPw	Diphtheria-tetanus-whole-cell Pertussis
DTPw-HBV	Diphtheria-tetanus-whole-cell pertussis and hepatitis B vaccine
DTwP	Diphtheria, Tetanus, and whole-cell Pertussis
EB	Executive Board
ECMO	Extracorporeal membrane oxygenation
ECPR	Extracorporeal cardiopulmonary resuscitation
ECT	Electroconvulsive therapy
EEG	Electroencephalogram
EV71	Human Enterovirus 71
FANCL	Fanconi anemia complementation group L
GABBR1	Gamma-aminobutyric acid type B receptor subunit 1
GABRA	Gamma-Aminobutyric Acid
GABRD	Gamma-aminobutyric acid type A receptor subunit delta
GABRG	Gene
HFMD	Hand, foot, and mouth disease
HHE	Hypotonic hyposensitive episode

HHV-6	Human herpesvirus 6
HiB	Haemophilus influenzae type b
Hib-MenAC	Haemophilus influenzae type b and Neisseria meningitidis serogroups A and C
HIC	High Income Countries
HPV	Human papillomavirus
HPV4v	Human papillomavirus quadrivalent vaccine
HPV9v	Human papillomavirus nonavalent vaccine
ICD	International Classification of Diseases
IIV	Inactivated influenza vaccine
IIV3	Trivalent inactivated influenza vaccine
IIV4	Quadrivalent Inactivated Influenza Vaccine
IOM	Institute of Medicine
JEV	Japanese Encephalitis Virus
JE-VC	Japanese Encephalitis-Vero Cell-derived vaccine
JME	Juvenile Myoclonic Epilepsy
KCNQ	Gene
KCTD	Gene
LAIV3	Trivalent live attenuated influenza vaccine
LAIV4	Quadrivalent Live Attenuated Influenza Vaccine
LMIC	Low-Middle Income countries
LOC	Level of diagnostic certainty
MedDRA	Medical Dictionary for Regulatory Activities
MELAs	Mitochondrial Encephalomyopathy, Lactic Acidosis, and Stroke-like Episodes
MenACWY-D	Meningococcal groups A, C, W, and Y polysaccharide diphtheria toxoid conjugate vaccine
MERS-CoV	Middle East respiratory syndrome coronavirus
MMR	Measles Mumps Rubella
MMR+V	Measles, Mumps, Rubella, and Varicella
MMRV	Measles Mumps Rubella Varicella
MR	Measles, Rubella
MV	Measles, Varicella
NMDA	N-methyl-D-aspartate
NOS	Non-specified
OPV	Oral Polio Vaccine
PCV7/10/13	Pneumococcal conjugate vaccine; number 7, 10 or 13
PDAT	Publication date (pubmed search term)
PDYN	Prodynorphin gene
POLG1	Polymerase gamma-1
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRRT	Peptide Receptor Radionuclide Therapy
RBFOX1	Gene
RSV	Respiratory Syncytial Virus

RV	Rotavirus Vaccine
SCD	Sickle Cell Disease
SCN	Sodium Channel
SLC	Solute Carrier family
SNOMEDCT	Systematized Nomenclature of Medicine – Clinical Terms
SPEAC	Safety Platform for Emergency Vaccines
SUDEP	Sudden unexpected death in epilepsy
Tdap	Tetanus, diphtheria and acellular pertussis
TGB	Tiagabine
TIV	Trivalent Inactivated Influenza Vaccine
TSC1/TSC2	Tuberous Sclerosis Complex 1 gene/ tuberous sclerosis complex 2
UMLS	Unified Medical Language System
VGKC	Voltage-Gated Potassium Channel
VRK2	Vaccinia Related Kinase 2
VZV	Varicella Zoster Virus
wP	whole-cell Pertussis
WP2	Work Package 2

1. INTRODUCTION

1.1 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. Having identified relevant AESI, SPEAC then works to ensure tools and resources are available to facilitate a standard approach to global vaccine safety research and pharmacovigilance activities.

SPEAC Work Package 2 created 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, SNOMEDCT 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 relevant to the Brighton case definition.
 - b. Rules for creating new variables relevant to the case definition criteria, if needed.
 - c. Tabular formulae for determining Brighton Level of Diagnostic Certainty (LOC) based on the final value of each case definition criterion (YES, NO or UNKNOWN).
 - d. Pictorial algorithm showing the path to each LOC (1-5) based on criterion values. This contains all the information needed to determine LOC and thus can be used as a stand-alone tool.
 - e. Glossary of terms relevant to the case definition.

Initially these resources and tools were developed as separate documents but starting in 2020 they were pulled together into a single 'Companion Guide' for each published Brighton Collaboration Case Definition. The first Guide for Generalized Convulsive Seizure (V1.0) was finalized Nov 5, 2020 [1]. In November 2022, SPEAC began a new contract with CEPI as SPEAC 2.0. A new key feature was to embark on Digital Transformation of tools and resources developed as part of the original SPEAC project from 2019 through October 2022. The original data abstraction forms, tabular checklist and level of certainty algorithms published in V1.0 of the Companion Guides have been revised as part of the digital transformation process.

Another initiative of SPEAC 2.0 was to extend and update the original guide background rate and risk factor sections based on a more thorough literature review than was done for the first versions of several companion guides including Generalized Convulsive Seizure.

1.2 Objective of this deliverable

To update the Companion guide for Generalized Convulsive Seizure to incorporate changes made to harmonize across all guides: language, order of appendices and provision of SNOMEDCT codes (in addition to MedDRA, ICD-9-CM and ICD-10-CM); to update the data abstraction forms and algorithms so they match what are being used for Digital Transformation including the Automated Brighton Classification (ABC Tool) and other digital data collection tools; to provide newly

published data for generalized convulsive seizure background incidence and risk factors; and to expand the section on vaccines as a risk factor for generalized convulsive seizure.

2. Methods

The methods for developing each of the tools are briefly described in Appendix 6 of this Guide along with links to source documents which have more detailed methodology. More detail regarding the literature review done to capture newly published evidence on generalized convulsive seizure background incidence and risk factors as well as a new section related to all published evidence on vaccine – generalized convulsive seizure associations is presented below.

A scoping literature review was done using two different search strategies: 1) the incidence and risk factors for the outcome, 2) vaccine association with generalized convulsive seizure.

The search strategy to update the background incidence and risk factor section from the first guide was as follows:
 ("Seizures"[Mesh] OR "Seizures, Febrile"[Mesh] OR "Epilepsy"[Mesh] OR "seizure*" [tiab] OR "convulsion*" [tiab] OR "epilepsy" [tiab] OR "epilepsies" [tiab])
 AND ("Incidence"[Mesh:noexp] OR "incidence*" [tiab] OR "attack rate*" [tiab] OR "person time rate*" [tiab] OR "background rate*" [tiab] OR "Epidemiology"[Mesh:noexp] OR "epidemiology" [tiab] OR "etiology" [Subheading] OR "etiology" [tiab] OR "pathogenesis" [tiab] OR "causes" [tiab] OR "causality" [tiab] OR "Risk Factors"[Mesh] OR "risk factor*" [tiab] OR "population at risk" [tiab] OR "populations at risk" [tiab] OR "risk score*" [tiab] OR "health correlate*" [tiab])
 AND ("2006/01/01"[PDAT] : "3000/12/31"[PDAT])
 AND English[lang]
 AND ("Meta-Analysis"[ptyp] OR "Systematic Review"[ptyp])
 NOT ("animals"[Mesh] NOT "humans"[Mesh])

The search strategy to identify articles looking at evidence for vaccine association with generalized convulsive seizure was as follows:

("Vaccines"[Mesh] OR "vaccine" [tiab] OR "vaccines" [tiab] OR "Vaccination"[Mesh] OR "vaccination" [tiab] OR "vaccinations" [tiab] OR "vaccinate" [tiab] OR "vaccinated" [tiab] OR "Immunization"[Mesh] OR "immunization" [tiab] OR "immunizations" [tiab] OR "immunisation" [tiab] OR "immunisations" [tiab] OR "immunize" [tiab] OR "immunized" [tiab] OR "immunise" [tiab] OR "immunised" [tiab])
 AND ("Seizures"[Mesh] OR "Seizures, Febrile"[Mesh] OR "Epilepsy"[Mesh] OR "seizure*" [tiab] OR "convulsion*" [tiab] OR "epilepsy" [tiab] OR "epilepsies" [tiab])
 AND ("2000/01/01"[PDAT] : "3000/12/31"[PDAT])
 AND English[lang]
 NOT (Comment[ptyp] OR Editorial[ptyp] OR Letter[ptyp] OR News[ptyp] OR Newspaper Article[ptyp])
 NOT ("animals"[Mesh] NOT "humans"[Mesh])

The results of each search were uploaded into a separate COVidence file. For the vaccine association search, two investigators (BL, HA) screened title/abstract first. Any conflicts were resolved to reach consensus on the final list for full text review which was done by a single investigator (HA). For the incidence and risk factors search, one investigator (BL) screened title/abstract. All articles related to background incidence were further screened by one investigator (MRV) to identify articles that had original incidence rate data in the general population. A standard excel spreadsheet was used to extract the incidence data. Subsequently the excel file was reviewed by a different investigator (BL) before updating the background incidence table. Data extraction for all articles related to general risk factors (not including vaccine as a risk factor) was done by one investigator (HA) using a word document to capture key findings. For both searches, additional

articles were found via hand search of the included articles citation lists. Citations included in all reviews and meta-analyses were obtained to ensure only original data would be captured.

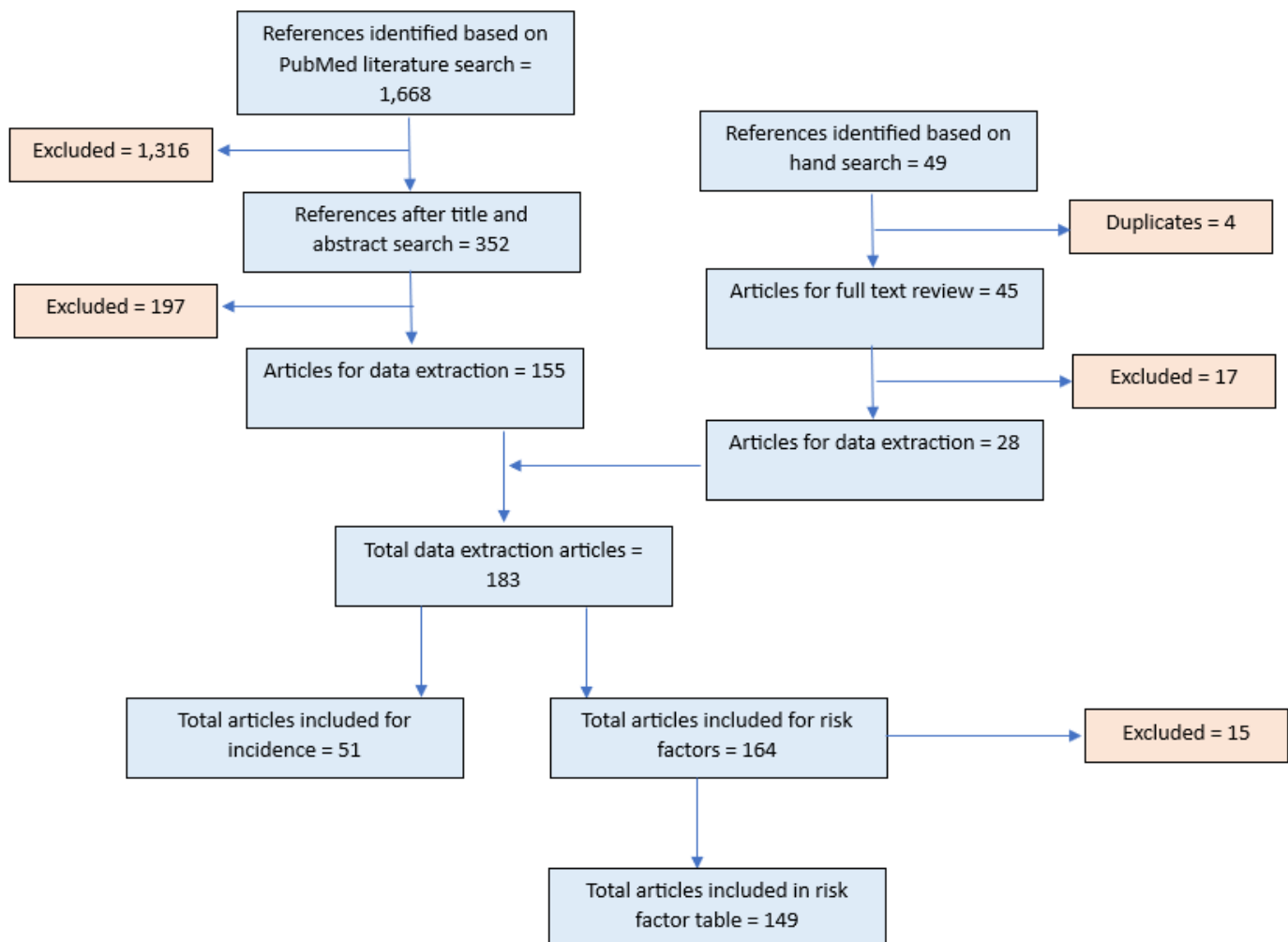
Data extraction for all articles related to possible or proven vaccine-associations was done by Putnam Inizio Advisory using a formatted excel spreadsheet created by WP2 (HA, BL). The extracted data were reviewed by one WP2 investigator (HA) and summary tables prepared for presentation in the Guide (HA). A brief summary of the key findings by vaccine from the tables was prepared by another WP2 investigator (BL) to include in the main guide risk factor table.

PRISMA flow diagrams for each of the two literature reviews were prepared.

3. Results

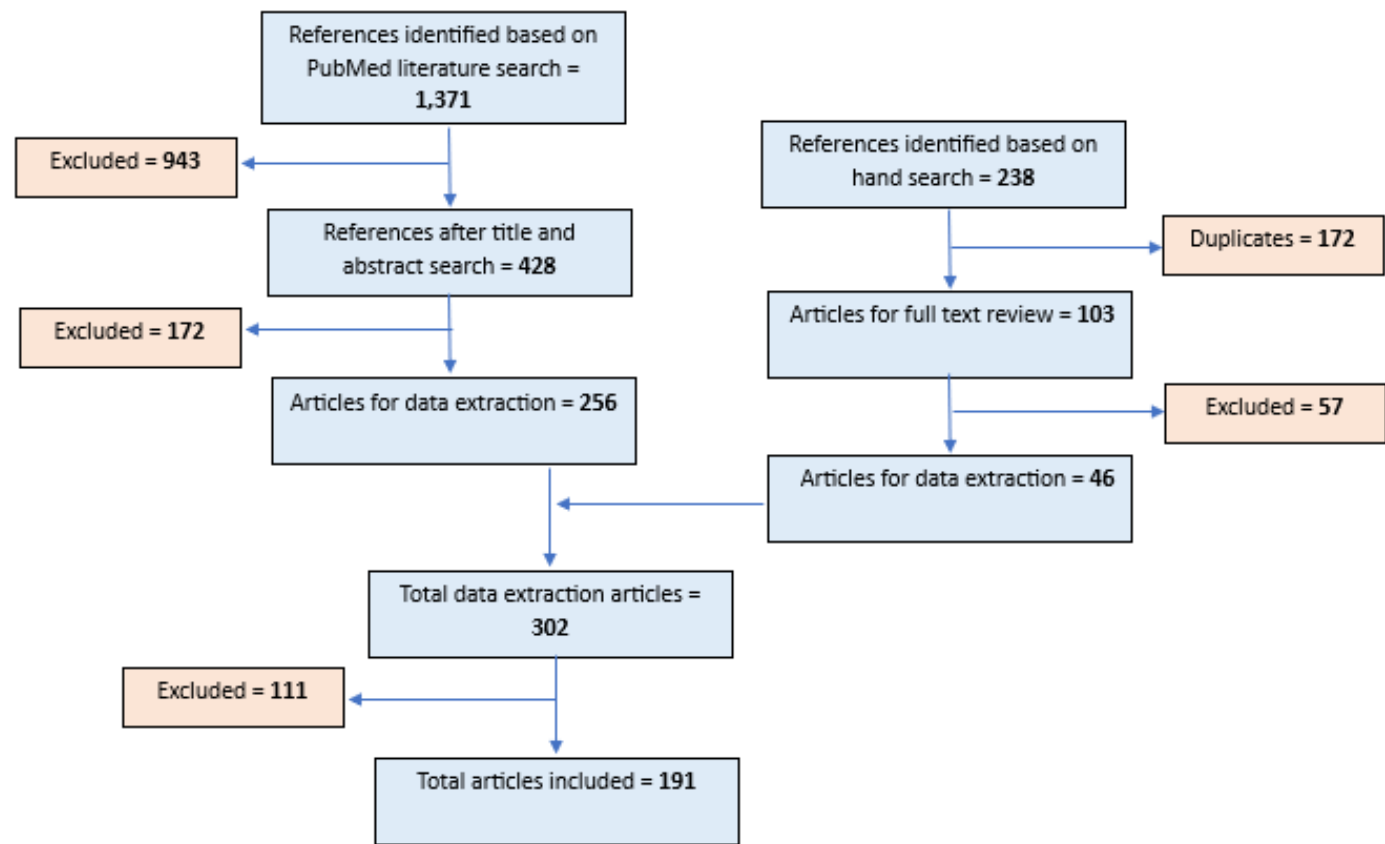
Both search strategies were run on 19 July 2024 (MD). Figures 1 and 2 show the literature search results for incidence/non-vaccine risk factors and vaccine risk factors respectively, following PRISMA guidelines (<https://www.prisma-statement.org/>).

Figure 1. PRISMA diagram for articles retrieved for incidence and non-vaccine risk factors.



Main reasons for exclusion: duplicate references, references not including information/data on seizures, references not including data on incidence or risk factors.

Figure 2. PRISMA diagram for articles retrieved for vaccine-related risk factors.



Main reasons for exclusion: duplicate references, references not including information/data on seizures, references not including data on vaccine association or references not providing complete data or no denominator information. Table 1 below provides a summary of changes in the Companion Guide from V1.0 to V2.0.

TABLE 1. Summary of the changes from V1 to V2 of the Generalized Convulsive Seizure Companion Guide

Change category	Guide Version 1 (V1.0)	Guide Version 2 (V2.0)
1. Order of Appendices	1. Risk Factors; 2. Background rates; 3. CD caveats; 4. Diagnostic codes; 5. Data abstraction form; 6 Tabular algorithm; 7. Pictorial algorithm; 8. Methods	1. Diagnostic codes; 2. Background rates; 3. Risk factors; 4. CD caveats; 5. Data abstraction form and algorithms to determine level of certainty; 6. Methods. Reference order updated to match the new order of appendices
2. Diagnostic codes	MedDRA, ICD-9-CM, ICD-10-CM	SNOMEDCT codes added. Separate tables generated for codes relevant to searching electronic health care data (ICD-9-CM, ICD-10-CM, SNOMEDCT) and those relevant to pharmacovigilance (MedDRA). The updated MedDRA table is based on version 28.1 and includes both Preferred and Lower Level Terms (PT, LLT).
3. Background rates	For Generalized convulsive seizure - provided from 33 studies, with	New evidence added to the V1 table based on scoping literature review.

	distribution by country (1 unless otherwise specified): Egypt, Ethiopia, Kenya, 2 Tanzania, Uganda, 4 USA, Canada, Martinique, Honduras, Chile, Ecuador, 2 India, 2 Denmark, 2 Estonia, Finland, Germany, Iceland, Italy, Netherlands, 4 Sweden, Switzerland, 2 UK. For epilepsy – provided from 6 studies: 3 US, Germany, Switzerland, UK.	
4. Risk Factors	<p>Provided in a table for Age, Gender, Genetics, Geography, Vaccine and Other.</p> <p>Additional table provided comparing typical features of seizure associated with Epilepsy versus Febrile Seizure.</p>	<p>New evidence added to the V1 table based on scoping literature review.</p> <p>Section expanded with multiple tables showing evidence on vaccine association with generalized convulsive seizure by study design (Table 3.3 – 3.13)</p>
5. Data collection form	Single data form used to collect information AND to define new criterion variables if needed.	<p>Step 1 – data collection form only</p> <p>Step 2 – new criterion variables defined as needed</p>
6. CD criterion values	Summary table for all criterion values (Y=YES, N=NO, U=UNKNOWN) as determined in 1. above.	Same as in V1 but now labelled as Step 3 rather than a numbered table.
7. Level of Certainty (LOC) algorithms	Tabular algorithm with formulae to determine LOC based on criterion values in the summary table.	Same as in V1 but now labelled as Step 4 rather than a numbered table.
8. Guide appendices	<p>3 separate appendices for:</p> <ul style="list-style-type: none"> i. Data collection and interpretation form ii. Tabular checklist for determining LOC iii. Pictorial algorithm for determining LOC 	Single appendix contains the Data collection and interpretation forms and the tabular (Step 4) and pictorial (Figure) algorithms.
9. Seizure Terminology	Generalized Convulsion used throughout the Companion Guide including title page	Generalized Convulsive Seizure substituted for all instances of Generalized Convulsion, to match the terminology in the published BC CD
10. Glossary of Terms	Link provided to Neurologic Glossary of Terms	Table of terms specific to generalized convulsive seizure provided at end of appendix. Terms yellow highlighted in the data form to alert user to presence of glossary.
8. Criteria specific to Generalized Convulsive Seizure (Note – none of the changes in V2 vs V1 of the Guide reflect a change in the BC CD. Rather V2 provides a more complete picture of the case definition as laid out by the BC CD Working Group)		
Motor manifestations	Single Criterion B for type of movements: Tonic, clonic, tonic-clonic, atonic, other	<p>Separate Criteria for:</p> <p>B. Generalized Motor Movements Need to be bilateral movements, right and left side of the body, to be considered generalized</p> <p>C. Type of movements: Tonic, clonic, tonic-clonic, atonic, other</p>

Conditions that exclude atonic movements from being considered part of seizure	Not defined	Criterion D: specifies that concurrent episode of HHE (hypotonic hyporesponsive episode) OR myoclonic jerks OR syncope disqualifies atonic movements from being considered part of a generalized seizure
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The outputs are provided as separate appendices to simplify printing as needed. These are provided for Generalized Convulsive Seizure as shown below:

1. Diagnostic Codes: ICD-9CM, ICD-10CM, MedDRA and SNOMEDCT
2. Background Rates
3. Risk Factors
4. Case Definition key caveats for diagnosis, data analysis and presentation
5. Data Abstraction and Interpretation Forms with algorithms for assessing level of diagnostic certainty and a glossary of relevant terms.
6. Summary of methods. Also provides links, as appropriate, to the original deliverable documents with more detailed methodology.

4. Recommendations & discussion

This guide brings together many resources and tools related to the AESI of generalized convulsive seizure, several of which have been updated as follows: SNOMEDCT codes added; Separate code tables provided for ICD-9/10-CM /SNOMEDCT (for searching electronic health databases) and MedDRA codes for pharmacovigilance. The MedDRA table now distinguishes Preferred Terms (PT) and Lower-Level Terms (LLT) and provides the version; new evidence added to background rate and risk factor sections based on a scoping literature review. The risk factors have a greatly expanded section on evidence for vaccine-generalized convulsive seizure association; key caveats and guidance for real time investigation; a simplified data abstraction form and algorithms for assigning level of diagnostic certainty that matches what is available in the online ABC tool and redcap forms; and a glossary of terms for generalized convulsive seizure.

SPEAC recommends that the tools be used in order to assign level of diagnostic certainty for all identified AEFI with features of generalized convulsive seizure. This standard, harmonized approach will facilitate signal detection and assessment as well as the capacity to combine data across trials for meta-analyses.

APPENDIX 1.

ICD-9 – CM, ICD-10-CM, SNOMEDCT and MedDRA Codes for Generalized Convulsive Seizure

1.1 Generalized Convulsive Seizure Diagnostic Codes: ICD-9/10-CM and SNOMEDCT

TABLE 1.1 Diagnostic codes to identify GENERALIZED CONVULSIVE SEIZURE AND EPILEPSY in electronic healthcare databases.

UMLS		Medical Diagnostic Terms and Codes			
CUI	Name	Term	ICD-9-CM	ICD-10-CM	SNOMEDCT
C0036572	Seizures	Convulsions	780.3		
		Unspecified convulsions		R56.9	
		Convulsion			32631004 271788002
		[D] Convulsions			158138006 206732001
		[D]Convulsion NOS			158142009 206738002
		Seizure	780.39		91175000
		Seizures	780.39		
		Fit – convulsion			312078006
		Fits – convulsions			313290005
		[D]Fit			158141002 206735004
C0038220	Status Epilepticus	Status epilepticus		G41	13973009 155039002 230456007
		[X]Status epilepticus, unspecified		G41.9	193019007 194499008
C0751494	Convulsive seizures	Seizure(s) (convulsive) NOS		R56.9	
C0495698	Convulsions, not elsewhere classified	Convulsions, not elsewhere classified		R56	
C0490011	Other convulsions	Other convulsions	780.39		
C0494475	Tonic-clonic seizures	Grand mal seizure			192995009
		Grand mal			65155005
		Grand mal seizure NOS		G40.4	
		Grand mal seizures, unspecified (with or without petit mal)		G40.6	
		Tonic-clonic seizure			54200006
C0009952	Febrile convulsions	Febrile convulsions		R56.0	
		Febrile convulsions(simple) unspecified	780.31		
		Febrile convulsion			41497008 140804007 269033007 323091004
		Febrile convulsion NOS		R56.00	
		[D]Convulsions, febrile			158139003

					206733006
C0149886	Seizure, Febrile, Simple	Seizure, Febrile, Simple	780.31	R56.00	
C0751057	Seizure, Febrile, Complex	Complex febrile convulsions	780.32	R56.01	
		Complex febrile seizure			433083002
C0311335	Grand Mal Status Epilepticus	Grand mal status	345.3		13973009 192998006
		Grand mal status epilepticus		G41.0	
C0270823	Petit mal status	Petit mal status	345.2		7033004
		Petit mal status epilepticus		G41.1	
C2875137	Other seizures	Other seizures		G40.89	
C0477372	Other status epilepticus	[X]Other status epilepticus			194492004
C0478149	Other and unspecified convulsions	Other and unspecified convulsions		R56.8	
		[X]Other and unspecified convulsions			207622007 274828008
		Convulsions in newborn	779.0		157162003 230436006
		Convulsions in the newborn			87476004
C0014544	Epilepsy	Epilepsy		G40	84757009
		Epilepsy unspecified	345.9	G40.9	
		Epilepsy NOS		G40.909	155045005 193026007 267593008
		Epileptic attack			271788002
		Attack - epileptic			267698007
		(Epilepsy) or (epileptic attack)			155036009
		EF – Epileptic fit			246545002
		Seizure disorder			128613002
C3263970	Epileptic seizures related to external causes			G40.5	
	Epileptic seizures related to external causes, NOS			G40.509	
C0154719	Other forms of epilepsy and recurrent seizures, without mention of intractable epilepsy		345.80		
C0154720	Other forms of epilepsy and recurrent seizures, with intractable epilepsy		345.81		
C0311334	Generalized convulsive epilepsy		345.1		
C0154709	Generalized convulsive epilepsy, without mention of intractable epilepsy		345.10		
C0270850	Idiopathic generalized epilepsy			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		

1.2 Generalized Convulsive Seizure Diagnostic Codes: MedDRA codes.

TABLE 1.2 Search and/or coding terms for generalized convulsive seizure and epilepsy in pharmacovigilance data. Preferred Terms (PT) and Lower-Level Terms (LLT) were obtained using MedDRA V 28.1. * indicates inactive LLTs. These are kept in the table because they may be relevant to searches in databases in which coding may have been based on earlier MedDRA versions.

inUMLS		MedDRA Terms and Codes		
CUI	Name	Preferred Term (PT)	Lower Level Terms (LLT)	Code
C0234533	Generalized seizures	SEIZURE	Convulsions generalised	10010916
C0036572	Seizures			10010917
			Generalized convulsion	10018079
			Convulsions	10010914
			Convulsion	10010904
			Convulsion (NOS) [inactive]*	10010906
			Convulsions (NOS)	10010922
			Seizure	10039906
			Seizures	10039910
			Fit [inactive LLT]*	10016731
			Fits NOS [inactive LLT]*	10016735
Fitting [inactive LLT]*	10039910			
C0856799	Classic fit		Classic fit	10009234
C0234975	Convulsions aggravated		Convulsions aggravated	10010915
			Convulsions NOS aggravated	10010923
C0751494	Convulsive seizures		Convulsive seizure	10010926
C0751056	Non-epileptic convulsion		Fit (non-epileptic)	10016733
C0863106	Afebrile seizure		Afebrile seizure	1001436
			Afebrile convulsion	1001435
C0494475	Tonic-clonic seizures	GENERALISED TONIC-CLONIC SEIZURE	Grand mal seizure	1008663
			Grand mal fit	10018662
			Grand mal epileptic fit	10018661
			Seizure grand mal	10039909
			Generalised tonic-clonic seizures	10018101
C0311334	Generalized convulsive epilepsy		Generalized convulsive epilepsy	10018109
			10073920	
C0154709	Generalized convulsive epilepsy, without mention of intractable epilepsy		Generalized convulsive epilepsy, without mention of intractable epilepsy [inactive LLT]*	10018111
C0234535	Seizures, Clonic	CLONIC CONVULSION	Clonic convulsion	10009340
			Clonic seizures	10053398
C0270844	Seizures, Tonic	TONIC CONVULSION	Tonic convulsion	10043994
			Tonic seizure	10043996
			Tonic convulsion	10043997
C0009952	Febrile convulsions		Febrile convulsion	10016284
			Convulsion febrile	10010908

		FEBRILE CONVULSION	Febrile convulsion seizure	10016285
			Febrile seizure	10016290
			Febrile fits	10016287
			Fever convulsions	10016560
			Pyrexial fit	10037670
C0311335	Grand Mal Status Epilepticus	STATUS EPILEPTICUS	Grand mal status,	10018664
			Status epilepticus grand mal	10041963
			Convulsive status epilepticus	10057955
C0270823	Petit mal status	PETIT MAL STATUS	Petit mal status, epileptic;	10034760
			Status epilepticus petit mal	10041964
C0863106	Afebrile seizure	NEONATAL SEIZURE	Convulsions in newborn	10010921
			Neonatal convulsion	10028932
			Neonatal seizures	10061197
			Neonatal fit	10028939
C0270846	Epileptic drop attack	ATONIC SEIZURES	Atonic seizures	10003628
			Drop seizures	10071377
C0014544	Epilepsy	EPILEPSY	Epilepsy	10015037
			Epilepsy unspecified	10015047
			Epilepsy NOS	10015402
			Epileptic fit	10015051
			Epileptic seizure	10015052
C0270850	Idiopathic generalized epilepsy	IDIOPATHIC GENERALIZED EPILEPSY	Idiopathic generalized epilepsy	10071096 (LLT) 10071081 (PT)
C0220669	Familial benign neonatal epilepsy	BENIGN FAMILIAL NEONATAL CONVULSIONS	Benign familial neonatal convulsions	10067866

APPENDIX 2.

Generalized convulsive seizure Background Rates

2.1 Generalized convulsive seizure Background Rates

TABLE 2.1. GENERALIZED CONVULSIVE SEIZURE BACKGROUND RATES

Unless otherwise specified the incidence rates in this table are for first onset epilepsy, which was usually defined as at least two or more unprovoked seizures, excluding febrile and neonatal seizures as well as provoked seizures (such as following head trauma or in the context of neurologic infection). A few of the studies provide data on first epileptic seizure^{21,27, 67,68,73} and these are identified in the first column under Country. Two studies provide data on febrile seizures^{29, 54} A detailed methodology for each study is provided in Table 2.3. The rationale for including epilepsy incidence rates is that when a first seizure occurs following immunization it isn't known whether or not there will be a recurrent episode.

Country reference	Study years	Population (age in years)	Incidence rate per 100,000 person years [95% confidence interval] (total cases)		
			All	Males	Females
AFRICA					
Benin[2]	2006-2007	All ages	69.4[30.0–136.8] (12)		
Egypt[3]	2010	All ages	1.52 [0.53-2.51] (75)		
Egypt[4]	2011-2013	All ages	123[80.6-175.74] (22)		
Egypt[5]	Not reported	0 to <2 2 to <6 6 to <12 12 to <18 18 to <40 40 to <60 ≥60 All ages	322.0 [296.2–349.0] (4) 100.8 [99.8–101.0] (3) 51.7 [50.1–53.3] (2) 24.9 [23.6–26.3] (1) 7.6 [7.15–8.07] (1) 32.9 [31.72–34.10] (2) 142.4 [127.9–158.2] (3) 48.0 [47.46–48.54] (16)		
Egypt[6]	2009–2012	All ages	48		
Egypt[7]	2007	All ages	43.14		
Ethiopia[8]	Not provided (3.5 yr Period overall)	0-9	94 (68)	103 (37)	86 (31)
		10-19	74 (42)	77 (23)	71 (19)
		20-29	73 (16)	115 (10)	46 (6)
		3-39	38 (9)	39 (4)	38 (5)
		40-49	-- (0)	-- (0)	-- (0)
		50-59	9.4 (1)	19 (1)	-- (0)
		60-69	24 (2)	23 (1)	25 (1)
		≥ 70	16 (1)	-- (0)	30 (1)
		All ages	64 (139)	72 (76)	57 (63)
Kenya[9]	2003-2007	6-12	96.1 [78.4-117.9] (189)		
		13-17	91.2 [66.9-124.3] (82)		
		18-38	82.3 [60.7-111.9] (84)		
		29-49	37.4 [25.7-54.7] (56)		
		≥50	79.6 [56.6-111.9] (68)		
		All ages	77.0 [67.7-87.4] (479)		

Kenya[10]	2001-2020	5–14		89.06[31.7-98]	88.86[36.02-97.27]
Kenya[11]	2003–2008	0–5 6–12 13–18 19–28 29–49 50+ year All ages		85.19[29.05–93.32] 53.07[7.42–56.75] 39.64[6.26–42.72] 28.53[5.93–30.39] 24.07[6.30–25.64] 43.52[6.05–46.73] 48.00[10.92–51.80]	69.44[14.50–74.37] 48.20[7.60–50.88] 41.36[6.77–44.35] 33.83[5.56–36.69] 14.95[4.74–15.96] 27.30[5.46–29.31] 39.16[7.47–41.89]
Kenya[12]	2001–2004	6-12	189[133–256] (39)		
Tanzania[13]	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[14]	1999-2003	All ages	81.1 [65-101] (29)		
Uganda[15]	1991-1995	2-23	156 (40)		
AMERICAs					
USA[16]	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[17]	1935–1984	All ages	44(880)	49(418)	41(462)
USA[18]	1980-1984	<1 1-4 5-9 10-14 15-24 25-34 35-44 45-54 55-64 65-74 75-84 85+ All ages	56.8(3) 74.3(13) 58.5(11) 56(11) 39.5(22) 31.4(18) 31.2(11) 26.7(7) 58.8(13) 85.8(14) 155(17) 391.6(16) 52.3(156)		

USA[19]		<5	67.0 (38)	51.8 (15)	82.9 (23)
		5-14	59.6 (65)	64.9 (36)	54.0 (29)
		15-24	45.0 (34)	53.1 (16)	39.7 (18)
		25-34	17.5 (21)	20.2 (9)	15.9 (12)
		<i>Incidence</i>	35-44	14.1 (17)	10.3 (5)
		<i>rates for</i>	45-54	12.4 (9)	15.8 (5)
		<i>epilepsy</i>	55-64	20.9 (8)	16.7 (3)
		65-74	20.3 (2)	0 (0)	41.9 (2)
		75+	0 (0)	0 (0)	0 (0)
	1988-1994	<5	93.5 (53)	76.0 (22)	111.7 (31)
		5-14	79.7 (87)	84.7 (47)	74.5 (40)
		15-24	59.6 (45)	76.3 (23)	48.5 (22)
		<i>Incidence</i>	25-34	23.3 (28)	22.5 (10)
		<i>rates for</i>	35-44	20.0 (24)	16.4 (8)
		<i>first</i>	45-54	24.8 (18)	25.3 (8)
		<i>unprovoked</i>	55-64	36.5 (14)	33.4 (6)
		<i>seizure</i>	65-74	64.0 (5)	72.6 (3)
		75+	99.2 (1)	0 (0)	182.8 (1)
USA[20]	Not reported	45-59	10.6[2.2-30.9] (3)	0.0[0.0- 33.3] (0)	17.4[3.6-50.7] (3)
		60-74	25.8[10.4-53.1] (7)	28.2[5.8-82.6] (3)	24.2[6.6-62.0] (4)
		75-89	101.1[41.4-160.8] (11)	144.7[53.1-315.0] (6)	74.2[24.1-173.3] (5)
		45-99 (all)	31.5[18.0- 44.9] (21)	34.6[15.9-65.8] (9)	29.4[12.8-46.1] (12)
USA[21] (New York)	2003-2005	<1	134.4 [51.1-217.7]	104.7 [2.1-207.3]	165.7 [33.1-298.3]
		1-4	50.4 [24.9-75.9]	65.4 [24.9-106.0]	34.5 [4.3-64.8]
		5-9	41.5 [21.8-61.3]	52.7 [21.6-83.9]	29.9 [6.0-53.8]
		10-14	30.7 [13.3-48.1]	45.8 [15.9-75.6]	15.5 [-2.0-32.9]
		15-24	39.8 [26.4-53.1]	50.0 [29.1-70.9]	28.9 [12.6-45.3]
		25-34	13.1 [5.7-20.5]	15.5 [4.0-27.0]	10.8 [1.3-20.2]
		35-44	21.3 [11.4-31.1]	26.8 [11.0-42.7]	16 [4.2-27.9]
		45-54	31.5 [18.0-44.9]	39.0 [16.9-61.1]	25 [8.7-41.3]
		55-64	35.3 [17.4-53.2]	42.7 [13.1-72.3]	29.5 [7.6-51.3]
		65-74	45.3 [20.7-69.9]	43.8 [5.4-82.2]	46.2 [14.2-78.3]
		75-84	144.7 [88.0-201.5]	212.6 [92.3-332.9]	111.8 [51.0-172.6]
		≥ 85	235.5 [123.6-347.5]	108.3 [-41.8-258.5]	279.2 [137.9-420.5]
		All ages	41.1 [35.4-46.8] (209)	46.6 [378-55.4] (113)	35.9 (28.7-43.1) (96)
USA[22] (Minnesota, Olmsted Country)	1980-2004	1-4	65.3 (122)	77.7 (75)	52.0 (47)
USA[23] (National data)	1990	All ages	40.6[28.7-52.8]		
	2017	All ages	47.6[32.3-62.1]		
USA[24] New Mexico	1998-2001	All ages	47		
	1996-2001	All ages	71		

Canada[25]	1977-1985	<13 months	118[98-143] (112)		
		1	42[30-57] (40)		
		2	46[34-62] (45)		
		3	58[44-76] (57)		
		4	49[36-66] (47)		
		5	47[34-63] (45)		
		6	53[40-69] (53)		
		7	46[34-62] (46)		
		8	33[23-47] (34)		
		9	39[28-53] (41)		
		10	46[35-61] (51)		
		11	19[12-29] (22)		
		12	28[20-40] (33)		
		13	26[18-37] (29)		
		14	17[10-26] (19)		
		15	16[10-26] (19)		
		Total	41[38-45] (693)		
Canada[26]	1986-2001	29 days to 15.5 years	63 (648)		
Martinique[27] <i>Rates are for first epileptic seizure</i>	1994-1995	1-9	94 (59)	111.5 (35)	76.6 (24)
		10-19	63 (36)	78.6 (23)	46.6 (13)
		20-29	38 (24)	45.5 (14)	31 (10)
		30-39	50 (33)	74.8 (24)	26.6 (9)
		40-49	52.5 (24)	79 (17)	28.9 (7)
		50-59	89.7 (30)	151.6 (24)	34 (6)
		60-69	146.6 (41)	192.5 (25)	106.7 (16)
		≥ 70	224 (62)	331 (37)	151.5 (25)
		All ages	80.5 (309)	331 (199)	55.4 (110)
Honduras[28]	1996-1997	All ages	92.7 [18.5-166.9] (6)		
Brazil[29]	2003–2007	0–4 Epilepsy Febrile seizures	7.0[3.0-12.0] (11) 160 [11.0-24.0] (27)		
Chile[30]	1984-1988	0-14	124.4 (43)	151.6 (24)	101.4 (19)
		15-29	144.8 (29)	147.5 (15)	142.1 (14)
		30-44	81.0 (29)	85.1 (11)	76.5 (9)
		45-59	103.9 (10)	97.9 (6)	114.4 (4)
		> 59	-- (0)	-- (0)	-- (0)
		All ages	113.0 (102)	125.3 (56)	100.9 (46)

Ecuador[31] (Andean region)	1986-1987	0-9	174.4 (35)		
		10-19	268.3 (49)		
		20-29	180.3 (17)		
		30-39	55.9 (4)		
		40-49	255.9 (16)		
		50-59	141.2 (7)		
		60-69	126.0 (4)		
		70-98	177.6 (5)		
		All ages	190.0 (137)		
Peru[32]	1999–2000	<1–99	112.7(1)		
	2001	<1–99	128.5(1)		
	2002	<1–99	130.9(1)		
	2003	<1–99	410(3)		
	2005	<1–99	0(0)		
	1999–2004	<1–99	162.3(6)		
ASIA					
China[33]	2016–2017	All ages	23.99		
India[34]	1990-1991	<10	74.5 (11)	90.9 (7)	56.6 (4)
		10-<20	46.9 (7)	37.8 (3)	57.3 (4)
		20-<30	62.8 (7)	54.3 (3)	71.1 (4)
		30-<40	32.2 (3)	43.3 (2)	21.3 (1)
		40-<50	-- (0)	-- (0)	-- (0)
		50-<60	74.2 (3)	47.1 (1)	104.2 (2)
		60-<70	-- (0)	-- (0)	-- (0)
		70-<80	91.9 (1)	195.3 (1)	-- (0)
		≥ 80	-- (0)	-- (0)	-- (0)
		All ages	49.3 (32)	50.7 (17)	47.4 (15)
India[35]	2003-2008	0-4	63.35	59.17	68.17
		5-9	10.41	0	21.52
		10-14	24.72	39.90	8.51
		15-19	46.85	44.17	49.87
		20-24	11.96	14.75	8.68
		25-29	8.35	16.19	0
		30-34	4.64	0	9.62
		35-39	9.12	17.71	0
		40-44	16.47	30.53	0
		45-49	16.47	19.59	24.98
		50-54	17.47	16.03	19.19
		55-59	21.25	38.87	0
		60-64	66.26	65.22	67.34
		65-69	45.25	60.42	30.12
		70-74	35.81	69.08	0
		75-79	37.17	0	84.75
		80-84	205.65	307.69	103.09
		≥85	160.64	0	296.3

		All ages *	27.27 [21.03-34.80] (66)	30.54 [21.06-42.83]	23.34 [16.18-35.71]
India[36]	2003–2008	All ages	38.37[33.23–44.09] (197)	44.35[32.08–58.90] (118)	33.19[23.00–45.90] (79)
India[37]	2014–2017	Total	38.28		
India[38]	2006–2012 Unprovoked seizure (≥1)	5–15	71.35[50.2–98.35] (37)		
	Epilepsy (≥2 unprovoked seizures)	5-10	45.24[27.24–70.64]		
		11-15	111.61[55.71–199.7]		
		5-15	57.85[39.0–82.6]	64.99 36.3–107.2	52.13[29.17–85.97]
India[39]	2004	All ages	57.26[42.26–72.25](56)		
	2005	All ages	74.16[57.26–91.06](74)		
	2006	All ages	68.82[52.70–84.94](70)		
	2007	All ages	60.76[45.75–75.76](63)		
India[40]	1992-1998	0–4	129(10)		
		5–9	120(9)		
		10–14	85(6)		
		15–19	40(3)		
		20–29	11.8(2)		
		30–39	11.2(2)		
		40–49	30(4)		
		50–59	11(1)		
		60–69	12(1)		
		70+	0(0)		
		All ages	36.66(38)		
Japan[41]	1975	0-1	122.5(37)	123.1(19)	121.9(18)
		1-2	378.9(120)	439.0(71)	316.1(49)
		2-3	219(70)	232.1(38)	205.3(32)
		3-4	178.3(56)	190.8(31)	165.0(25)
		4-5	75.6(23)	69.8(11)	81.8(12)
		5-6	81.9(24)	93.3(14)	70.0(10)
		6-7	105.1(30)	129.2(19)	79.6(11)
		7-8	98.4(27)	113.9(16)	82.2(11)
		8-9	69.7(19)	85.0(12)	53.3(7)
		9-10	65.1(14)	63.1(7)	67.4(7)
		All ages	145(420)	159.8(238)	129.4(182)
Japan[42]	2007–2015	1-4	108.6 (13)		
		5-9	38.5 (5)		
		10-14	67.7 (11)		
		All ages	70.4[44.8–96.0] (29)		
S Korea[43]	2017	0–4	26.9	26.9	26.9
		5–9	30.0	34.3	25.7
		10–14	26.0	28.9	23.1

		15–19	25.9	28.3	23.4
		20–24	21.6	27.4	15.4
		25–29	20.8	22.3	19.3
		30–34	17.6	19.3	16.0
		35–39	18.1	18.4	17.9
		40–44	21.2	23.6	18.9
		45–49	26.1	29.9	22.4
		50–54	33.9	36.9	31.1
		55–59	39.0	45.0	33.4
		60–64	48.0	55.3	41.5
		65–69	57.3	67.5	48.8
		70–74	69.5	81.7	60.4
		75–79	94.2	120.5	76.9
		80–84	116.0	144.1	102.2
		85–89	129.8	164.7	118.2
		90–94	139.0	185.5	127.0
		≥95	95.0	135.6	83.5
		All ages	35.2	38.5	32.3
Taiwan[44]	2007	<20	0.53[0.51–0.54] (2884)	0.57[0.54–0.60] (1627)	0.46[0.44–0.49] (1125)
		20–34	0.31[0.30–0.32] (1735)	0.37[0.35–0.39] (1036)	0.25[0.23–0.27] (653)
		35–49	0.43[0.41–0.44] (2391)	0.56[0.53–0.59] (1570)	0.43[0.41–0.46] (1217)
		50–64	0.76[0.73–0.79] (2857)	0.99[0.95–1.04] (1846)	0.74[0.70–0.77] (1844)
		≥65	2.10[2.04–2.15] (4980)	2.35[2.26–2.44] (2747)	1.80[1.73–1.87] (2540)
		All ages	0.72 [0.70–0.73](14847)	0.83[0.81–0.85](8826)	0.60[0.59–0.62] (6021)
	2015	<20	0.45[0.43–0.47] (2095)	0.48[0.45–0.50] (1257)	0.43[0.41–0.46] (970)
		20–34	0.21[0.20–0.23] (1098)	0.25[0.23–0.27] (699)	0.18[0.16–0.19] (445)
		35–49	0.33[0.31–0.34] (1870)	0.29[0.27–0.31] (821)	0.23[0.21–0.24] (653)
		50–64	0.57[0.55–0.59] (2909)	0.53[0.50–0.56] (1011)	0.41[0.38–0.43] (1065)
		≥65	1.60[1.55–1.64] (4810)	1.85[1.77–1.93] (2233)	1.42[1.36–1.48] (2270)
		All ages	0.54[0.53–0.55] (12782)	0.63[0.61–0.64](7379)	0.46[0.45–0.47] (5403)
Taiwan[45]	2001–2003	0–19	100(19579)		
		20–24	71(4271)		
		25–29	62(3312)		
		30–34	54(3052)		
		35–39	60(3502)		

		40–44 45–49 50–54 55–59 60–64 65–69 70–74 75+ All ages	72(3968) 78(3856) 115(3783) 115(2811) 136(3130) 165(3243) 205(3553) 330(6677) 97(64737)		
VietNam[46]	2005 and 2008 combined	1–15 16–50 >50 All ages	96.8[58.1–135.6] (24) 22.7[9.9–35.5] (12) 21.5[0.4–42.6] (4) 41.6[28.7–54.4] (40)	93.2[40.5–146.0] (12) 34.8[12.1–57.5] (9) 52.7[1.1–104.4] (4) 53.9[32.8–75.1] (25)	100.7[43.8–157.7] (12) 11.1[0–23.7] (3) 0.0[0] (0) 30.1[14.9–45.3] (15)
EUROPE					
Denmark[47]	1995-2002	All ages	83.3 (33)		
Denmark[48]	1979-1983	60-64	63 (20)		
		65-69	83 (26)		
		70-74	101 (31)		
		75-79	90 (22)		
		≥80	47 (13)		
		All ages	77 (112)		
Estonia[49]	1994-1996	20-29	20.6 [8.4-32.8] (11)	32.6 [11.3–53.9] (9)	7.7 [0.0–18.4] (2)
		30-39	32.8 [15.6-50.0] (14)	49.2 [18.7–79.7] (10)	17.9 [0.3–35.5] (4)
		40-49	29.3 [12.0-46.6] (11)	35.2 [7.1–63.3] (6)	24.5 [3.1–45.9] (5)
		50-59	41.2 [20.4-62.0] (15)	57.4 [19.9–94.9] (9)	28.9 [5.8–52.0] (6)
		60-69	56.0 [30.1-81.9] (18)	109.1[52.0–166.2] (14)	20.7 [0.4–41.0] (4)
		70-79	39.9 [10.3-69.5] (7)	91.8 [11.3–172.3] (5)	16.5 [0.0–39.4](2)
		≥80	55.1 (6.8-103.4) (5)	92.0 [0.0–219.5] (2)	43.5 [0.0–92.7](3)
		All ages	35.4 [27.7-43.1] (81)	54.4 [40.0–68.8] (55)	20.4 [12.6–28.2](26)
Estonia[50]	1973-1974	<1	95.7 (3)		
		1-4	139.9 (17)		
		5-9	52.1 (9)		
		10-15	71.0 (14)		
		All ages	82.3 (43)		
Finland[51]	1960-1979	16-19	27 (25)	31 (14)	22 (11)
		20-29	16 (36)	22 (24)	10 (12)
		30-39	22 (32)	24 (19)	19 (13)
		40-49	23 (36)	26 (23)	20 (13)
		50-59	32 (46)	46 (29)	20 (17)
		60-69	26 (31)	42 (22)	15 (9)
		≥ 70	29 (23)	50 (14)	18 (9)
		All ages	24 [16-32] (230)	32 [20-44] (145)	17 [9-25] (85)
East Finland[52]	2008	0–15	68.7(79)		
		16–64	58.5(256)		
		≥65	145.4(188)		
		All ages	76.7(523)		

Middle Finland[52]	2008	0–15 16–64 ≥65 All ages	49.0 (52) 50.2 (167) 110.8(91) 59.5(310)		
West Finland[52]	2008	0–15 16–64 ≥65 All ages	62.9 (463) 47.5 (1285) 104.5(711) 59.6(2459)		
Germany[53]	1965-1966	0-1	201.6	230.5	170.6
		1-2	111.4	143.4	77.0
		2-3	66.3	56.3	77.0
		3-6	44.3	54.8	33.0
		6-8	37.1	44.6	29.2
Germany[54]	Epilepsy				
	1982	0-14	48.4		
	1983	0-14	64.2		
	1984	0-14	50.3		
	1985	0-14	45.6		
	1982-1985	0-14	52.1		
	Febrile seizure				
	1982	0-5	214.6		
	1983	0-5	219.7		
	1984	0-5	269.0		
	1985	0-5	259.9		
	1982-1985	0-5	240.8		
Germany[55]	1999-2000	<1	145.8 [47.4-340.1] (5)		
		1-<5	62.1 [29.8-114.2] (10)		
		5-<10	49.7 [23.8-91.3] (10)		
		10-<15	55.9 (27.9-100.0) (11)		
		All ages	60.3 (36)		
Greece[56]	2004-2005	All ages	58.4[43.9–72.9] (68)		
Greece[56]	2004-2005	All ages	32.6(37)		
Greece[56]	2004-2005	All ages	15.0(17)		
Iceland[57]	1993	<1	256.49(4)	375.49(3)	131.48(1)
		1–4	77.48(5)	89.95(3)	64.14(2)
		5–9	52.90(4)	50.92(2)	55.04(2)
		10–14	36.90(3)	47.28(2)	25.65(1)
		15–24	33.52(5)	51.80(4)	13.90(1)
		25–34	7.01(1)	0.00(0)	14.39(1)
		35–44	15.85(2)	15.03(1)	16.76(1)
		45–54	58.15(5)	66.50(3)	0.00(0)
		55–64	44.06(3)	56.90(2)	91.08(1)
		65–74	95.63(5)	186.68(5)	0.00(0)
		75–84	99.22(3)	70.42(1)	124.72(2)
		≥85	187.51(2)	0.00(0)	315.00(2)
		All ages	46.54(42)	55.86(26)	36.62(16)

Iceland[57]	1993	<1	256.49(4)		
		1-4	46.49(3)		
		5-14	25.49(4)		
		15-34	16.92(5)		
		35-44	0.00(0)		
		45-54	34.89(3)		
		55-64	58.75(4)		
		65-74	57.38(3)		
		75-84	66.15(2)		
		≥85	93.75(1)		
		All ages	32.14(29)		
Iceland[58]	1995-1999	<1	130.2 (18)	127.6 (9)	132.9 (9)
		1-4	54.0 (31)	47.6 (14)	60.8 (17)
		5-9	65.8 (48)	77.3 (29)	53.6 (19)
		10-14	56.0 (37)	62.4 (21)	49.5 (16)
		15-24	71.2 (98)	64.1 (45)	78.5 (53)
		25-34	36.1 (48)	31.5 (21)	40.8 (27)
		35-44	31.9 (42)	32.8 (22)	30.8 (20)
		45-54	34.4 (35)	38.4 (20)	30.2 (15)
		55-64	48.3 (32)	45.8 (15)	50.7 (17)
		65-74	70.5 (41)	86.3 (24)	55.9 (17)
		75-84	168.5 (55)	186.3 (26)	155.1 (29)
		≥85	151.9 (16)	238.3 (9)	103.6 (7)
		All ages	56.8 [51.8-61.8] (501)	57.7 (255)	55.9 (246)
Italy[59]	1964–1978	<1	212(20)	353.2(16)	81.3(4)
		1-4	100.4(35)	81.4(14)	118.8(21)
		5-9	89.1(41)	115.4(27)	61.8(14)
		10-14	80.3(38)	106.9(25)	54.3(13)
		15-19	53.3(24)	58.7(13)	50.0(11)
		20-39	20.3(37)	18.5(17)	22.2(20)
		40-59	13.6(25)	15.5(14)	11.7(11)
		≥ 60	7.5(10)	11.7(7)	4.2(3)
		All ages	33.1(230)	39.1(133)	27.3(97)
Italy[60]	1996-2005	<1	109.4 [69.4-164.1] (23)	77.8 [35.6-147.8] (9)	134.1[73.2-225.3] (14)
		1-4	58.9 [43.9-78.5] (51)	62.5 [41.5-90.6] (28)	55 [35.2- 81.9] (23)
		5-9	67.76 [53.4-84.7] (76)	74.27[53.5-100.2] (42)	64.9 [45.0-90.9] (34)
		20-24	33.8 [23.9-52.1] (38)	32.9 [19.8-61.1] (19)	34.9 [21.0-54.4] (19)
		All ages	57.1 [49.3-65.9] (188)	57.5 [46.7–70.1] (98)	56.6 [45.5–69.6] (90)
Netherlands[61]	1990–1991	0-4	44(18)	28(6)	60(12)
		5-9	65(27)	81(17)	50(10)
		10-14	48(20)	52(11)	44(9)
		15-24	68(64)	74(36)	61(28)
		25-34	67(66)	60(30)	73(36)
		35-44	73(71)	73(36)	72(35)
		45-54	84(58)	87(31)	80(27)
		55-64	92(47)	96(24)	87(23)

		65-74 All ages	103(43) 72(414)	102(19) 73(210)	104(24) 71(204)
Netherlands[62]	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)
Norway[63]	1968-1972	0-6 7-14 15-19 20-29 30-39 40-49 50-59 60-69 70+ All ages	84.3(130) 48.2(73) 31.2(29) 20.7(35) 14.9(17) 17.6(21) 20.2(23) 16.7(14) 11.9(8) 32.8(350)		
Norway[64]	1999-2012	<1 1-4 5-10 All ages	144[122-168] 61[54-68] 54[45-62] 70[64-75]	158[124-189] 65[54-75] 53[41-65] 73[65-81]	130[102-163] 57[47-66] 55[42-68] 66[58-74]
Spain[65]	2002-2005	1-12 mo 1-<6 6-<10 10-<15 All ages	95.3[82.8-107.8] (22) 63.6[61.4-65.8] (66) 69.7[61.1-78.3] (54) 48.7[45.4-52.0] (49) 62.6[62.3-62.9] (191)	 66.6[55.4-77.8] (105)	 58.1[42.8-73.4] (86)
Sweden[66]	1973-1974	< 1 1-4 5-9 10-15 All ages	95.7(3) 139.9(17) 52.1(9) 71(14) 82.3(43)		
Sweden[67] First epileptic seizure	1985-1987	≥17	33.6[25.4-41.3] (107)	38.5[26.6-51.0] (61)	28.70[18.0-39.4] (46)
Sweden[68] First epileptic seizure	1985-1987	0-15	88.8		
UK[74]	2005	0-4 5-9 10-19 20-29 30-39 40-49 50-59 60-69 70-79 80-89	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		

		All ages	50.1[47.1-53.3] (1014)		
UK[75]	1995-1996	0-4	86		
		5-9	46		
		10-14	94		
		15-19	52		
		20-24	33		
		25-29	19		
		30-34	24		
		35-39	54		
		40-44	18		
		45-49	50		
		50-54	50		
		55-59	31		
		60-64	34		
		65-69	37		
		70-74	142		
		75-79	50		
		80-84	32		
		85-89	29		
		All ages	46 [36-60]		
European ACCESS (The Vaccine covid-19 monitoring readiness project[76] Generalized Convulsion)					
Italy, Spain, UK	2017-2020	All ages GP only	73.64[43.77-103.51]		
Netherlands	2014-2020	All ages INPATIENT only	80.68[9.66-151.70]		
Italy	2017 - 2020	All ages INPATIENT & EMR	142.56[134.83-150.30]		
Spain, Netherlands	2017-2020	All ages GP & IN-OUTPATIENT	152.35[78.67-226.02]		
Denmark, France	2010-2013 (Denmark) + 2017-2020 (France)	All ages IN-OUTPATIENT	194.28[175.77-212.79]		
MIDDLE EAST					
Qatar[77]	2001	≥13	174(1217)		
Qatar[78]	2018-2019	0-18	75(1422)		

TABLE 2.2 Incidence of Status Epilepticus

Country ^{reference}	Study years	Population (age in years)	Incidence rate per 100,000 person years [95% confidence interval] (total cases)		
			All	Males	Females
AFRICA					
La Reunion[79]	2004-2005	0–9	6.6 (9)	8.6(6)	4.5(3)
		10–19	2.9 (4)	4.2 (3)	1.4 (1)
		20–29	2.6 (3)	5.3 (3)	0.0 (0)
		30–39	3.3 (4)	3.4 (2)	3.2 (2)
		40–49	6.6 (7)	9.6 (5)	3.7 (2)
		50–59	19.3 (13)	21.1 (7)	17.6 (6)
		60–69	35.0 (15)	54.5 (11)	17.6 (4)
		70–79	33.1 (8)	29.4 (3)	35.8 (5)
		≥80	17.6 (2)	26.8 (1)	13.1 (1)
		All ages	8.5[6.5–10.5] (65)	10.9[7.6–14.2] (41)	6.2[4.0–8.4] (24)
AMERICA					
USA[80] (Minnesota)	1965-1984	<1	135.2 (28)		
		1-4	35.3 (26)		
		5-9	12.2 (12)		
		10-14	3.7 (3)		
		15-19	6.5 (6)		
		20-29	2.8 (6)		
		30-39	4.7 (7)		
		40-49	6.5 (7)		
		50-59	10.9 (10)		
		60-69	29.5 (21)		
		70-79	88.3 (45)		
		≥80	98.9 (28)		
		All ages	18.3 [15.9-21.1] (199)		
USA[81] (Virginia)	1989-1991	≥ 31 days	41 (166)		
USA[82] (California)	1991-1998	0-4	7.52		
		5-19	2.57		
		20-54	4.58		
		55-74	11.93		
		≥75	22.32		
		All ages	6.18 (15601)		
USA[83] National data	1979	All ages	3.5		
	2010	All ages	12.5		
	1979-2010	<10	14.3		
		≥50	28.4		

USA[84] National data	2006, 2009, 2012	>28 days to ≤20 yrs	3.6(9048)		
ASIA					
Thailand[85]	2010	≥18	5.10(2190)	5.71[5.40–6.02] (1413)	2.90[2.69–3.12] (777)
EUROPE					
Germany[86]	1997– 1999	18–59 ≥ 60 All ages	4.2 54.2 17.1	26.1	13.7
Italy[87]	1999– 2000	20–29	4.2[0.5–15.2] (2)	4.1[0.1–22.8] (1)	4.4 [0.1–24.5] (1)
		30–39	0[-] (0)	0[-] (0)	0[-] (0)
		40–49	6.0[1.2–17.5] (3)	8.2[1.0–29.6] (2)	4.0 [0.1–22.3] (1)
		50–59	11.0[4.0–24.0] (6)	15.7[4.3–40.2] (4)	6.9 [0.8–24.9] (2)
		60–69	20.9[10.4–37.4] (11)	17.1[4.7–43.8] (4)	23.9 [9.6–49.2] (7)
		70–79	27.1[14.4–46.3] (13)	26.5[8.6–61.7] (5)	27.4 [11.8–54.0] (8)
		>79	35.8[16.4–68.0] (9)	12.5[0.3–69.6] (1)	46.7 [20.1–92.0] (8)
		All ages	10.7[7.5–13.8] (44)	9.7[5.4–16.0] (17)	11.5[7.1–17.6] (27)
Italy[88]	1999– 2001	20–39	1.9(1)	3.8 (1)	0.0 (0)
		40–59	4.0(2)	4.1 (1)	4.0 (1)
		60–79	28.5(14)	13.6 (3)	40.7 (11)
		80+	76.1(10)	43.6 (2)	93.6 (8)
		All ages	16.5[10.9–23.9] (27)	9.0 [3.6–18.5] (7)	23.2 [14.2–35.7](20)
Italy[89]	2003	0–19	49.1 [22.5–93.3] (9)	84.6 [36.5–166.7] (8)	11.3 [0.3–62.9] (1)
		20–29	13.8 [1.7–49.8] (2)	13.7 [0.3–76.3] (1)	13.9 [0.3–77.4] (1)
		30–39	12.7 [2.6–37.1] (3)	16.8 [2.0–60.6] (2)	8.5 [0.2–47.3] (1)
		40–49	9.0 [1.1–32.5] (2)	9.2 [0.2–51.2] (1)	8.9 [0.2–49.5] (1)
		50–59	23.6 [7.6–54.9] (5)	29.3 [6.0–85.5] (3)	18.2 [2.2–65.7] (2)
		60–74	29.9 [13.7–56.8] (9)	44.6 [16.4–97.2] (6)	18.1 [3.7–52.8] (3)
		75+	54.1[26.0–99.5](10)	62.8 [17.1–160.7](4)	49.7 [18.2–108.3] (6)
		All ages	27.0[19.3–36.7](40)	36.0 [23.3–53.2] (25)	19.1 [10.7–31.5] (15)
Switzerland[90]	1997– 1998	0–4	38.7 [27–50.4] (42)		
		5–14	10.9 [16.3–5.4] (22)		
		15–29	4.4 [2.2–6.6] (15)		
		30–44	3.9 [2.0–5.7] (16)		
		45–59	7.8 [4.8–10.8] (26)		
		60–74	15.1 [10–20.3] (33)		
		≥75	15.5 [8.3–22.7] (18)		
		All ages	9.9[8.4–11.4](172)		
UK[91]	2002– 2004	<1	50.7 (42)	56.6 (24)	44.5 (18)
		1–4	29.2 (94)	31.2 (51)	27.1 (43)
		5–15	5.0 (31)	4.9 (20)	5.1 (20)
		All ages	13.3 [12.6–14.0] (176)	14.0 [13.0–15.0] (95)	12.5 [11.5–13.4] (81)

TABLE 2.3. Methodology used for incidence studies in Table 2.1 and Table 2.2

Country ^[Reference]	Methodologic Details
AFRICA	
Benin[2]	<p>Case Sources: entire population of Djidja (14,500). Phase 1 surveyed 11,668 (80.4%). Of these 11,520 did not have epilepsy. These were followed for 18 months (Jan06-Jun07) to identify new cases.</p> <p>Database/Codes: not used</p> <p>Case Definition: ≥2 unprovoked epileptic seizures</p> <p>Validation: Neurologist examination of all new cases</p> <p>Note: <i>Djidja a rural population in central Benin with 10 villages and total of 14,500 inhabitants</i></p>
Egypt[3]	<p>Case Sources: community households.</p> <p>Database/Codes: not used</p> <p>Case Definition: Epilepsy defined as a condition characterized by recurrent (≥2) epileptic seizures, unprovoked by any immediate identified cause.</p> <p>Validation: Used a standard 12 question form that had 95% sensitivity and 88% specificity</p> <p>Note: <i>Prospective, cross-sectional study. Excluded individuals with only febrile or neonatal seizures, or acute seizures associated with systemic illness, intoxication, substance abuse/withdrawal or acute neurological insults, or persons with a single unprovoked seizure.</i></p>
Egypt[5]	<p>Case Sources: All those living in Al-Quseir, Red Sea Governorate, for ≥6 months (33,818). Found by door-to-door survey by 15 female social workers using a standardized questionnaire with 96% sensitivity and 93.2% specificity.</p> <p>Database/Codes: not used</p> <p>Case Definition: ≥2 unprovoked seizures occurring ≥24 hrs apart</p> <p>Validation: Any with ≥1 positive answer evaluated in person by neurologist plus EEG, and if indicated neuroimaging.</p> <p>Note: <i>Excluded febrile seizures or any with acute symptomatic seizures in close temporal association with acute systemic, metabolic, substance abuse or acute CNS insults, or any with solitary unprovoked seizure.</i></p>
Egypt[6]	<p>Case Sources: Al-Quseir City (33,283), Red Sea Governorate.</p> <p>Database/Codes: not used</p> <p>Case Definition: Epilepsy: two or more clinical afebrile seizures not resulting from withdrawal of drugs or alcohol and not related to an acute metabolic event.</p> <p>Validation: Neurologist examination and investigation as appropriate</p> <p>Note: <i>Study conducted from July 1/09 to Jun 31/12. Screened with standard questionnaire administered by female social workers in a door-to-door survey. Incidence of epilepsy, stroke and Bell's palsy.</i></p>
Egypt[7]	<p>Case Sources: All those living in Al Kharga district for ≥6 months (62,583);</p> <p>Database/Codes: not used</p> <p>Case Definition: Epilepsy: two or more clinical afebrile seizures not resulting from withdrawal of drugs or alcohol and not related to an acute metabolic event.</p> <p>Validation: by one of 7 senior Neurology Department hospital staff</p> <p>Note: <i>Door-to-door survey by female social workers and 3 neurologists using a standardized questionnaire incidence of epilepsy, stroke, cerebral palsy, Bell's palsy</i></p>
Egypt[4]	<p>Case Sources: South Upper Egypt, Qena governorate – 6 rural villages and 4 urban areas</p> <p>Database/Codes: not used</p> <p>Case Definition: ≥2 unprovoked epileptic seizures</p> <p>Validation: Neurologist examination at Qena University Hospital with EEG, CT and/or MRI done as needed</p> <p>Note: <i>Door-to-door survey by social workers, neurologists and a psychiatrist use a standardized screening questionnaire (95% sensitivity, 88% specificity).</i></p>
Ethiopia[8]	<p>Case Sources:</p> <p>Database/Codes: not used</p> <p>Case Definition: Epileptic seizure defined as a sudden and transitory event of motor, sensory, autonomic or psychic nature which is assumed to be the result of transient excessive discharge of a hyperexcitable population</p>

	<p>of neurons in the brain. Epilepsy defined as a condition characterized by recurrent (at least 2) unprovoked seizures (defined as seizure occurring without an identified proximate precipitant that excluded seizures associated only with an acute insult to the CNS or with generalized systemic metabolic disturbance (acute symptomatic seizures)</p> <p>Validation: Neurologist examination</p>
Kenya[9]	<p>Case Sources: community</p> <p>Database/Codes: not used</p> <p>Case Definition: Acute convulsive epilepsy defined as ≥ 2 unprovoked convulsions (tonic and/or clonic seizures) of which one occurred in the 12 months preceding the survey.</p> <p>Validation: Direct examination by a clinician trained in epilepsy.</p> <p>Note: <i>Identified a cohort of individuals without epilepsy, and then revisited them after 5 years to see how many had developed acute convulsive epilepsy. Excluded children <6 years old – because of difficulty distinguishing neonatal seizures, febrile seizures and epilepsy</i></p>
Kenya[10]	<p>Case Sources: Rural population of children aged 5-14 years living in Kilifi Health system in coastal Kenya.</p> <p>Database/Codes: not used</p> <p>Case Definition: Epilepsy; no case definition provided</p> <p>Validation: Questionnaire screen followed by comprehensive clinical and neuropsychological assessments at a local research hospital.</p> <p>Note: <i>Modelled incidence based on epidemiologic studies done between 2001 and 2020.</i></p>
Kenya[11]	<p>Case Sources: Kilifi – rural coastal area of Kenya (~260,000)</p> <p>Database/Codes: not used</p> <p>Case Definition: ‘active convulsive epilepsy’ = ≥ 2 unprovoked convulsive seizures, with at least 1 within the last 12 months. Primary = genetic or unknown cause; secondary = due to structural/metabolic cause (e.g., head injury, CNS infection, focal abnormalities on clinical and/or EEG exam). Excluded any cases of undetermined epilepsy.</p> <p>Validation: Neurologic assessment</p>
Kenya[12]	<p>Case Sources: Kilifi district, Coastal Kenya: children born from Jun 1/91 to Dec 31/95. I.e., children >6yrs – to avoid difficulty of distinguishing febrile from unprovoked seizures in younger children.</p> <p>Database/Codes: not used</p> <p>Case Definition: Epilepsy - ≥ 2 unprovoked convulsion with at least one having occurred within the preceding 12 months.</p> <p>Validation: Physician examination, EEG</p> <p>Note: <i>Two community surveys: 1st from June 2001 to April 2002 to identify children with seizures (sensitivity 100%, specificity 93%); second from Sept 2003 to January 2004. Used second survey to identify children with new onset epilepsy.</i></p>
Tanzania[13]	<p>Case Sources: 11 villages in rural Ulanga district (sampled 18,183 of a total population of 138,837). Household survey conducted by a team that included psychiatrist, neurologist, general-duty MDs, RNs, medical students to screen for epilepsy.</p> <p>Database/Codes: not used</p> <p>Case Definition: Epilepsy - ≥ 2 nonfebrile seizures unrelated to any acute metabolic disorder or to withdrawal of alcohol or drugs.</p> <p>Validation: Neurologist reviewed case and clinical features to diagnose epilepsy.</p>
Tanzania[14]	<p>Case Sources: Haydom and surrounding community for 30 km in all directions. Total population of 41,937 living in 6577 households. Enrolled 7399 from 1190 households.</p> <p>Database/Codes: not used</p> <p>Case Definition: Epilepsy ≥ 2 epileptic seizures unprovoked by any immediate identified cause</p> <p>Validation: Screened for epilepsy via in person questionnaire. All potential cases confirmed by neurologist assessment.</p>
Uganda[15]	<p>Case Sources: Kabende parish in Kabarole district, West Uganda. Total population of 4743 in 13 villages. Door to door survey of entire parish.</p> <p>Database/Codes: not used</p> <p>Case Definition: Active epilepsy defined as ≥ 2 unprovoked seizures during prior 2 years.</p>

	Validation: All possible epilepsy identified by survey confirmed via neurologic examination.
AMERICAS	
USA[16]	<p>Case Sources: Inpatient, outpatient and MD visits.</p> <p>Database/Codes: Medicare administrative claims database (has health care data for 95% of US population ≥65 years); ICD-9 codes for epilepsy (345.xx) or seizures (780.3x)</p> <p>Case Definition: Incident epilepsy if no seizure codes for period of 2 years prior to the claim-based epilepsy diagnosis. Included cases with a single claim coded 345.xx or two claims at least 30 days for code 780.3. Included codes for febrile seizures (780.31, 780.32) because older population.</p> <p>Validation: Not done</p>
USA [17] and USA [18]	<p>Case Sources: Residents of Rochester, Minnesota</p> <p>Database/Codes: Rochester Project diagnostic record system / codes not provided</p> <p>Case Definition: Epilepsy defined as recurrent unprovoked seizures.</p> <p>Validation: Study neurologist reviewed records of all possible cases to classify seizure events.</p>
USA[19]	<p>Case Sources: Patients enrolled in the HMO.</p> <p>Database/Codes: Kelsey-Seybold Clinics HMO, Houston, Texas.</p> <p>ICD-9 codes: 345.0-345.9, 333.2, 779.0, 780.3</p> <p>Case Definition: Initial diagnosis of unprovoked (absence of an acute cause) seizure disorder or epilepsy. Excluded febrile convulsions, traumatic brain injury, CNS infection, metabolic insult.</p> <p>Validation: Medical chart review</p>
USA [20]	<p>Case Sources: ≥70 year olds participating in the Einstein Aging study (longitudinal study of community residing elderly individuals) who screened positive for seizures on the intake medical examination</p> <p>Database/Codes: not used</p> <p>Case Definition: Epilepsy – not defined</p> <p>Validation: Medical record review and detailed telephone interview.</p>
USA[21]	<p>Case Sources: North Manhattan residents admitted to hospital or in nursing home.</p> <p>Database/Codes: North Manhattan hospital medical records / ICD-9 codes 780.3, 345.0-345.9</p> <p>Case Definition: First unprovoked seizure (without an identified proximate precipitant) or multiple such seizures within a 24 hour period. Epilepsy defined as recurrent unprovoked seizures.</p> <p>Validation: All potential study participants assessed clinically and followed every 4 months for one year.</p> <p>Note: <i>Case ascertainment via: daily screening of pediatric and adult ED logs for following chief complaints: seizure, convulsion, fainted, unresponsive, loss of consciousness, falls, dizziness, paresthesias, numbness, syncope, near syncope and unilateral weakness; weekly review for ICD-9 codes; Epilepsy and Neurology clinics, Epilepsy Monitoring Unit and epileptologist private offices for incident cases.</i></p>
USA[22]	<p>Case Sources: Inpatient, outpatient and emergency room visits to all medical care facilities in Olmsted County, Minnesota, involving children aged 1 month – 17 years.</p> <p>Database / Codes: Rochester Epidemiology Project Diagnostic Index / used all Index seizure and convulsion diagnosis codes (not specified).</p> <p>Case Definition: Epilepsy defined as predisposition to unprovoked seizures. Included those with ≥2 unprovoked seizures and those with a single unprovoked seizure if there was also evidence of an enduring alteration of the brain that increased the likelihood of further seizures (included any of: abnormal neurodevelopmental examination, focal abnormality on brain imaging, initial presentation in status epilepticus or specific EEG findings of epileptiform discharge or intermittent rhythmic focal delta activity).</p> <p>Validation: All possible cases based on diagnostic codes had medical chart review by a pediatric epileptologist.</p>
USA[23]	<p>Case Sources: <i>All available epidemiological data, published and unpublished plus routinely collected data such as vital registration, hospitalizations, medical claims.</i></p> <p>Database / Codes: 2017 Global Burden of Disease Study data for USA</p> <p>Specific codes not provided</p> <p>Case Definition: Idiopathic epilepsy – case definition not provided</p> <p>Validation: not described</p>
USA[24]	<p>Case Sources: Developed algorithms based on diagnostic codes and use of antiepileptic drugs.</p> <p>Database / Codes: Lovelace Health Systems (New Mexico MCO) / Several ICD-9 codes used across several models but final model codes not provided in paper.</p>

	<p>Case Definition: Epilepsy based on ICD-9 codes</p> <p>Validation: Medical record review of sample of 617 cases to develop algorithm. Applied algorithm to new data set and reviewed 644 cases. Final model had sensitivity of 82% and specificity of 94%.</p>
Canada[25]	<p>Case Sources: Children aged 1mo to 16 years old, resident in Nova Scotia (population 226,700) with EEG evidence of a seizure</p> <p>Database/Codes: EEG records / no codes used. The study lead authors personally reviewed all pediatric EEGs done in the province.</p> <p>Case Definition: ≥ 2 unprovoked seizures. Excluded neonatal seizures and any with acute provoking factors including fever or within 7 days after head injury or evidence of progressive neurologic disease</p> <p>Validation: Review of the hospital or neurologist chart plus a phone call to the family doctor.</p>
Canada[26]	<p>Case Sources: All live births in Nova Scotia province between Jan 1986 and Dec 2001.</p> <p>Database / Codes: Canadian Epilepsy Database and Registry (CEDaR); Nova Scotia province EEG records; specific codes not provided.</p> <p>Case Definition: Epilepsy defined as occurrence of at least 2 postneonatal (≥ 28 days old) non-febrile seizures during study period.</p> <p>Validation: 3 pediatric neurologists reviewed data on EEG requisition information, clinical history obtained by EEG technician and EEG record, and came to consensus regarding diagnosis of epilepsy.</p>
Martinique[27]	<p>Case Sources: Entire population of Martinique, with ascertainment of new-onset seizures based on referrals to neurologists, pediatricians or emergency room settings.</p> <p>Database / Codes: not used</p> <p>Case Definition: First diagnosis of provoked or unprovoked epileptic seizure based on clinical and EEG data. Excluded neonatal seizures (occurring before 1 month of age) and febrile seizures.</p> <p>Validation: Chart review by epileptologist.</p>
Honduras[28]	<p>Case Sources: population-based from rural Salama County (population 7384). Screened all households via door to door questionnaire survey.</p> <p>Database/Codes: not used</p> <p>Case Definition: Active Epilepsy ≥ 2 seizures during the last 5 years; excluded febrile and single seizure episodes</p> <p>Validation: complete history and physical exam at local health center</p>
Brazil[29]	<p>Case Sources: 2003 birth cohort from City of Passo Fundo in S Brazil, followed until 2007.</p> <p>Database/Codes: not used</p> <p>Case Definition: Defined epilepsy as condition characterized by recurrent unprovoked seizures. Febrile seizures counted separately but not defined.</p> <p>Validation: Neuroclinical assessment done by a pediatric neurologist, including EEG and neuroimaging.</p> <p>Note: <i>Identified possible cases in children's homes using standard questionnaire and trained interviewers.</i></p>
Chile[30]	<p>Case Sources: Copiapo Province (mining localities: el Salvador, Potrerillos, Diego de Almagro, Barquitos – total population 17,694). Hospital records of all patients seen by the two practicing neurologists between 1984 and 1988.</p> <p>Database/Codes: District health care computerized health record archives.</p> <p>Case Definition: Active epilepsy defined as a chronic brain disorder of various etiologies, characterized by ≥ 2 non-febrile convulsions and non-symptomatic seizures at different times. Excluded seizures that were: single, neonatal, with obvious precipitant or occurred during an acute illness. Used ILAE 1981 seizure classification.</p> <p>Validation: Medical record review</p>
Ecuador[31]	<p>Case Sources: Andean region of Ecuador with population of 72,121. Screened via house to house survey for all persons with possible history of non-febrile epileptic seizures.</p> <p>Database/Codes: not used</p> <p>Case Definition: Active epilepsy defined as ≥ 2 non-febrile epileptic seizures within the 12 month period prior to the study or were on anti-epileptic medication at the time of the study. Incident cases had to have epileptic seizures for the time in the 12 months prior to inclusion in the study. Excluded febrile seizure defined as a convulsive seizure occurring between the ages of 2yrs and 5 yrs in the context of a febrile illness.</p> <p>Validation: Possible cases screened by trained rural MDs, then by specialist neurologists followed by standardized neurological interview and exam. Final assignment to probable and definite cases determined by international neurologic panel review.</p>

	<p>Note: Re-examined random sample of 1.4% of all negatives from door-to-door screening and of 4.6% of false positives from the exam by specialist neurologists. Used these to determine a range for incident cases.</p>
Peru[32]	<p>Case Sources: Matapalo – rural northern district with 7 villages (population 1004 of whom 903 participated in study); q6month screening questionnaire for 5 years to detect incident cases of epilepsy and epileptic seizures. Household surveys conducted to identify possible cases of epilepsy.</p> <p>Database / Codes: not used</p> <p>Case Definition: Epilepsy - ≥ 2 unprovoked seizures; epileptic seizure – clinical manifestation resulting from abnormal and excessive discharge of a set of neurons in the brain; excluded febrile seizures and eclampsia.</p> <p>Validation: by direct neurologist interview for all screened positives.</p>
ASIA	
China[33]	<p>Case Sources: 4 locales in Hainan, China (Population by locale: Chengmai – 483,900; Danzhou City – 977,700; Baoting Autonomous County – 150,200; Dangan County – 291,400). Random sampling done within the study region – 6-12 villages per region with final study population of 16,676.</p> <p>Database/Codes: not used</p> <p>Case Definition: Epilepsy: ≥ 2 unprovoked seizures occurring >24 hours apart or diagnosis of epileptic syndrome or one unprovoked seizure with risk factors present that made it at least a 60% likelihood for recurrence.</p> <p>Validation: Neurologist examination of all suspect cases.</p>
India[34]	<p>Case Sources: Yelandur sub-district of Karnataka state in S India (population 66,290);</p> <p>Database / Codes: not used</p> <p>Case Definition: Epilepsy - ≥ 2 non-febrile seizures in any of its varied manifestations, unrelated to an acute illness, therapeutic drugs or alcohol or drug abuse; Epileptic seizure – sudden and transitory motor, sensory, autonomic or psychic phenomenon with or without disturbance of consciousness, irrespective of cause</p> <p>Validation: by specialist examination</p>
India[35]	<p>Case Sources: Kolkata municipality (population about 4.5 million). Study population determined by stratified random sampling of city blocks (5200 for entire city). Door-to-door screening survey conducted by field work team headed by neurologist.</p> <p>Database / Codes: not used</p> <p>Case Definition: Epilepsy = ≥ 2 unprovoked seizures; multiple seizures within <24 hours considered a single event.</p> <p>Validation: Clinical history and exam by neurologist to eliminate 14 false-positive cases (breath-holding spells, chills&rigor due to fever; pseudo seizure; syncope) and 246 seizures not considered epilepsy (213 febrile convulsion; 26 single unprovoked seizure; 7 acute symptomatic seizures).</p> <p>Note: Community-based longitudinal, observational study.</p>
India[36]	<p>Case Sources: Kolkata city; annual door-to-door questionnaire survey for 5 years</p> <p>Database / Codes: not used</p> <p>Case Definition: Epilepsy - ≥ 2 epileptic seizures, unprovoked by any immediate identified cause. Multiple seizures occurring within a 24 hour period considered a single event. Excluded single, acute symptomatic and febrile seizures.</p> <p>Validation: Screen-positive cases evaluated by a neurologist who did a direct history and examination and reviewed available investigational reports.</p> <p>Note: Population-based longitudinal survey. Stratified randomized sample of 100,802 subjects living in Kolkata</p>
India[37]	<p>Case Sources: City of Kolkata, stratified random sample of 100,802, surveyed annually for 5 years</p> <p>Database/Codes: not used</p> <p>Case Definition: Epilepsy - ≥ 2 seizures, unprovoked by any immediate identified cause. Multiple seizures in a 24 hour period considered a single event.</p> <p>Validation: Neurologist examination to establish diagnosis for all those identified via screening questionnaire.</p> <p>Note: Population-based longitudinal survey (Mar 2003-Feb 2008). Used WHO epilepsy screening questionnaire</p>
India[40]	<p>Case Sources: West Bengal region with 12 villages (Population 20,966). Door-to-door screening questionnaire to identify possible cases of epilepsy.</p> <p>Case Definition: Epilepsy - ≥ 2 unprovoked seizures. Multiple seizures in <24 hour period considered single episode. Excluded single, symptomatic and febrile seizures.</p> <p>Validation: neurologic assessment of all possible cases</p>

	Note: <i>Prospective longitudinal study in a rural population of West Bengal.</i>
India[39]	<p>Case Sources: Rural district of Punjab consisting of 74 contiguous villages – about 100,000 population.</p> <p>Database/Codes: not used</p> <p>Case Definition: Epilepsy - Not described</p> <p>Validation: All suspect cases examined by senior neurologists to confirm or refute epilepsy diagnosis.</p> <p>Note: <i>Door to door screening survey by trained field workers with second review of suspect cases by private health workers.</i></p>
India[38]	<p>Case Sources: 18 schools in Hyderabad district in Telangana state, S India. 7408 children aged 5-15 years registered as of Jan 1, 2006.</p> <p>Database/Codes: not used</p> <p>Case Definition: Epilepsy – ≥ 2 unprovoked seizures occurring >24 hours apart; OR one unprovoked seizure and an at least 60% probability of further seizures; OR diagnosis of an epilepsy syndrome.</p> <p>Validation: Assessment by neurologists</p> <p>Note: <i>Longitudinal follow-up study of epilepsy in cohort of school children in government primary schools in south India. Followed cohort from Jan 1, 2006 through Dec 31, 2012. Recruited all new-onset seizures with help of school teachers/coordinators and then subsequent assessment in neurology outpatient clinics.</i></p>
Japan [41]	<p>Case Sources: Diagnosis of epilepsy in children admitted to Okayama Prefecture hospitals and institutions</p> <p>Database/Codes: Hospital discharge data. No codes provided.</p> <p>Case Definition: Epilepsy – one or more attacks of cerebral origin, manifesting convulsions, disturbance of consciousness, autonomic symptoms, disturbance of sensory or perception, or automatism. Excluded simple febrile and neonatal convulsions as well as acute convulsions due to infection or within one week after head trauma.</p> <p>Validation: no detail provided.</p> <p>Note: <i>EEG examined on 96% of 2378 enrolled children.</i></p>
Japan[42]	<p>Case Sources: Uwajime city (83,000).</p> <p>Database/Codes: Japan public insurance database; ICD codes for epilepsy, but specifics not provided</p> <p>Case Definition: Epilepsy ≥ 2 unprovoked seizures separated by ≥ 24 hours; or one unprovoked seizure and $>60\%$ probability of further seizures; or diagnosis of an epileptic syndrome.</p> <p>Validation: Cases reviewed by two independent specialists in epilepsy and pediatric neurology</p> <p>Note: <i>Identified 3 population-based age cohorts of children: aged 1-4 years, born between 2006 and 2010; 5-9 years, born between 2002 and 2005 ; 10-14 years, born between 1997 and 2000. Followed cohorts for new onset epilepsy from 2007 through 2015. Excluded febrile seizures.</i></p>
S Korea[43]	<p>Case Sources: Entire population of S Korea registered in NHIS database between 2009 and 2017 (includes all medical facilities in the country).</p> <p>Database/Codes: South Korea National Health Insurance Service (NHIS) database. ICD-10 codes: G40 (epilepsy), G41 (status epilepticus), F803 (Landau-Kleffner syndrome), R56 (convulsion). Excluded R56.0 (febrile convulsion)</p> <p>Case Definitions: Epilepsy - ≥ 2 visits with ≥ 1 diagnostic code for epilepsy AND prescription of anticonvulsants for at least 180 days.</p> <p>Validation: not done</p>
Taiwan[44] And Taiwan[45]	<p>Case Sources: Health service claims for epilepsy.</p> <p>Database/Codes: Taiwan national NHI database including individual diagnostic information and pharmaceutical claims for prescriptions approved for epilepsy / ICD-9 code for epilepsy (345.xx)</p> <p>Case Definition: ICD-9 code</p> <p>Validation: cross-checked the ascertained cases against a gold standard dataset derived by a 2001 community-based survey on epilepsy prevalence in Keelung city, Taiwan.</p>
Viet Nam[46]	<p>Case Sources: Bavi district of HaTay province (population about 240,000). Included sample of entire villages (69 of 352 in the district, including 48,911 people living in 12,960 households). Screened household-to-household with a WHO questionnaire (validated in Vietnam pilot study with sensitivity of nearly 100% and specificity of 97.6% for epilepsy).</p> <p>Database/Codes: not used</p>

	<p>Case Definition: Epileptic seizure = clinical manifestations presumed to result from abnormal and excessive discharge of a set of neurons in the brain; Epilepsy = ≥ 2 epileptic seizures, unprovoked by any immediate identified cause.</p> <p>Validation: history and examination by a neurologist followed by EEG study and CT scan.</p> <p>Note: <i>Population-based community study.</i></p>
AUSTRALIA/OCEANIA - No studies found	
EUROPE	
Denmark[47]	<p>Case Sources: Admitted to hospital or seen in hospital outpatient department for epilepsy between 1995 and 2002.</p> <p>Database / Codes: Danish National Hospital Register / ICD-10 G40-G41.</p> <p>Case Definition: Epilepsy – first time admission or outpatient care for a diagnosis coded as epilepsy</p> <p>Validation: not done</p>
Denmark[48]	<p>Case Sources: Patients ≥ 60 years old admitted to hospital with first time seizures.</p> <p>Database / Codes: Hospital diagnosis registers</p> <p>Case Definition: Epilepsy not defined.</p> <p>Validation: Medical record review</p>
Estonia [49]	<p>Case Sources: Persons ≥ 20 years old living in Tartu (University town; population of 75,245 – 77,066 during study period: Jan 1 1994-Jan 1, 1997). Searched regional epilepsy-related databases including family doctor and neurology clinic files; Tartu University Clinic in- and out-patient and emergency department records; medical prescriptions of antiepileptic drugs; EEG unit register; social welfare institution files; membership of Estonian Epilepsy Association.</p> <p>Case Definition: Epilepsy defined as ≥ 2 epileptic seizures, unprovoked by any immediate identified cause. Multiple seizures occurring in a 24 hour period considered single event. Excluded provoked or acute symptomatic seizures.</p> <p>Validation: Examination by neurologist (first author of study) to confirm or refute epilepsy diagnosis.</p> <p>Note: <i>Retrospective community-based study.</i></p>
Estonia[50]	<p>Case Sources: enlisted participation of all sources of medical care available to children with seizures in the study area.</p> <p>Database / Codes: none used</p> <p>Case Definition: Epilepsy - ≥ 2 unprovoked seizures. Excluded cases with acute provoking factors for seizures, including febrile seizures, seizures ≤ 7 days after head trauma and neonatal seizures.</p> <p>Validation: All new cases of epilepsy examined by ≥ 1 study author. If needed to confirm diagnosis, hospital admission arranged for additional tests.</p> <p>Note: <i>Population-based study done in seven counties in South and Northeast Estonia (total population 581,887; Ages 1 month – 19 yrs about 161,000).</i></p>
Finland[51]	<p>Case Sources: Persons living in KUCH (Finnish district with 251,715 population; four towns and rural areas). Multiple sources to identify patients with seizures including KUCH hospital inpatients and outpatients, psychiatric/mental hospital records, nursing homes, health centers, EEG laboratories.</p> <p>Database / Codes: not used</p> <p>Case Definition: Epileptic seizure defined as a paroxysmal alteration of intellectual, sensory, motor, autonomic or affective activity which is time-limited and presumably associated with neuronal hypersynchronous overactivity. Epilepsy defined as ≥ 2 unprovoked, nonfebrile epileptic. Seizures separated by a minimum time interval of 24 hours. Excluded seizures due to acute cerebral illnesses, exogenous or metabolic causes, alcohol or drug withdrawal or fever.</p> <p>Validation: 88% of identified subjects re-examined to confirm or refute diagnosis of epilepsy.</p>
Finland[52]	<p>Case Sources: National population</p> <p>Database / Codes: Social Insurance Institution (SII) re refundable drugs including antiepileptic drugs / no specific codes but spectrum of antiepileptic drugs covered.</p> <p>Case Definition: Epileptic seizures / syndromes based on receipt of antiepileptic drugs</p> <p>Validation: Not done, but authors cite several other studies that validated the SII registry</p>
Germany[53]	<p>Case Sources: Children born between 1957 and 1966 in Kiel.</p> <p>Database/Codes: Epilepsy center registry</p>

	<p>Case Definition: Epilepsy - at least one epileptic seizure prior to the 9th birthday and seen at the Pediatric Hospital. Excluded febrile seizures unless the child had a subsequent afebrile seizure. Also excluded neonatal seizures and seizures that were symptoms of acute disease.</p> <p>Validation: Medical chart review</p>
Germany[54]	<p>Case Sources: Children aged 0-14 years living in Altenburg district (population about 20,000)</p> <p>Database/Codes: not used</p> <p>Case Definition: Epilepsy defined as ≥ 2 seizures unrelated to fever, other drugs, acute metabolic or inflammatory disturbances or alcohol. Febrile seizures involved only children between ages of 6 months and 5 years, were generalized and lasted less than 15 minutes.</p> <p>Validation: not described</p>
Germany[55]	<p>Case Sources: Children aged 0-<15 years living in Heidelberg and Mannheim cities. Sought all children with suspected seizure via requests to all private pediatricians, four EEG labs, and children's hospitals.</p> <p>Database / Codes: not used</p> <p>Case Definition: Epilepsy - ≥ 2 unprovoked seizures. Excluded children with first unprovoked seizure or recurrent or complicated febrile convulsions.</p> <p>Validation: Two pediatric neurologists reviewed history, neurologic exam, EEG, MRI and lab tests for each case.</p>
Greece[56]	<p>Case Sources: Corfu district (population of 113,479). Multiple sources for epilepsy and epileptic seizures: in-/out-patients referred to Neurology Clinic of Corfu General Hospital, or Psychiatric Hospital; referrals to practices of Social Security Foundation; referrals to 6 private neurologists practising inside the study area.</p> <p>Database / Codes: not used</p> <p>Case Definition: Epilepsy - ≥ 2 unprovoked seizures occurring >24 hours apart</p> <p>Validation: Neurologists completed a questionnaire with demographic, clinical and lab data for each case to confirm classification; Used CT and/or MRI data if available (found for 75% of cases)</p>
Iceland[57]	<p>Case Sources: 37 rural medical districts with population of 90,237. Identified cases of first seizure episode via local health care centers and hospital records plus records from only EEG laboratory in Iceland.</p> <p>Database / Codes: not used</p> <p>Case Definition: Epilepsy - ≥ 2 recurrent unprovoked seizures</p> <p>Validation: Sought additional information from practicing neurologists and pediatricians; 39% of index cases examined in consultation by one of the study investigators.</p>
Iceland[58]	<p>Case Sources: All residents of Iceland with newly diagnosed epilepsy. Countrywide surveillance system used to regularly contact all healthcare facilities, including hospitals, emergency rooms, nursing homes, health-care centres, 4 radiology departments and two EEG laboratories.</p> <p>Database / Codes: not used</p> <p>Case Definition: Epilepsy ≥ 2 unprovoked seizures occurring more than 24 hours apart. Excluded provoked, acute symptomatic seizures including neonatal and febrile seizures.</p> <p>Validation: Case synopsis reviewed by study neurologists and further information obtained from treating MD if needed.</p>
Italy [59]	<p>Case Sources: Copparo district of Emilia Romagna. Possible cases drawn from multiple sources including hospital in-/out-patient records, mental hospital archives, EEG laboratories, direct referrals from doctors and private neurologists; teacher interviews.</p> <p>Database / Codes: Local hospital records / no codes provided</p> <p>Case Definition: Epilepsy - ≥ 2 nonfebrile and non-symptomatic seizures at different times</p> <p>Validation: Medical record review of all potential cases</p>
Italy[60]	<p>Case Sources: Ferrara province children aged 1mo to 14 years (32,953); multiple sources included notifications from local pediatricians, EEG laboratory results, epileptic case codes in outpatient as well as pediatric, neurologic and neuropsychiatric services.</p> <p>Database / Codes: Hospital discharge diagnoses with ICD9 code 345</p> <p>Case Definition: Epilepsy - ≥ 2 unprovoked seizures. Excluded patients with first unprovoked seizure as well as all acute symptomatic seizures, febrile or neonatal seizures.</p> <p>Validation: Research group consensus after reviewing all available clinical, EEG and instrumental data.</p>

Netherlands [61]	<p>Case Sources: Individuals aged 0-75 living in one of six Dutch cities and with one or more prescriptions for anti-epileptic drugs.</p> <p>Database/Codes: PHARMO Record Linkage System (drug dispensing data from all 28 pharmacies in six medium-sized Dutch cities) / ATC codes</p> <p>Case Definition: Epilepsy - used an algorithm based on specific antiepileptic drugs and combinations with special consideration. Considered clonazepam monotherapy as probable only because of potential use for non-epilepsy conditions</p> <p>Validation: Compared positive algorithm identifications to medical diagnoses from GPs and hospital records.</p>
Netherlands[62]	<p>Case Sources: Maastricht (population 190,860 – focused on the 83.4% aged ≥ 14 years). Asked area GPs, neurologists and neurology residents to refer patients with newly diagnosed seizures to the study team; also reviewed all EEG and neuroradiology reports done during the study; also reviewed all patients given diagnoses of syncope, convulsion, epilepsy or attacks of unknown type during study period. Excluded acute symptomatic seizures.</p> <p>Database / Codes: not used</p> <p>Case Definition: ≥ 2 epileptic seizures unprovoked by any immediate identified cause</p> <p>Validation: Two neurologists independently evaluated files of all cases, including clinical manifestations, EEG findings, neuroimaging, laboratory and ECG data to confirm and classify the seizure. Disagreements resolved by conferring with a third neurologist.</p>
Norway [63]	<p>Case Sources: Two northernmost counties (Troms, Finnmark; population 215,000) identified from Tromsø Neurologic Department in- and out-patient records and EEG laboratory records during study period.</p> <p>Database/Codes: not used</p> <p>Case Definition: Epilepsy defined as chronic brain disorder of various etiologies characterized by recurrent seizures due to excessive discharge of cerebral neurons associated with a variety of clinical and laboratory manifestations. Excluded febrile convulsions and suspected convulsions with normal EEGs</p> <p>Validation: Clinical record review</p>
Norway[64]	<p>Case Sources: All liveborn MoBa children residing in Norway until death or end of registry follow-up. Mothers recruited at time of ultrasound examination around gestational week 17-19. MoBa study data plus health registry data, questionnaires, medical records and parental interviews. Possible epilepsy cases identified by a case-cohort study nested within MoBa which included children diagnosed with epilepsy by specialist health services.</p> <p>Database / Codes: Norwegian Patient Registry (includes all hospital in- and out-patient clinics owned by government and private specialist practices reimbursed by government) / ICD-10 G40</p> <p>Case Definition: Epilepsy - ≥ 2 unprovoked epileptic seizures occurring ≥ 24 hours apart. Also included those with single unprovoked seizure if they were considered to have a high ($>60\%$) risk of further seizures and/or met criteria for defined epilepsy syndrome (based on ILAE 2014 revision)</p> <p>Validation: Medical record reviews and/or clinical telephone interviews with parents by 4 physicians using standardized data collection form.</p>
Spain[65]	<p>Case Sources: Children <15 years of age with a newly diagnosed epilepsy according to the Navarre neuropediatric reference center.</p> <p>Database / Codes: not stated</p> <p>Case Definition: Epileptic seizures and syndromes – ≥ 2 unprovoked seizures ≥ 24 hours apart; Excluded neonatal, febrile and other acute symptomatic seizures.</p> <p>Validation: Clinical information including EEG, neuroimaging, genetic and metabolic studies</p>
Sweden [66]	<p>Case Sources: Children identified as having had a first seizure in a prior study.</p> <p>Database/Codes: Not used</p> <p>Case Definition: Epilepsy – repeated epileptic seizures during the last 3 years irrespective of EEG findings;</p> <p>Epileptic seizures – paroxysmally appearing, spontaneously ceasing symptoms of cerebral origin, usually with disturbances of consciousness and/or motor, sensory, psychical and autonomous manifestations;</p> <p>Validation: Re-examined hospital records of cohort from first study 3 years after the first seizure to see if case definition of epilepsy met.</p> <p>Note: Follow-up of an earlier study that looked at the first seizure in children, classifying 110 as febrile convulsion and 70 as epileptic seizure. Of those initially classified as febrile convulsion, 4 (3.6%) had additional convulsions and were reclassified as epilepsy. Also of the number of children classified as having epilepsy after 3 years of</p>

	<i>follow-up was 43, which was down from the total of 74 found in the first study. The 43 cases were the basis for the incidence of epilepsy.</i>
Sweden [67]	<p>Case Sources: Population-based prospective study in Vasterbotten county focused on those aged ≥ 17 yrs (total population 191,356); study team requested all district nurses and doctors to report/refer all patients with a newly diagnosed or suspected seizure disorder. Also identified cases based on EEG findings.</p> <p>Database/Codes: not used</p> <p>Case Definition: First epileptic seizure – defined as result of transient dysfunction of part or all of the brain due to excessive discharge of a hyperexcitable population of neurons, causing sudden and transitory phenomena of a motor, sensory, autonomic or psychic nature. Seizure had to have been observed by a physician, or described by a person who observed the phenomena. Only included nonprovoked seizure, without an identifiable causative metabolic or acute structural abnormality;</p> <p>Validation: For cases based on EEG findings but not reported to the study team, medical files reviewed</p>
Sweden [68]	<p>Case Sources: Population-based prospective study in Vasterbotten county focused on those aged 0-15 years old with newly diagnosed unprovoked seizures. Cases found by request to all district nurses and doctors anticipated to come into contact with seizures to report/refer patients with newly suspected or diagnosed seizure disorder. Also reviewed EEG results to find possible cases.</p> <p>Database/Codes: not used</p> <p>Case Definition: First epileptic seizure – defined as result of transient dysfunction of part or all of the brain due to excessive discharge of a hyperexcitable population of neurons, causing sudden and transitory phenomena of a motor, sensory, autonomic or psychic nature. Seizure had to have been observed by a physician, or described by a person who observed the phenomena. Only included nonprovoked seizure, without a history of head trauma, intoxication, infection, febrile disease or metabolic disorder during the week preceding the first seizure.</p> <p>Validation: Assessment by pediatric specialist trained in child neurology based on full history, clinical examination and EEG recordings. Seizures had to have been observed by one of the investigators or described in a personal interview with the patient or his/her parents.</p>
Sweden[69] (Stockholm)	<p>Case Sources: Northern Stockholm (998,500); set up a network of reporting MDs and other health care professionals (all private/public neurologists; pediatricians; geriatricians; nurses in nursing homes) and reviewed all EEG requests to central EEG lab for investigation on suspicion of new onset seizures; also reviewed pediatric emergency room records).</p> <p>Database / codes: Karolinska University Hospital Discharges / ICD-10 G40, G41 or R56.8</p> <p>Case Definition: Single unprovoked seizure – excluded neonatal seizures; Epilepsy - ≥ 2 unprovoked seizures occurring < 5 years apart. Incidence calculated for total single unprovoked seizure and epilepsy cases together.</p> <p>Validation: Medical charts of all potential cases reviewed by a panel including a neurologist, neuropsychiatrist, neurology resident, trained nurse, study coordinator.</p> <p>Note: 1015 individuals included on the basis of a first single unprovoked seizure in 430 (42.4%) and epilepsy in 585 (57.6%).</p>
Sweden[70]	<p>Case Sources: population-based study of children < 16 years in catchment area of Huddinge University Hospital (< 16 population 74,496)</p> <p>Database / Codes: not used</p> <p>Case Definition: Epilepsy – recurrent unprovoked seizures of cerebral origin.</p> <p>Validation: Clinical chart review and EEG findings</p>
Sweden[71]	<p>Case Sources: Umea catchment area (eligible population 101,583); all residents ≥ 17 years old with initial diagnosis of epileptic seizures during study period. Cases identified by MDs in study area; nurses in geriatric and psychogeriatric wards and community nursing homes; EEG reports; diagnoses of syncope, convulsion, seizures, epilepsy in all hospital departments dealing with persons with possible seizures.</p> <p>Database / Codes: not used</p> <p>Case Definition: First unprovoked epileptic seizure – a sudden and transitory event of motor, sensory, autonomic or psychic nature assumed to result from transient excessive discharge of a hyperexcitable population of neurons in the brain. Excluded any seizure with an identified proximate precipitant.</p> <p>Validation: Medical files, EEG, brain CT or MRI and if appropriate blood chemistry and CSF examination.</p>

Sweden[72]	<p>Case Sources: 1mo-16 year old children living in Uppsala county (population 60,192). Searched hospital data register for children diagnosed with convulsions or epilepsy – included in- and out-patient visits as well as rehabilitation center.</p> <p>Database / Code: Uppsala hospital data registers</p> <p>Case Definition: Epilepsy - ≥ 2 unprovoked epileptic seizures. Excluded neonatal, febrile, single seizures; status epilepticus only; non-active epilepsy; doubtful diagnoses (syncope, sleep disorders, migraine; behaviour disorders.</p> <p>Validation: Thorough review of medical chart</p>
Switzerland[73]	<p>Case Sources: Geneva canton (total population 384,657) based on EEG results for suspected first seizures.</p> <p>Case Definition: First epileptic seizure – included unprovoked seizures and epilepsies of known or unknown origin as well as provoked and acute symptomatic seizures (except excluded febrile seizure).</p> <p>Database / Codes: not stated other than use of EEG results.</p> <p>Validation: not described</p>
UK[74]	<p>Case Sources: All patients in the GPRD</p> <p>Database / Codes: General Practice Research Database (GPRD) / Read and OXMIS (Oxford Medical information System) medical codes for epilepsy (specific codes not provided).</p> <p>Case Definition: Code for epilepsy and patient received two or more prescriptions for an antiepilepsy drug in the same year</p> <p>Validation: Used free text in conjunction with Read Codes that included specialist letters, test results, hospital discharge notes, nature of or reason for referral.</p>
UK[75]	<p>Case Sources: 13 General Practices in the National Hospital for Neurology and Neurosurgery (NHNN) Linkage Scheme (population served of 100,230). Cases ascertained via GP referrals to NHNN, GP practice databases searched for neurologic diagnoses and medications;</p> <p>Database / Codes: not defined</p> <p>Case Definition: Epilepsy - ≥ 2 unprovoked seizures; also looked for acute symptomatic and single seizures.</p> <p>Validation: not clearly described</p>
Willame Europe[76]	<p>Case Sources: varied by country but could include hospital admissions, emergency room visits, physician offices. Specified in table 2.1.</p> <p>Databases / Codes: Different databases for each country – specified in table 2.1 Codes unique to each database and system but are published at this link: https://zenodo.org/records/5236723</p> <p>Not validated</p>
MIDDLE EAST	
Qatar[78]	<p>Case Sources: Neurology outpatient clinics of a single tertiary pediatric center (Sidra Medicine) which cares for all pediatric patients with epilepsy in the country. Included ages 0-18 with diagnosis of epilepsy and at least two documented neurology clinic visits. Excluded cases with one unprovoked seizure and children with provoked seizures (fever, post-trauma, neonatal).</p> <p>Database / Codes: Neurology outpatient clinic electronic medical records / ICD-9 345 (epilepsy)</p> <p>Case Definition: Epilepsy - ≥ 2 unprovoked epileptic seizures</p> <p>Validation: Medical chart review</p>
Qatar[77]	<p>Case Sources: Hospital admissions for epilepsy to Hamad General Hospital involving persons >13 years of age,</p> <p>Database / Codes: Hamad General Hospital discharge database / not provided</p> <p>Case Definition: Epilepsy - not defined</p> <p>Validation: Medical record review</p>

TABLE 2.3. Methods for studies of background incidence of status epilepticus

1 st Author and Locale	Methodologic Details
AFRICA	
La Reunion[79]	<p>Case Sources: Recruited cases of status epilepticus from hospital neurology services, emergency rooms, pediatric and neuroradiology services, emergency medical aide service, emergency and admission services of clinics, neurologists (8 public/6 private practice); private pediatricians and rural hospital practitioners. Study panel included 1 neurologist and 1 epileptologist</p> <p>Database/Codes: not used</p> <p>Case Definition: Status epilepticus = single clinical seizure lasting > 30 minutes or repeated seizures over a period of >30 minutes without intervening recovery of consciousness. Clinically classified as convulsive (primary and secondary generalised), non-convulsive (subtle, typical and atypical absence and complex partial included) and partial (simple partial included); classified epidemiologically as provoked, unprovoked symptomatic and cryptogenic. Excluded febrile, neonatal and non-epileptic seizures as well as those lasting <30 minutes.</p> <p>Validation: Cases classified by an epileptologist bases on clinical, EEG and imaging data.</p> <p>Note: Prospective, observational, multicentre epidemiologic study from July 1, 2004 – June 30, 2005 trying to ascertain all cases of SE</p>
AMERICAS	
USA[80]	<p>Case Sources: All medical contacts of Olmsted County residents including inpatient, outpatient and home visits.</p> <p>Database/Codes: Rochester Epidemiology Project database / not provided</p> <p>Case Definition: Status epilepticus – single clinical seizure lasting >30 minutes or repeated seizures over a period of >30 minutes without intervening recovery of consciousness. Included status associated with fever in young children. Unprovoked episode - occurred in the absence of an identified acute insult; further classified into progressive symptomatic (in presence of nonstatic CNS conditions such as tumors or degenerative neurologic diseases); remote symptomatic (in the presence of a history of a CNS insult such as stroke, head trauma or meningitis); and idiopathic/cryptogenic (absence of an acute precipitating factor or a history of a prior neurologic insult). Acute symptomatic episode – occurred in association with onset of brain trauma, CNS infection, cerebrovascular disease, acute diffuse encephalopathy or toxic/metabolic insults including alcohol or drug withdrawal. Classified febrile episode separately if occurred during a febrile illness in a child in the absence of another acute symptomatic cause such as CNS infection. .</p> <p>Validation: Medical charts of all cases with any type of convulsive disorder reviewed by two neurologists.</p>
USA[81]	<p>Case Sources: Prospective, population-based study in Richmond</p> <p>Database/Codes: Virginia Commonwealth University Comprehensive Epilepsy Institute study of all status epilepticus from 1989 to 1991.</p> <p>Case Definition: Status epilepticus - seizure lasting ≥30 minutes or intermittent seizures lasting more than 30 minutes where the patient did not regain consciousness between seizure episodes. Classified by etiology as: acute symptomatic (anoxia, hypoxia, cerebrovascular disease, hemorrhage, tumor, infection – CNS or non-CNS, metabolic, low levels of anticonvulsant drugs, drug overdose, alcohol intoxication or withdrawal, head trauma; remote symptomatic (prior history of CNS insult (cerebrovascular accident, CNS infection, congenital cause, trauma, hemorrhage or tumor); idiopathic.</p> <p>Validation: Over 1 month for each year of the study, complete chart review of all hospital ICD-9 codes for seizures, 911 reports for seizures in the ER, presentation of status epilepticus on hospital rounds, all EEG laboratory reports and ICU and ER records and personnel to document cases of status epilepticus. Found that 90% of cases from tertiary care center (Medical College of Virginia) were valid versus only 33% of cases from community hospitals (explanation was lack of referral of community hospital cases to neurology specialists). Used these estimates to correct for underrepresentation of the true incidence.</p>
USA[82]	<p>Case Sources: Nonfederal hospital admissions (includes 571 of 594 hospitals in the state).</p> <p>Database/Codes: Nonfederal Hospital Discharge Database / ICD-9 code for: grand mal status (345.3)</p> <p>Case Definition: Generalized convulsive status epilepticus – defined as ICD-9 code 345.3. (extended convulsive seizures with tension of limbs (tonic) and/or rhythmic contractions (clonic)</p>

	Validation: not done
USA[83]	<p>Case Sources: USA national hospital discharges</p> <p>Database / Codes: National Hospital Discharge data 1979-2010; ICD-9 code for status epilepticus (345.3).</p> <p>Case Definition: Status epilepticus defined as neurologist documentation of continuous clinical seizure activity for ≥ 5 minutes or ≥ 2 discrete seizures without interictal return to baseline or EEG consistent with status epilepticus based on board certified neurophysiologist interpretation</p> <p>Validation: Not done but cited a study showing 100% sensitivity, specificity, PPV and NPV for the status epilepticus ICD-9 code.</p>
USA[84]	<p>Case Sources: US Pediatric (≤ 20 years) hospitalizations; excluded neonatal cases</p> <p>Database / Codes: Kids' Inpatient Database (KID). ICD-9 code for status epilepticus (not specified in text).</p> <p>Case Definition: Not specified but based on ICD-9 code for status epilepticus</p> <p>Validation: not done</p>
ASIA	
Thailand[85]	<p>Case Sources: Patients hospitalized with status epilepticus.</p> <p>Database/Codes: 3 Thai health insurance systems: Universal Health Coverage Insurance, Social Security, Government Welfare system / ICD-10 code for status epilepticus (G41)</p> <p>Case Definition: Status epilepticus defined as continuous seizure of >5 minutes or repeated seizures over a period of >30 minutes without gaining consciousness between seizures.</p> <p>Validation: not done</p>
EUROPE	
Germany [86]	<p>Case Sources: Population of adult residents within the primary service area of the University Hospital Marburg (population 123,353 adult residents). Possible patients reported to study team by neurologists, intensive care and emergency department doctors and nurses.</p> <p>Database/Codes: not used</p> <p>Case Definition: single clinical seizure lasting >30 minutes or repeated seizures over a period of >30 minutes without intervening recovery of consciousness.</p> <p>Validation: Referred cases evaluated within 5 days by a study team member using a standardized data-entry form capturing clinical features, seizure type, concomitant diseases, 30 day outcome, diagnostic procedures, demographic data and medical history.</p>
Italy[87]	<p>Case Sources: Prospective study – active surveillance in neurological wards, EEG recordings, Emergency departments in Bologna. Retrospective study – hospital discharges for epilepsy</p> <p>Database / Codes: Medical records of all public general hospitals in Bologna and University Dept of Neurological Sciences / ICD-9 for epilepsy (345.X)</p> <p>Case Definition: Status epilepticus – single epileptic seizure of >30 minutes duration or series of seizures during which function not regained between ictal events in a >30 minute period.</p> <p>Validation: review of clinical description of status epilepticus, laboratory tests, radiologic investigations, drugs</p>
Italy[88]	<p>Case Sources: ≥ 20 year old residents of 3 north Italy rural health districts (Ravenna, Emilia-Romagna region, Lugo di Romagna – population of 81,974).</p> <p>Methods were same as for Bologna study noted above.</p>
Italy[89]	<p>Case Sources: Hospital discharges plus EEG archives, emergency unit visits and territorial emergency services in Ferrara study area.</p> <p>Database / Codes: University Hospital of Ferrara discharge diagnoses / ICD-9 epilepsy 345.xx</p> <p>Case Definition: Status epilepticus – single epileptic seizure of >30 minutes duration or series of seizures during which function not regained between ictal events in a >30 minute period. Included provoked and unprovoked seizures.</p> <p>Validation: Medical chart review</p>
Switzerland[90]	<p>Case Sources: Western Switzerland (1,7435,420 population). Suspect cases prospectively identified by neurologists, pediatricians, emergency room and intensive care unit personnel of University Hospitals of Geneva and Lausanne, EEG departments, psychiatric and geriatric hospitals, district and community hospitals.</p> <p>Database/Codes: not used</p> <p>Case Definition: Single epileptic seizure lasting >30 minutes or repeated seizures lasting over a period of >30 minutes without recovery of consciousness</p>

	Validation: medical chart review by an epileptologist
UK[91]	<p>Case Sources: Prospective, population-based North London Convulsive Status Epilepticus in Childhood Surveillance Study (NLSTEPSS) which sought telephone notifications of potential cases from a clinical network of 18 hospitals with 24 hour accident and emergency services, five pediatric intensive care units, and regional centralised ICU transport service. Also sought cases via reporting cards mailed to all pediatricians in north London and daily calls to the Children’s Acute Transport Service research team.</p> <p>Database/Codes: Admission databases of 6 north London hospitals / ICD-10 codes for status epilepticus (G41) and febrile seizures (R56.0)</p> <p>Case Definition: Status epilepticus – tonic, clonic or tonic-clonic seizure (continuous convulsive status epilepticus) or ≥2 such seizures between which consciousness was not regained (intermittent convulsive status epilepticus), which lasted for at least 30 minutes.</p> <p>Validation: Medical chart review</p>

APPENDIX 3

Risk Factors for Generalized Convulsive Seizure

3.1 Risk Factors for Generalized convulsive seizure

TABLE 3.1. RISK FACTORS for Generalized convulsive seizure

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	<ul style="list-style-type: none"> • Incidence of epilepsy higher in youngest (including congenital, developmental, and genetic causes) and oldest (including cerebrovascular causes) age groups.[92, 93](see appendix 2, Background Rates) • Febrile seizure[94]: 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 <ul style="list-style-type: none"> ○ 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 ○ Prolonged seizures (>30 minutes) and multiple complex features have been linked to later unprovoked seizures and increased epilepsy risk[95]. • Status epilepticus episodes in infants and elderly patients last longer on average compared those ages 1-65.[80] • In childhood-onset epilepsy, about half of cases with an identified cause are linked to cerebral palsy or intellectual disability[17].
Sex	<ul style="list-style-type: none"> • Incidence and prevalence of epilepsy slightly higher in men than in women[80, 93, 96-98] • After mild brain injury (concussions), women were found to have a higher risk of developing epilepsy long-term[99]
Genetic	<ul style="list-style-type: none"> • Family history: <ul style="list-style-type: none"> ○ Family history of a close family member (parents/sibling) with epilepsy indicated a significantly higher risk for epilepsy[97, 100, 101] ○ Parent or sibling with a past history of febrile seizure[94, 102] • Genetic epilepsies and channelopathies: <ul style="list-style-type: none"> ○ 1506 genes have been identified to be associated with epilepsy[103] ○ SCN1A: Mutations are strongly associated the risk of epilepsy, Dravet syndrome, generalized epilepsy with febrile seizures plus, other severe epileptic encephalopathies, and other therapy-resistant epilepsies. Specific polymorphisms including rs11890028, rs10188577 (Chinese populations), rs2298771 (Indian populations), rs7587026, rs3812718 (IVS5N+5G ,ÜíA) have been linked to increased epilepsy risk and the same mutation can lead to variable phenotypes.[104-108] • SCN2A rs12467383 is associated with increased risk of epilepsy and SCN2B rs602594 is associated with idiopathic epilepsy.[109] <ul style="list-style-type: none"> ○ 5q34 locus confers risk to a broad spectrum of epilepsies. Susceptibility loci such as 2p16.1 (harboring VRK2 and FANCL), 2q34, 13q13.3, and recurrent microdeletions at 15q13.3, 15q11.2, and 16p13.11, and rare deletions in NRXN1 and RBFOX1 show significant risk of epilepsy.[110, 111] ○ De novo genetic deletions in Angelman syndrome have links to status epilepticus in children 13-24 months of age, but with seizure freedom later in life.[112] ○ Porphyria can also lead to seizures and status epilepticus during acute attacks.[112]

	<ul style="list-style-type: none"> <ul style="list-style-type: none"> ◦ Mutations in SCN2A, SCN3A, SCN8A, KCNQ2, KCNQ3, CLCN2, CACNA1A, CACNB4, CACNA1H, GABRG2, GABRA1, GABRD, SLC2A1, PRRT2, TSC1/TSC2, and others are linked to various epilepsy syndromes [104, 105, 113] ◦ Autosomal-recessive mutation in the KCTD7 gene leads to progressive myoclonic epilepsy and photoparoxysmal response (PPR) in some people [114](~12% of cases). • In juvenile myoclonic epilepsy (JME), there are several risk factors for refractoriness identified (e.g., different seizure types, psychiatric comorbidities, earlier age at seizure onset, etc.)[115]Gene polymorphisms: <ul style="list-style-type: none"> ◦ Interleukin genes IL-1B IL-1α -889 1/1 (recessive model) polymorphisms are associated with febrile seizure susceptibility in some populations. IL-1α -889 1/1 (recessive model) and IL-6 polymorphisms are also associated with epilepsy.[116] [117-119] Elevated cerebrospinal fluid (CSF) IL-1β levels and serum IL-6 levels have been shown to increase the risk of febrile seizures in children.[120] ◦ MTHFR C677T polymorphism is associated with higher epilepsy susceptibility across several genetic models.[121, 122] ◦ Apolipoprotein E ϵ4 allele is linked to increased epilepsy risk and earlier onset of epilepsy.[123, 124] ◦ GABBR1 and PDYN polymorphisms, and PDYN promoter polymorphism in particular, are associated with temporal lobe epilepsy. [125] [126] ◦ CAMSAP1L1 and BRD2 variants are linked to epilepsy.[127, 128] ◦ GABRG2 polymorphism rs211037 and haplotypes rs211037–rs210987 and rs2422106–rs211014–rs401750 are linked to seizure susceptibility and status epilepticus in Chinese populations.[129, 130] • Ring chromosome 20 syndrome is a chromosomal abnormality strongly associated with refractory epilepsy and status epilepticus, particularly in children.[112] • Familial epilepsy syndromes include those with ‘febrile seizures +’ meaning febrile seizures that persist beyond the age of 6 years [94]. These include mutations in sodium channel 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.
Pregnancy	<ul style="list-style-type: none"> • No evidence found
Pre-, Peri-, Post-natal condition	<ul style="list-style-type: none"> • Premature infants have an increased risk of developing epilepsy. The risk is higher the earlier a baby is born, with those born before 32 weeks at highest risk.[126, 131, 132] • Home births and complicated deliveries significantly raise the risk for epilepsy in children, especially in resource-limited settings where access to skilled perinatal care is less common.[132] • Babies who are small for gestational age or have restricted fetal growth are at increased risk of epilepsy.[126] • Prenatal stroke, neonatal seizures, neonatal encephalopathy, neonatal sepsis, and neonatal haemolytic disease are associated with epilepsy.[126, 133] • Additional risk factors for epilepsy associated with the perinatal period include birth trauma, problems after delivery, congenital abnormalities, low apgar score, and abnormal perinatal history.[126, 134-137] • Developmental venous abnormalities are associated with epilepsy. Seizures may occur due to thrombosis, hemorrhage, or abnormal venous drainage.[138, 139]

	<ul style="list-style-type: none"> • Prenatal antibiotic exposure: associated with a higher incidence of epilepsy.[140]
Social/Culture	<ul style="list-style-type: none"> • No evidence found
Occupation	<ul style="list-style-type: none"> • No evidence found
Season	<ul style="list-style-type: none"> • No evidence found
Geo-location	<ul style="list-style-type: none"> • Incidence and prevalence of epilepsy is higher in Low-Middle Income countries (LMIC) versus High Income countries (HIC).[93, 98, 134, 141] (see Appendix 2, Background Rates) • West Asia has elevated rates of active and lifetime epilepsy (see specific rates in tabl2 2.1).[142] • IL-1b-511 C/T gene polymorphism are significantly associated with febrile seizures in Asia.[143]
Environment	<ul style="list-style-type: none"> • Light flashes, visual patterns, or color changes can provoke seizures in photosensitive individuals.[144]
Diet	<ul style="list-style-type: none"> • Iron deficiency anemia is associated with an increased risk of febrile seizures in children, especially when diagnosed based on plasma ferritin, mean corpuscular volume, or serum iron levels.[145, 146] • Reduced serum zinc levels are significantly associated with febrile seizures in children.[147] • Caffeine can trigger acute seizures in some cases.[148]
Behavior	<ul style="list-style-type: none"> • Alcohol: Alcohol consumption has a strong association with epilepsy and unprovoked seizures [Overall relative risk (95% CI): 2.19 (1.83-2.63)] [149]. Risk increases with higher daily intake. Alcohol withdrawal can also precipitate seizures or status epilepticus.[126, 149, 150] • Smoking: Smoking initiation and lifetime smoking are associated with increased epilepsy risk.[151] • Marijuana: Use of synthetic cannabinoids has been linked to seizures, including generalized tonic-clonic seizures and occasional status epilepticus.[152] • Sleep: Reduced sleep duration is linked to epilepsy progression with each additional hour of sleep lowering seizure odds.[126] • Stress/anxiety: High levels of stress or anxiety have been associated with increased seizure recurrence risk.[126] • Poor sanitation: Living in households with poor sanitation (e.g. latrines near the house, absence of indoor toilets) increases epilepsy risk.[97] • Video gaming: Stimulus overload (e.g. excessive video gaming) is hypothesized as a seizure trigger in isolated cases.[153]
Comorbidity	<ul style="list-style-type: none"> • Autoimmune and inflammatory diseases: Autoimmune conditions, including multiple sclerosis, are associated with higher risk of epilepsy.[92, 113, 154, 155] Younger age at MS onset is associated with higher epilepsy risk. MRI-based studies suggest cortical and cortico-juxtacortical lesions are more frequently observed in MS patients with epilepsy, indicating these lesions may play an epileptogenic role.[156] • Cerebrovascular and cardiovascular conditions: Stroke and related factors such as cortical involvement, cerebral hemorrhage, hemorrhagic transformation, and hypertension are associated with higher risk of epilepsy[157-161]. • Neurodegenerative diseases: Alzheimer's disease and other neurodegenerative conditions are frequently associated with epilepsy onset, particularly in the elderly.[161, 162] • Brain neoplasms: <ul style="list-style-type: none"> ◦ Brain tumors are significant contributors to epilepsy in both children and adults, often presenting with seizures as the first symptom.[113, 161, 163]

- About 80% of patients with preoperative seizures can be seizure free after tumor removal, with some postoperative risk factors as well.[164]
- Neurocutaneous syndromes: Tuberous sclerosis complex, Sturge-Weber syndrome, and some other cases of neurofibromatosis type 1 are strongly associated with epilepsy. Epilepsy prevalence with NF1 was lower in children compared to adults and [113, 154, 165]
- Immunological disorders: paraneoplastic encephalitis, Hashimoto's encephalopathy, bullous pemphigoid, celiac disease, and anti-NMDA receptor encephalitis are risk factors for status epilepticus, with seizures being more common among younger patients.[166, 167] Anti-NMDA receptor encephalitis is notable among young women, and Hashimoto's encephalopathy is associated with higher risk for status epilepticus with elevated thyroid antibodies.[112, 168, 169]
- Allergic diseases such as asthma and eczema may be associated with epilepsy risk, although the underlying mechanisms remain unknown.[170, 171]
- Neurological antibody (VGKC, glycine receptor, GAD, NMDA) prevalence is similar between new and established epilepsy and between generalized and focal epilepsy. Significantly higher prevalence of positive antibodies in patients with focal epilepsy of unknown cause than in those with structural/metabolic focal epilepsy.[172]
- Gaucher disease, a rare lysosomal storage disorder, can present with neurological manifestations including seizures.[173]
- Sickle cell disease (SCD) is associated with seizures and epilepsy.[174]
- Down syndrome is associated with an elevated prevalence of epilepsy, partial seizures, infantile spasms, and generalized tonic-clonic seizures. Seizure onset in persons with Down syndrome shows a bimodal distribution, with many cases presenting in infancy and again later in adulthood.[175]
- Psychiatric comorbidities have been associated with an increased risk of seizure recurrence.[176]
- Cavernous malformations (CMs): CMs can cause epileptic seizures. Epilepsy is frequently observed in patients with supratentorial and superficial brain lesions, with seizures reported as the first presentation in about a third of cases.[177-179]
- Cerebral proliferative angiopathy (CPA) commonly presents with seizures and headaches.[180]
- Mitochondrial disorders: POLG1 mutations and MELAS are risk factors for status epilepticus. POLG1-related disorders, including Alpers disease, are especially associated with early-onset, treatment-resistant epilepsy and status epilepticus.[112]
- Central nervous system anomalies in incontinentia pigmenti include seizures.[181]
- Supratentorial neurenteric cysts present with seizures.[182]
- An inflammatory cytokine profile may contribute to epileptogenesis.[183]
- 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[184]
- Status Epilepticus etiologies:
 - The majority of SE cases are symptomatic (98.2%), with cerebrovascular events the leading cause (45.2%), followed by trauma, metabolic disturbances, and tumors.[185]
 - Cryptogenic etiology is the most common cause of new-onset refractory status epilepticus (NORSE) in adults (49.9%), followed by autoimmune causes (36.2%), with less frequent infectious, structural, vascular, toxic, and genetic etiologies.[186]

	<ul style="list-style-type: none"> • Type 1 diabetes mellitus is associated with a significantly increased risk of epilepsy, including those under 18 years of age.[187, 188]
Injury	<ul style="list-style-type: none"> • Traumatic brain injury is a long-term risk factor for epilepsy. Risk increases with injury severity and can persist for more than 10 years post-injury. Skull fractures and hospitalization following TBI are strong predictors of epilepsy onset.[19, 92, 99, 126, 134] • Diffuse axonal injury and cortical contusions, with or without intracranial hematoma, predispose individuals to epilepsy development.[189] • Seizure was found to be a common neurological disorder in renal transplant patients.[190] • Among athletes experiencing convulsions immediately after violent collisions, no players developed epilepsy during a mean 3.5 year follow-up period.[191]
Infection	<ul style="list-style-type: none"> • Parasitic and bacterial infections including <i>Onchocerca volvulus</i> [192-194], <i>Toxocara canis</i>, [195, 196], <i>Toxoplasma gondii</i> [197], and <i>Bartonella henselae</i> are reported as risks of epilepsy. Neurocysticercosis, caused by <i>Taenia solium</i>, is a common cause of seizures and epilepsy, with more than three-quarters of symptomatic patients presenting with seizures [97, 197-200]. Rare presentations include intrasellar cysticercosis, which has also been reported to cause seizures and chronic headaches.[201] • Congenital zika infection is strongly associated with high epilepsy incidence.[202-204] • Severe childhood diseases such as measles, cerebral malaria, meningitis, encephalitis, and neonatal sepsis contribute to increased seizure risk.[97, 98, 205, 206] • HIV and related factors (e.g., alcohol withdrawal, ARV toxicity) increase seizure risk due to both direct viral effects, advanced HIV infection, and secondary infections or effects.[112, 207] • Human herpesvirus 6 (HHV-6) infection has been identified in some children with febrile seizures, including some with severe presentations such as status epilepticus.[208] • Hand, foot, and mouth disease (HFMD) in children can be associated with neurological complications, including seizures.[209] • Advanced Creutzfeldt–Jakob disease is associated with non-convulsive or convulsive status epilepticus in its advanced stages.[112] • Severe RSV infections can cause hyponatremia, leading to seizures.[210] • COVID-19 and MERS-CoV infections occasionally present with seizures.[211-213] Seizures occur more frequently in severe COVID-19 compared with non-severe cases. The Omicron wave was associated with significantly more seizure cases, especially nonfebrile and in children with prior seizure disorders.[214, 215]
Medication	<ul style="list-style-type: none"> • The rate of seizures is higher in those receiving carbapenems, particularly, imipenem, though the difference may depend on population and comparison groups. β-lactam antibiotics, especially penicillins and fourth-generation cephalosporins, are also associated with increased risk, with higher risk among patients with renal dysfunction, brain lesions, epilepsy, or high drug dosage. Piperacillin, ertapenem, and intravenous penicillin are also cited as provoking seizures.[216-220] • Antimicrobials, such as cephalosporins, and chemotherapeutic agents, like ifosfamide, are known triggers for status epilepticus.[112] • Tranexamic acid therapy in adult cardiac surgery significantly increases seizure incidence.[221, 222] • Tramadol is associated with seizures. Risk is higher with long-term use, abuse, or concurrent drug use.[223]

	<ul style="list-style-type: none"> • Electroconvulsive therapy (ECT), while generally safe, has occasionally triggered status epilepticus in some individuals. Neurosurgical complications can also precipitate status epilepticus post-operatively.[112] • Hematopoietic cell transplantation drugs are associated with seizures, frequently attributed to busulfan and calcineurin inhibitors.[224] • Botulinum toxin type A is reported to trigger seizures in some children with cerebral palsy undergoing treatment.[225] • Seizures occur in some neonates and children undergoing extracorporeal membrane oxygenation (ECMO) with higher rates linked to extracorporeal cardiopulmonary resuscitation (ECPR) and veno-arterial ECMO use.[226, 227] • Seizures and epilepsy are reported as adverse effects of antipsychotic drugs in genetically susceptible individuals.[228] • Some antiepileptic drugs like Tiagabine (TGB) may provoke SE.[112] • Cases of drug or treatment-related seizures have been associated with insulin-induced hypoglycemia, intravenous lignocaine, phenothiazines, prednisone, peritoneal dialysis, high-dose isoniazid, ephedrine, and vitamin K oxide injections.[220] • Use of new-generation antidepressants, particularly SSRIs and SNRIs, is associated with an increased risk of seizures, with the risk more pronounced in short-term users.[229] • Paradoxical drug-induced seizures are a recognized complication in patients receiving Lamotrigine (LTG) and other anticonvulsants, particularly children, and a frequent reason for treatment discontinuation.[230, 231] Underlying causes differ by age group.
Toxin /Toxic exposure	<ul style="list-style-type: none"> • Natural toxins such as domoic acid and star fruit have been associated with neurotoxicity leading to status epilepticus.[112] • Environmental toxins and pollutants such as CO, NO₂, and mosquito repellent vaporizer have associations with seizure occurrence.[232, 233] • Cases of generalized seizure were discovered after eucalyptus oil ingestion or topical exposure, often resolving after discontinuation of use[234].
Vaccine	<ul style="list-style-type: none"> • No evidence that vaccines cause epilepsy • Vaccines associated with an increased risk of febrile seizure in <6 years old[235]: <ul style="list-style-type: none"> ◦ MMR & MMRV: <ul style="list-style-type: none"> • MMR: 26.4/1000 person years 7-10 days after vaccination[235] • MMRV: 86.4/1000 person years 7-10 days after vaccination[235] • MMRV has a higher relative risk than MMR+V, examples: <ul style="list-style-type: none"> ◦ Adjusted RR: 1.46 (0–42 d) and 2.04 (7–10 d)[236] ◦ Adjusted RR: 1.99 (7–10 d)[237] ◦ Influenza & pneumococcal conjugate vaccines <ul style="list-style-type: none"> • 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[238] 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 seizure[235]

	<ul style="list-style-type: none"> • Our review added information on additional vaccines: <ul style="list-style-type: none"> ◦ no increased risk detected for HPV vaccines[239] ◦ very low reporting rates for febrile seizures for JE vaccine (0.3–0.4 per million doses for live/inactivated JE in China[240]) ◦ rare seizures with rotavirus vaccine[241, 242] • Risk window for convulsion as a vaccine product related reaction relates to the period of reactogenicity when fever may occur <ul style="list-style-type: none"> ◦ 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	<ul style="list-style-type: none"> • History of a 1st unprovoked seizure is associated with an increased risk of recurrence [93, 243] <ul style="list-style-type: none"> ◦ 36-37% within 1 year; 43-45% by 2 years ◦ Presence of absence seizures and combined seizure types have been linked to higher recurrence risk.[244] • High seizure frequency, prior status epilepticus, multiple AED failures, prior seizure clusters, history of head trauma or CNS infections, and complex seizure types are risk factors for seizure clusters.[245] • Epileptiform EEG <ul style="list-style-type: none"> ◦ Presence of epileptiform discharges on EEG after a first seizure is a strong predictor for seizure recurrence, alongside focal seizure onset and positive family history.[246] Electrographic features such as generalized polyspike trains are also associated with increased recurrence risk.[244] Remote symptomatic seizures carry a higher recurrence risk compared to idiopathic seizures.[247] ◦ Predictors for epileptic versus non-epileptic seizures of organic origin were an epileptiform EEG pattern versus a history of hypertension or cardiovascular disease. [62] • Provoked seizures are associated with acute CNS or systemic insults (e.g., head injury, infection, hypoglycemia), while unprovoked seizures occur without an acute insult and may follow prior brain insults or be idiopathic.[17]

TABLE 3.2. COMPARISON OF TYPICAL FEATURES OF EPILEPSY AND FEBRILE SEIZURE

	Epilepsy[93]	Febrile Seizure[94]
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 [94] 2 unprovoked seizures occurring 24 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.	<ul style="list-style-type: none"> most are generalised tonic-clonic 30-35% have ≥ 1 complex feature <ul style="list-style-type: none"> 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)	<ul style="list-style-type: none"> 1 in 30 individuals overall 1 in 5 if one sibling affected 1 in 3 if both parents & a sibling affected
Main Risk factors	<ul style="list-style-type: none"> family history of epilepsy complex febrile seizures neurodevelopmental impairment 	<ul style="list-style-type: none"> age <6 years Parent or sibling with history of febrile seizure
Risk of recurrence	After first unprovoked seizure: <ul style="list-style-type: none"> 36-37% at 1 year 43-45% at 2 years Time frame for recurrence <ul style="list-style-type: none"> 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): <ul style="list-style-type: 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: <ul style="list-style-type: none"> <16years: 1.1 (95%CI 0.5-2.3) >50years: 1.3 (95%CI 0.9-1.8) SUDEP risk factors: <ul style="list-style-type: none"> generalized tonic-clonic seizures nocturnal seizures persistence of seizures 	
Global Burden	2016 estimate: 46 million people with 80% residing in LMIC	

TABLE 3.3 Studies reporting on risk of Seizure after vaccination with Measles containing vaccines, by study type

Author, year	Location	Study Years	Age Group	Type of seizures	Number of Seizure Cases	Specific Vaccine	Risk Estimate	Risk estimate value	Relevant Additional Study Details
SCCS (n=11)									
Macartney, 2015[248]	Australia	2012 - 2013	<5 years	Febrile seizure	33	MMR dose 1	Relative incidence (95% CI) first FS, compared to background rates with 1-month intervals, p-value	5-12 days=1.90 (1.26, 2.86); 0.002 13-30 days=0.84 (0.56, 1.25); 0.394	Case ascertainment= ICD-10 AM Risk period = 5-30 days
Hambidge, 2014[241]	USA	2004 - 2010	38 - 730 days	Febrile seizure	Age at receipt: 361-488 days=63	MMR	IRR (95% CI)	2.65 (1.99, 3.55)	Case ascertainment= ICD-9 Risk period = 0-7 days Vaccinated n = 5,667
					489-730 days=14			6.53 (3.15, 13.53)	
					361-488 days=75	MMRV		4.95 (3.68, 6.66)	
					489-730 days=14			9.80 (4.35, 22.06)	
Gold, 2010[249]	Australia	1997 - 2002	0-7 years	Febrile seizure	789	MMR	IRR (95% CI); SE (β); p-value	Risk interval 6 to 11 days= 2.11 (1.43, 3.10); 0.42; <0.001 Risk interval 15 to 35 days 0.90 (0.65, 1.25); 0.15; 0.54	Case ascertainment= ICD Vaccinated n = 122,435
Miller, 2007[250]	UK	1998 - 2002	12 - 23 months	Febrile seizure	50	Priorix, MMRII	Relative incidence, compared to pre-	6-11 days: 4.09 (3.14, 5.33) 15-35 days: 1.13 (0.87, 1.48)	Risk period = 6-11 days Vaccinated n = 894

						Priorix	vaccine period (95% CI)	6-11 days: 6.26 (3.85, 10.18)	
								15-35 days: 1.48 (0.88, 2.50)	
						MMRI		6-11 days: 3.64 (2.44, 5.44)	
								15-35 days: 1.28 (0.89, 1.84)	
Andrews, 2001[251]	UK	1997 - 1998	12 - 23 months	Convulsion	73	MMR	Relative incidence compared to pre-vaccine period (95% CI)	6-11 Days: 4.62 (3.68, 5.80)	Vaccinated n = 1,160
								15 - 35 Days: 1.08 (0.85, 1.38)	
McClure, 2019[252]	USA	2003 - 2015	-	Seizure	Pre-term =22	MMR	IRR (95% CI); 7-10 days versus 15-42 days after vaccination	3.2 (1.9, 5.3)	Case ascertainment= ICD 9 Risk period = 7-10 days Number of doses: Pre-term MMR= 37,262, MMRV= 8,081 Full term MMR= 403,238, MMRV= 83,794
					Full term =163			2.7 (2.2, 3.2)	
					Pre-term =9	MMRV		7.9 (3.0, 20)	
					Full term =69			5.7 (4.1, 7.8)	
Wang, 2018[253]	USA	1995 - 2015	11 - 23 months	Seizure	6	MMR	IRR (95% CI); p-value	3.5 (1.4, 8.8); 0.008	Case ascertainment= ICD-9 Risk period = 7-10 days vs control window (14-56 days)
Macartney, 2017[254]	Australia	2013 – 2014	11 - 23 months	Febrile seizure	-	MMR	Relative incidence compared to pre-vaccine period (95% CI); p-value	5-12 days: 2.71 (1.71, 4.29); <0.001	Case ascertainment= ICD-10-AM
						MMRV		13-30 days: 0.89 (0.54, 1.48); 0.66 5-12 days: 1.08 (0.55 ,2.13); 0.82	

								13-30 days: 1.08 (0.67, 1.74); 0.74	
Zerbo, 2022[255]	USA	1995 - 2012	-	Febrile seizure	28	MMR or MMRV	Rate ratio (95% CI)	1.64 (1.05 - 2.55)	Case ascertainment= ICD-9-CM and ICD-10-CM Risk period = 0-7 days vs control interval (14-28 days) Vaccinated n = 1,415,411
Hanf, 2013[256]	France	2009 - 2010	-	Febrile seizure	0 day =25	MMR	IRR (95% CI)	2.99 (2.02-4.44)	Case ascertainment= ICD-10 Vaccinated n: 2,913
					1-5 days =44			1.05 (0.78-1.42)	
					6-11 days =76			1.50 (1.20-1.89)	
					15-35 days =184			1.06 (0.91-1.23)	
Xu, 2021[257]	China	2016 - 2019	-	Febrile seizure	33	MR	Relative incidence (95% CI, p)	1.17 (0.65 - 2.11, p=0.609)	Case ascertainment= BC Risk period = 0-42 days Vaccinated n: MR= 146, MMR= 691
					92	MMR		0.90 (0.64 to 1.27, p=0.538)	
Cohort studies (n=23)									
Hanson, 2023[258]	USA	2010 - 2018	-	Seizure	14	MMR	RR (95% CI) vs control period (50-92 days)	1.17 (0.54, 2.52)	Case ascertainment= ICD-9 and ICD-10 Risk period = 0-42 days Number of doses = 230,636
Tartof, 2014[259]	USA	2003 - 2011	6 months - 3 years	Febrile seizure	3348	MMR	RR (95% CI) compared to non-vaccine associated (NVA) person-time	2.5 (2.1, 2.9)	Case ascertainment= ICD-9 Risk period = 0-15 days Vaccinated n = 265,275
Schink, 2014[260]	Germany	2006 - 2008	-	Febrile seizure	-	MMRV	Adjusted OR (95%CI)	Compared to MMR: 4.1 (1.3–12.7)	Case ascertainment= ICD-10-GM code Risk period = 5-12 days
								Compared to MMR+V:	

								3.5 (0.76–19.0)	
								Compared to MMR and MMR+V: 4.1 (1.5–11.1)	
Rowhani-Rahbar, 2013[261]	USA	2001 - 2011	12 - 23 months	Seizure	-	MMRV	IRR (95% CI) versus MMR+V	12-15 months: 2.0 (1.4-2.8) 15-23 months: 2.1 (1.3-3.3)	Case ascertainment= ICD-9 Risk period = 7-10 days Number of doses = MMRV: 120,377, MMR+V: 584,987
Klein, 2012[262]	USA	2000 - 2008	48 - 83 months	Febrile seizure	1	MMRV	Incidence rate per 100,000 doses (95% CI)	1.2 (0.03, 6.4)	Case ascertainment= ICD 9 Number of doses: 86,750
Esteghamati, 2011[263]	Iran	2006	-	Febrile seizure	Dose 1=8	MMR	Incidence rate (95% CI) in 100,000 children or 100,000 doses	56.7 (24.5, 111.7)	Case ascertainment= WHO definitions and confirmed by clinical examination Number of doses = 1 st dose: 14,109, 2 nd dose: 29,338
				Convulsions without fever	Dose 2=4			17 (5.5, 39.8)	
					Dose 1=7			49.6 (20.0, 102.2)	
Klein, 2010[236]	USA	2000 - 2008	-	Seizure	-	MMRV	Relative risk compared to MMR+V (95% CI)	0-42 days: 1.46 (1.11–1.92) 7-10 days: 2.04 (1.44–2.90)	Vaccinated n: MMRV= 83,107, MMR+V=376,354
Jacobsen, 2009[264]	USA	2006 - 2007	-	Febrile seizure	22	MMRV	IR (95% CI) per 1000 children during the specified risk period	5-12 days: 0.70 (0.44, 1.06)	Case ascertainment= BC Vaccinated n = 31,298 Number of doses = 31,298
					23	MMRV		0-30 days: 0.73 (0.47, 1.10)	
					10	MMR+V		5-12 days: 0.32 (0.15, 0.59)	
Vestergaard, 2004[265]	Denmark	1991 - 1999	15-17 months	Febrile seizure	17,986	MMR	Cumulative incidence per 1000 children	2.46	Case ascertainment= ICD-8 and ICD-10 Risk period = 0-14 days

							Risk difference compared to non-vaccinated	1.56 (1.44-1.68)	Vaccinated n = 439,251 Number of doses = 439,251
Barlow, 2001[266]	USA	1991 - 1993	-	Febrile seizure	1-7 days =8	MMR	RR compared to no vaccination (95% CI)	1.73 (0.72,4.15)	Case ascertainment= ICD-9 Number of doses = 137,457
					8-14 days =13			2.83 (1.44, 5.55)	
					15-30 days =11			0.97 (0.49,1.95)	
				Nonfebrile seizures	8-14 days =1			1.11 (0.11, 11.28)	
					15-30 days =1			0.48 (0.05, 4.64)	
Gvozdenovic, 2018[267]	Germany	2006 - 2008	-	Febrile seizure	-	MMRV	Risk difference (n/100,000) compared to MMR+V (95% CI)	21.8 (14.3, 57.8)	Case ascertainment= Jacobsen case definition Risk period = 5-12 days
Sanchayan, 2017[268]	Sri Lanka	2012 - 2014	Mean: 1 year 10 days	Febrile seizure	3	MMR	Incidence per 1,000 immunizations (95% CI)	1.25 (0.3, 3.7)	Case ascertainment= BC Risk period = 0-21 days
Narwaney, 2017[269]	USA	2004 - 2013	<2 years	Febrile seizure	Cohort 1 =14	MMR	Events per 10,000 doses (95% CI)	3.15 (1.87, 5.32)	Case ascertainment= Clinical guidelines from the American Academy of Pediatrics Number of doses = 44,416
					Cohort 2 =9			2.97 (1.55, 5.72)	
Cocchio, 2016[270]	Italy	2013 - 2014	Mean (SD): 14.9 months (2.3)	Febrile seizure	7	MMR+V	Relative risk (95% CI) compared to MMRV group	0.80 (0.30, 2.15)	Case ascertainment= A standardized clinical and causality assessment framework was applied Vaccinated n: MMRV= 5,265, MMR+V= 5,130

Klein, 2015[271]	USA	2000 - 2012	12 - 23 months	Seizure	18	MMRV	OR (95% CI) compared to MMR+V using case centered analysis	3.9 (1.75, 8.71)	Case ascertainment= ICD-9 Number of doses: MMRV= 123,200, MMR+V= 584,987
Gavrielov-Yusim, 2014[272]	Israel	2005 - 2009	Mean (SD): 12.6 months (1.5)	Febrile seizure	19	MMRV	Attributable Risk vs. MMR per 10,000 insurees (95% CI)	1.04 (0.65, 1.66); 0.875	Case ascertainment= BC Risk period = 0-40 days Vaccinated n: MMRV= 8,344, MMR= 90,294
MacDonald , 2014[237]	Canada	2006 - 2012	-	Febrile seizure	0-42 days =285	MMRV	Adjusted Relative Risk ratio (95% CI) compared to MMR+V	1.21 (0.93, 1.58)	Case ascertainment= ICD-9 and ICD-10-CA Vaccinated n: MMRV= 96,686, MMR+V= 181,088
					7-10 days =125			1.99 (1.30, 3.05)	
Svanstrom, 2010[273]	Denmark	1995 - 2007	-	Febrile seizure	30,979	MMR	Information component (expected vs observed)	1.23	Case ascertainment= ICD-10 code
Schäfer, 2022[274]	Germany	2004 - 2015	-	Febrile seizure	368	MMRV	Adjusted OR (95% Cis) after a second dose	Compared to MMR+V 1.25 (0.67-2.30)	Case ascertainment= Jacobsen et al / ICD-10 Risk period = 30 days Vaccinated n: MMRV= 392,634, MMR= 122,244, MMR+V= 13,761
								Compared to MMR 1.04 (0.82-1.32)	
Khetsuriani , 2010[275]	Georgia	2008 - 2009	6 - 21 years	Seizures /convulsion	1	MR	Calculated rate per 100,000 doses	0.2	Case ascertainment= WHO-UMC system Number of doses = ~493,000
Deng, 2022[276]	Australia	2013	-	Status epilepticus	1	MMR	Calculated rate per 100,000 doses	0.075	Number of doses = 1,331,303

Verbeek, 2015[277]	Netherlands	2009 - 2013	-	Generalized convulsive seizure	14	MMR +/- Meningococcal C	IRR (95% CI)*	2.3 (1.5-3.4)	Risk period = 5-12 days Vaccinated n = 68 * In patients with Dravet's syndrome
Klein, 2010[236]	USA	2000 - 2008	-	Seizure	189	MMRV	Adjusted RR (95% CI) vs MMR+V	0-42 days: 1.46 (1.11–1.92)	Vaccinated n = 83,107
					77			7-10 days: 2.04 (1.44–2.90)	
Pharmacovigilance Studies (n=11)									
Bellavite, 2020[278]	Italy	2017 - 2018	0-2 years	Febrile seizure	1	MMRV	Reporting rate per 1000	0.5	Case ascertainment= WHO causality assessment algorithm Number of doses = 2540
Aagaard, 2011[279]	Denmark	1998 - 2007	-	Febrile seizure	-	MMR	Reporting rates per 100,000 doses	8.31	Case ascertainment= MedDRA Vaccinated n = 849
Vahdani, 2005[280]	Iran	2003 - 2004	-	Seizure	9	MR	Calculated rate per 100,000 doses	0.05	Risk period = 48 hrs Vaccinated n = 2,049,170 Number of doses = 2,049,170
LeSaux, 2003[281]	Canada	1995 - 2001	-	Febrile seizure	107	MMR	Reporting Rate per month (1998-2001)	1.19	Case ascertainment= ICD-9
				Generalized afebrile seizure	33			0.35	
Patja, 2000[282]	Finland	1982 - 1996	-	Febrile seizure	28	MMR	Incidence per 100,000 doses	0.9	Case ascertainment=Clinical information Vaccinated n = 1,800,000 Number of doses = 2,990,000
				Epilepsy	1			0.03	

D'Souza, 2000[283]	Australia	1998 - 1999	4 - 13 years	Seizure	4	MMR	Rate per 100,000 doses	0.24	Case ascertainment= ADRAC criteria Number of doses = 1,700,000
				Febrile seizure	1			0.06	
Soriolo, 2024[284]	Italy	2007 - 2022	0 - 12 years	Afebrile seizures	5	MMRV	Reporting rate per 10,000 doses	0.086	Case ascertainment= BC Vaccinated n: MMRV= 5,662, MMR + V = 3,848
				Febrile seizure	146			1.79	
				Afebrile seizures	2	MMR+ V		0.058	
				Febrile seizure	38			1.08	
Stefanizzi, 2019[285]	Italy	2017 - 2018	Mean (SD): 14.8 months (4.2)	Clonic seizure	1	MMRV	Reporting rate per 100 children	0.05	Case ascertainment= WHO causality assessment algorithm Vaccinated n = 2,540
Bino, 2003[286]	Albania	2000	1-14 years	Seizure	1	MR	Rate per million	1.15	Case ascertainment= WHO guidelines Number of doses = 867,000
Klein, 2008[287]	USA	-	12-23 months	Febrile seizure	-	MMRV	Adjusted odds ratio (95% CI); p value compared to MMR+V	2.3 (1.6, 3.2); <0.0001	Case ascertainment= Medical records review Vaccinated n: MMRV= 43,353, MMR+V= 314,599
Meng, 2017[288]	China	2009 - 2014	-	Seizure	4	MR	Annual incidence rate, per million doses	1.0	Case ascertainment= BC Number of doses = 9.9 million
					3	MMR		0.8	
					7	MV		5.7	
RCT studies (n=2)									
Lieberman, 2006[289]	Multiple	2000 - 2001	11 – 23 months	Febrile seizure	5	MMRV	Calculated proportion	0.17%	Number of doses: 2,915

Marshall, 2016[290]	USA	2012 - 2014	-	Febrile seizure	2	MMRV	Calculated proportion	0.28%	Number of doses: 702
Meta-analysis (n=1)									
Klopfer, 2014[291]	USA	1998 - 2008	Mean (SD): 12.8 months (1.3)	Febrile seizure	Dose 1 =8	MMRV	Pooled incidence	0.26%	Number of doses = Dose 1: 3,019, Dose 2: 2695
					Dose 2 =2			0.07%	

TABLE 3.4 Studies reporting on risk of Seizure after vaccination with Covid-19 containing vaccines, by study type

Author, year	Location	Study Years	Age Group	Type of seizures	Number of Seizure Cases	Specific Vaccine	Risk Estimate	Risk estimate value	Relevant Additional Study Details
SCCS (n=8)									
Dorajoo, 2023[292]	Singapore	2021 - 2022	≥ 12 years	Seizure	Dose 1 =223	mRNA	Adjusted RR (95% CI); p value	0.88 (0.77 to 1.01); 0.076	Case ascertainment= BC Risk period = 0-42 days Number of doses= dose 1: 4,665,852 Vaccines: BNT162b2 or mRNA-1273
					Dose 2 =203			0.83 (0.72 to 0.96); 0.01	
					Booster =166			0.70 (0.60, 0.82); <0.01	
Yamin, 2023[293]	Israel	2021 - 2022	-	Seizure	1 st monovalent booster =63	BNT162b 2	Risk difference for events per 100,000 people (95% CI)	2.2 (0.4 to 4.1)	Case ascertainment= ICD-9 Risk period = 28 days Vaccinated n = 1,073,110
					2 nd monovalent booster =21			-0.5 (-3.8 to 2.8)	

					Bivalent booster =7			1.6 (−4.1 to 7.3)	
Takeuchi, 2022[294]	Japan	2020 - 2021	≥18 years	Seizure	Dose 1 =3	BNT162b 2 or mRNA-1273	Within-subject IRRs (95% CI) with first dose vs control period	1.11 (0.25, 4.83)	Case ascertainment= ICD-10 Risk period = 21 days Vaccinated n = 1 st dose: 136,667 2 nd dose: 127,322
					Dose 2 =2			1.22 (0.27, 5.64)	
Ab Rahman, 2022[295]	Malaysia	2021 and 2022	>18 years	Seizure	Dose 1 =116	BNT162b 2	IRR (95% CI) in 21-day risk period	1.15 (0.94, 1.42)	Case ascertainment: ICD-10 Risk period = 1- 21 days Number of doses: BNT162b2= 15,387,585 CoronoVac= 17,030,243 ChAdOx1= 2,744,507
					Dose 2 =111			1.39 (1.12, 1.72)	
					Dose 1 =83	CoronoVa c		1.12 (0.86, 1.47)	
					Dose 2 =70			1.17 (0.87, 1.57)	
					Dose 1 =19	ChAdOx1		1.55 (0.88, 2.75)	
					Dose 2 =2			0.85 (0.18, 3.94)	
Copland [#] , 2024[296]	UK	2020 - 2022	5-11 years	Epilepsy	61	BNT162b 2	IRR (95% CI) for dose 1	1.00 (0.76, 1.33)	Risk period = 1-42 days [#] Additional data in the paper
			12-17 years		215	BNT162b 2		1.02(0.88, 1.18)	
					15	ChAdOX1		1.93 (1.10, 3.39)	
Fang, 2022[297]	China	2021 - 2022	Median (IQR): 20.0 years (10, 35)	Seizure	108	BBIBP-CorV, CoronaVa c	Adjusted IR, (95% CI) p-value, one month versus baseline	Dose 1: 0.19 (0.11-0.34), p<0.001	Vaccinated n = 859
								Dose 2: 0.15 (0.08-30), p<0.001	
Wan, 2022[298]	China	2021 - 2022	-	Seizure	Dose 1 =15	BNT162b 2	IRR (95% CI) [#] ~	1.39 (0.75–2.58)	Case ascertainment= ICD-9-CM

					Dose 2 =11			1.36 (0.72–2.57)	Risk period = ~1-6 days Number of doses = BNT162b2: 1393, CoronaVac= 1230 # Additional data in the paper
					Dose 1 =6	CoronaVa c		1.19 (0.50–2.83)	
					Dose 2 =3			0.71 (0.22–2.30)	
Wan, 2022[299]	China	2021 - 2022	Mean (SD): 70.4 years (8.1)	Generalize d convulsive seizure	Dose 1 =11	CoronaVa c	IRR (95% CI)	1.20 (95% CI: 0.63- 2.27)	Case ascertainment= ICD-9-CM Number of doses = 1,229,423
					Dose 2 =5			0.68 (95% CI: 0.26- 1.76)	
					Dose 3 =1			0.60 (95% CI: 0.12- 3.07)	
Cohort studies (n=6)									
Hu, 2024[300]	USA	2019 - 2020	6 months - 17 years	Seizure	72	BNT162b 2, mRNA- 1273, or NVX- CoV2373	Calculated rate per 100,000	1.76	Vaccinated n = 4,102,016
Kenigsberg, 2023[301]	USA	2020 - 2022	≥ 5 years	Seizure	Dose 1 =210	BNT162b 2, mRNA- 127	Rate per 10,000 persons	0.26	Case ascertainment= ICD-10 Vaccinated n = 7,961,741
					Dose 2 =411			0.53	
Takeuchi, 2022[294]	Japan	2020 - 2021	-	Seizure	Dose 1 =3	BNT162b 2 or mRNA- 1273	Crude IRRs (95% CI) first dose vs control period	1.13 (0.35, 3.70)	Case ascertainment= ICD-10 Risk period = 21 days Vaccinated n = 1 st dose: 136,667, 2 nd dose: 127,322
					Dose 2 =2			0.82 (0.20, 3.42)	
Koh, 2021[302]	Singapore	2020 - 2021	Median: 59 years	Seizure	31	BNT162b 2	Calculated rate per 100,000	2.36	Case ascertainment= BC Risk period = 10 (0-38) Vaccinated n: 1,398,074
					2	mRNA- 1273			

Wong, 2022[303]	China	2021	18+ years	Generalized convulsive seizure	Dose 1 =57	BNT162b2	Cumulative incidence /100,000 doses	4.36	Case ascertainment= ICD-9-CM Vaccinated n = BNT162b2: Dose 1: 1,308,820, Dose 2: 1,116,677 CoronaVac: Dose 1: 955,859, Dose 2: 821,560
					Dose 2 =44			3.94	
					Dose 1 =42	CoronaVac		4.39	
					Dose 2 =22			2.68	
DeSilva, 2023[304]	USA	2020 – 2022	16-49 years	Generalized convulsive seizure	4	BioNTech or Moderna	Adjusted rate ratio (95% CI) compared to unvaccinated	3.45 (0.59–20.29)	Risk period = 1-42 day Vaccinated n = 40,208
Case Control studies (n=1)									
Barda, 2021[305]	Israel	2020 - 2021	27-53 years	Seizure	36	BNT162b2	Risk Ratio (95% CI), compared to unvaccinated	0.99 (0.62, 1.64)	Case ascertainment: ICD-10 and short free-text phrases that accompany diagnoses Risk period = 42 days Vaccinated n = 913,091
Pharmacovigilance Studies (n=8)									
Avasarala, 2022[306]	USA	2020 - 2021	-	Seizure	1,408	COVID-19	Incidence rate per 100,000 per year	3.191	Number of doses = 277,209,338
Yan, 2022[307]	USA	2010 - 2021	-	Focal dyscognitive seizure	693	BNT162b2	Reporting odds ratio (95% CI), compared to all other vaccines	1.12 (1.03, 1.21)	Vaccinated n: BNT162b2= 445,926, Ad26 COV2.S= 167,457
				Seizure	368	Ad26 COV2.S		1.61 (1.44, 1.78)	
Liu, 2024[308]	USA	2021 - 2023	-	Seizure	695	Pfizer/BioNTech, Moderna, Jassen, Novavax	Reported odds ratio (ROR) compared with the non-COVID-	0.59 (0.52 - 0.67)	Case ascertainment= MedDRA Risk period = 1 (1-2) Number of doses = 31,987,541

					691	Pfizer/Bio NTech, Moderna	19 vaccines (95% CI)	0.60 (0.53 - 0.68)	
					2	Jassen		0.10 (0.03 - 0.33)	
					2	Novavax		8.94 (2.30 - 34.9)	
Gallo, 2022[309]	Australia	2021 - 2022	-	Seizure	Dose 1 =4	ChAdOX1	Approximate rate per 100,000 doses	58.9	Case ascertainment= MedDRA
					Dose 1 =12	mRNA-1273		110.76	
					Dose 2 =1			9.52	
					Dose 3 =2			6.65	
					Dose 1 =2	BNT162b2		122.8	
					Dose 2= 1			4.52	
					Dose 3= 1			60.44	
Núñez, 2022[310]	Mexico	2020 - 2021	Median (IQR): 36 years (25-49)	Seizures including Status epilepticus	21	ChAdOx1	Seizures per million doses (95% CI)	0.55 (0.36–0.83)	Risk period = 19 (0.16–24) Number of doses: ChAdOx1= 38,516,372 Ad5-nCoV= 2,979,697 mRNA-1273= 2,318,057 BNT162b2=16,646,623 CoronaVac=14,532,954 rAd26-rAd5= 5,812,864
					3	Ad5-nCoV		1.01 (0.34–2.96)	
					4	mRNA-1273		1.73 (0.67–4.44)	
					17	BNT162b2		1.02 (0.64–1.64)	
					4	CoronaVac		0.28 (0.11–0.71)	
					4	rAd26-rAd5		0.69 (0.27–1.77)	
Frontera, 2022[311]	USA	2021	Median (IQR): 50 years (35-64)	Seizure	905	BNT162b2	Observed/expected ratio (95% CI)	0.633 (0.59-0.68)	Vaccinated n: BNT162b2= 90,063,644 mRNA-1273= 72,705,161 AD26.COV2.S= 11,465,768 Number of doses: BNT162b2= 166,981,930 mRNA-1273= 128,084,622
					680	mRNA-1273		0.59 (0.55-0.64)	
					340	AD26.CO V2. S		1.87 (1.68-2.08)	

									AD26.COVS.S= 11,606,202
Urdaneta, 2024[312]	Multiple	2020 - 2022	<2 - ≥75 years	Generaliz ed convulsiv e seizure	-	mRNA- 1273	Observed-to- expected ratio	0.22 (.21–.22)	Case ascertainment= MedDRA Risk period = 21 days Number of doses = 772,908,958
Klein, 2021[313]	USA	2020 - 2021	Mean: 49 years	Seizure	-	BNT162b 2, mRNA- 1273	Excess cases in risk interval per million doses (95% CI)	0.9 (–4.8, 5.6)	Risk period = 21 days Vaccinated n = 10.1 million
Cross-sectional Studies (n=2)									
Najjar, 2023[314]	Syria	2022	-	Seizure	1	ChAdOx1	Calculated rate per 100,000	181	Vaccinated n = 552
Zare, 2023[315]	Iran	2021	Median (IQR): 39 (20) years	Convulsion	40	AstraZene ca	Adjusted hazard ratio [(95% CI) p- value] compared to Sinopharm	0.30 (0.17-0.52) p<0.001	Vaccinated n: 10,033 (AstraZeneca= 4,478, Sinopharm= 5,555)

TABLE 3.5 Studies reporting on risk of Seizure after vaccination with Covid-19 containing vaccines, in persons with epilepsy, by study type

Author, year	Location	Study Years	Age Group	Type of seizures	Number of Seizure cases	Specific Vaccine	Risk Estimate	Risk estimate value	Relevant Additional Study Details
Cohort studies (n=7)									
Fang, 2023[316]	China	2021	10-80 years	Generalize d convulsive seizure increase	48	Sinophar m or Sinovac	Calculated rate per 100,000	11,794	Risk period = 14 days Vaccinated n = 407

Wang, 2023[317]	China	2021 - 2022	Media (IQR): 8.5 years (7, 11)	Seizure increase	24	COVID-19	Calculated rate per 100,000	10,714	Vaccinated n = 224
Martinez-Fernandez, 2022[318]	Spain	2021	-	Increase >50% seizure frequency	15~	COVID-19	Calculated rate per 100,000	3,589	Vaccinated n = 418
Romozzi, 2022[319]	Italy	2021	Mean (SD): 47.46 years (19.04)	Increase in seizure frequency	25	COVID-19	Calculated rate per 100,000	7,646	Vaccinated n = 327
Leung, 2024[320]	China	2021	≥18 years	Change in seizure frequency	19	BNT162b 2 or CoronaVac	Calculated rate per 100,000	3,242	Vaccinated n = 586
Huang, 2022[321]	China	2021 - 2022	Median (IQR): 27 years (13)	Seizure worsening	14	Sinopham & CoronaVac	Calculated rate per 100,000	17,721	Case ascertainment= ILAE 2010 & 2017 Vaccinated n = 79
Nonaka, 2023[322]	Japan	2021 - 2022	≥ 14 years	Definite seizure worsening	16	BNT162b 2, mRNA-1273, ChAdOx1 nCoV-19	Calculated rate per 100,000	5,674	Vaccinated n = 282
Cross-sectional Studies (n=9)									
Massoud, 2021[323]	Kuwait	2020 - 2021	-	Seizure worsening	Dose 1 =1	BNT162b 2	Relative risk, compared to no worsening	1.027 (0.891-1.183)	Vaccinated n = 82
					Dose 2 =2			1.019 (0.928-1.119)	
					Dose 1 =2	ChAdOx1 nCoV-19		1.026 (0.929-1.134)	
Zheng, 2024[324]	China	2021	-	Epileptic attack	3	COVID-19	Calculated rate per 100,000	515.5	Vaccinated n = 194

Delil, 2024[325]	Turkiye	2021	Mean (SD): 33.79 years (12.35)	Focal seizure increase	2	Sinovac	Calculated rate per 100,000	3,571	Vaccinated n: Sinovac= 56 Pfizer/BioNTech= 262
				Focal seizure increase	12	Pfizer/Bio NTech		45,802	
				Generalized seizure increase	5			19,084	
Ortiz-de la Rosa, 2023[326]	Columbia	2021 - 2022	3-17 years	Higher seizure frequency	3	Sinovac, Pfizer, Moderna, CoronaVac	Calculated rate per 100,000	2,970	Vaccinated n = 101
Pawlicka, 2023[327]	Poland	2022	Median (IQR): 36 years (29-42)	Seizure worsening	2	Pfizer/Bio NTech, Oxford/AstraZeneca, Moderna, Janssen	Calculated rate per 100,000	11,976	Vaccinated n = 167
Wang, 2023[328]	China	2021 - 2022	Median (IQR): 28 years (23-38)	Seizure aggravation	16	COVID-19	Calculated rate per 100,000	75,117	Vaccinated n = 213
Von Wrede, 2021*[329]	Germany	2021	20-89 years	New focal seizure	1	COVID-19	Calculated rate per 100,000	1,851	Vaccinated n = 54
Öcek, 2023[330]	Turkey	2022	Mean (SD): 42.62 (14.74)	Increase in monthly seizure frequency	51	COVID-19	Mean (SD) frequency, per year; p-value for frequency before and after vaccination	3.20 (5.82); <0.001	Vaccinated n: 307

Pang, 2023[331]	Australia	2021 - 2022	16-84 years	Seizure exacerbation	13	COVID-19	Calculated rate per 100,000	2,453	Vaccinated n = 530
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Table 3.6 Studies reporting on risk of Seizure after vaccination with Influenza containing vaccines, by study type

Author, year	Location	Study Years	Age Group	Type of seizures	Number of Seizure cases	Specific Vaccine	Risk Estimate	Risk estimate value	Relevant Additional Study Details
SCCS (n=12)									
Duffy, 2016[332]	USA	2006 - 2011	-	Febrile seizure	44	IIV3	Adjusted IRR (95% CI)	0.46 (0.21, 1.02)	Case ascertainment= ICD-9 Risk period = 0-1 days
Yih, 2016[333]	USA	2013 - 2014	6-23 months	Seizure	5	IIV	Relative risk-risk interval vs control interval	0.45	Case ascertainment= ICD-9 Risk period = 0-1 days Number of doses = 349,628
Li, 2016[334]	USA	2010 - 2011	6-59 months	Febrile seizure	3802	Influenza	RR (95% CI)	4.16 (3.30, 5.24)	-
Tse, 2012[335]	USA	2010 - 2011	6 - 59 months	Febrile seizure	8	TIV	IRR (95% CI) adjusted for concomitant PCV13	2.4 (1.2, 4.7)	Case ascertainment= BC Risk period = 0-1 days Vaccinated n = 206,174
Stowe, 2011[336]	UK	2000 - 2010	-	Convulsion	19	TIV	IRR (95% CI)	1.00 (0.64, 1.59)	Case ascertainment= ICD-10 Risk period = 0-7 days Vaccinated n = 2,366 Number of doses: TIV = 2,858 H1N1 - Pandemrix dose 1=1,895, dose 2=227
					Dose 1 =14	H1N1 - Pandemrix		0.89 (0.53, 1.52)	
					Dose 2 =3			1.96 (0.62, 6.14)	

Baker, 2020[337]	USA	2013 - 2015	6 - 23 years	Febrile seizure	29	Fluzone or Fluzone Quadrivalent	IRR (95% CI), adjusted for age and calendar time	0.94 (0.63, 1.42)	Case ascertainment= Current Procedural Terminology (CPT), Healthcare Common Procedure Coding System (HCPCS), National Drug Codes (NDC), and ICD-9-CM Risk period = 0-1 days Vaccinated n= 355,486
Wang, 2018[253]	USA	1995 - 2015	11 - 23 months	Seizure	27	Influenza	IRR (95% CI); p-value	1.3 (0.9, 1.9); 0.239	Case ascertainment= ICD-9 Risk period = 7-10 days vs control window (14-56 days)
Li, 2016[338]	USA	2013 - 2014	-	Febrile seizure	3	IIV3 for both seasons	RR (95% CI)	1.5 (0.39, 5.80)	Case ascertainment= ICD-9 CM Risk period = 0-1 days Number of doses: IIV3= 3,786,868 (in 2013-2014) & 3,429,406 (in 2014-2015) IIV4= 251,271 (in 2014-2015)
					1	IIV4 for 2014-2015		1.2 (0.12, 11.20)	
Bakken, 2015[339]	Norway	2009	-	Febrile seizure	0 day =3	Pandemrix	IRR (95 % CI)	1.39 (0.46, 4.35)	Case ascertainment= ICD-10 Risk period = 0-7 days Vaccinated n = 113,068 Number of doses = 113,068
					1-3 days =13			2.00 (1.15, 3.51)	
					4-7 days =7			0.81 (0.38, 1.73)	
Kawai, 2015[340]	USA	2010 - 2011	-	Febrile seizure	13	TIV	IRR (95 % CI)*	1.36 (0.78-2.39)	Case ascertainment= Seizure and fever documentation Risk period = 0-1 *Adjusted for age, seasonality, PCV and DTaP

Kawai, 2014[341]	USA	2012 - 2013	6-23 months	Seizure	4	IIV	Relative risk, (95%CI)*	1.1 (0.4, 3.3)	Case ascertainment= ICD-9 Risk period = 0-1-day Vaccinated n = 117,869 Number of doses = 117,869 *Compared to 14-20 days post-vaccination (control interval) in the same individual (SCRI)
			24-59 months		6			2.1 (0.8, 5.8)	
			5-17 years		5			1.6 (0.6, 4.6)	
Arnheim-Dahlström, 2012[342]	Sweden	2009 - 2010	Mean (SD): 41 (25)	Seizure	40	Pandemrix	Relative incidence (95% CI)*	0.95 (0.69, 1.32)	Risk period = 1-7 day *Compared with control period (day 90-31 before vaccination)
					5			0.99 (0.39, 2.53)	
Cohort studies (n=10)									
Yih, 2016[333]	USA	2013 - 2014	6 - 23 months	Seizure	8	IIV	Relative risk - Current vs Expected	0.57	Case ascertainment= ICD-9 Risk period = 0-1 days Number of doses = 349,628
McCarthy, 2013[343]	USA	2005 - 2011	6-59 months	Seizure	2	H1N1	IRR (95% CI)	0.58 (0.06, 2.62)	Risk period = 0-1 days Number of doses: H1N1 vaccine= 133, 872, TIV vaccine= 189,980 (2009-2010 season), 185,144 (2010 - 2011 season)
					2009 - 2010 =8	TIV		1.40 (0.53, 3.32)	
					2010 -2011 =5			0.88 (0.26, 2.40)	
Armstrong, 2011[344]	Australia	2010	0 - 5 years	Febrile seizure	35	Fluvax	Rate/1000 TIV doses (95% CI)	3.3 (2.4, 4.6)	Case ascertainment= BC Number of doses: Fluvax= 10,769, Fluvax Junior= 3,327
					27	Fluvax Junior		8.1 (5.6, 11.8)	
Layton, 2020[345]	USA	2010 - 2016	Mean (SD): 74.7 (7.0)	Seizure	97	High dose vaccine	SMR weighted HR* (95% CI)	1.3 (0.81-1.32)	Number of doses = 457,914 SDV, 36,611 HDV * Compared to Standard dose

Hall, 2018[346]	UK	2012 - 2015	Mean (SD): 60.5 years (16.5)	Convulsion	1	TIVc	Observed to expected ratio (95% CI)	3.3 (0.3, 31.7)	Case ascertainment= BC Risk period = 8-30 days
Baxter, 2017[347]	USA	2013 - 2014	2 - 49 years	Seizure	5	IIV	Event incidence rates per 1,000 person-months	0.76	Case ascertainment= ICD-9 Risk period = 0-3 days Number of doses: 57,185
Nordin, 2013[348]	USA	2002 - 2009	Mean (SD): 30.8 years (5.6)	Seizure	1	TIV	Rate per 10,000 vaccines	0.1	Vaccinated n = 75,906
Lambert, 2013[349]	Australia	2009 - 2010	6 months- 3 years	Febrile seizure	1	TIV	Calculated rate per 100,000	140.9	Vaccinated n = 710
Nazareth, 2013[350]	UK	2009	Mean (SD): 54.7 years (0.22)	Non-febrile convulsion	7	H1N1 Pandemrix	Standardised incidence ratio (95% CI)	2.65 (1.14 to 5.22)	Case ascertainment= BC Vaccinated n = 9,143
				Febrile seizure	1				
Moro, 2013[351]	Italy	2009 - 2010	-	Convulsion	4	IIV	OR (95% CI), p-value vs unvaccinated subjects	1.3 (0.3, 6.0); 0.7	Vaccinated n = 103,642
Case Control studies (n=1)									
Goodman, 2006[352]	USA	2002 - 2003	-	Seizure	Dose 1	TIV	Hazard Ratio (95% CI)	1.17 (0.36, 3.86)	Risk period = 0-42 days Vaccinated n = 3,697
					Dose 2			1.12 (0.36, 3.48)	
				Epilepsy	Dose 1			1.026 (0.19, 5.56)	
					Dose 2			1.22 (0.3, 5.02)	
Cross-sectional studies (n=1)									
Wood, 2014[353]	Australia	2013	Mean (SD): 3.6 years (2.4)	Febrile seizure	1	Influenza	Calculated rate per 100,000	117.4	Risk period = 1 Number of doses = 852

Pharmacovigilance Studies (n=9)									
Haber, 2015[354]	USA	2013 - 2014	-	Seizure	2013-2014 =3	LAIV4	Calculated rate per 100,000	0.024	Number of doses =12.7 million
Ropero-Álvarez, 2015[355]	Multiple	2009 - 2010	-	Febrile seizure	120	H1N1 pandemic	Calculated rate per 100,000	0.083	Case ascertainment= BC Number of doses = 144,621,593
				Seizure	61			0.042	
Banzhoff, 2011[356]	Multiple	2009 - 2010	Median: 44 years	Convulsion	60	IIV	Reporting rates per 100,000 doses	0.5	Case ascertainment= BC Number of doses = 12,000,000
Mayet, 2011[357]	France	2009 - 2010	18-56 years	Generalized convulsive seizure	1	A(H1N1) Pandemrix	Calculated rate per 100,000	2.04	Vaccinated n = 49,138
GattÅis, 2018[358]	Brazil	2013 - 2017	-	Febrile seizure	44	TIV	Calculated rate per 100,000	0.028	Number of doses = 158,735,729
Haber, 2016[359]	USA	2013 - 2015	-	Febrile seizure	4	IIV4	Calculated rate per 100,000	0.0057	Risk period = 12 hours (0, 12) Number of doses = 70 million
Haber, 2015[360]	USA	2005 - 2012	-	Febrile seizure	2	LAIV3	Calculated rate per 100,000	0.004	Risk period = 1 (0, 24) Number of doses = 50 million
				Generalized convulsive seizure	13			0.026	
Martin, 2013[361]	USA	2010 - 2011	-	Febrile seizure	41	IIV	Adjusted relative reporting ratio (95% CI)	3.84	Case ascertainment= Clinical review Vaccinated n = 2,095
Williams, 2011[362]	USA	2009 - 2010	Mean: 36.14 years	Seizure	5	TIV	Calculated rate per 100,000	0.0048	Case ascertainment= Modified WHO criteria Number of doses = 105,211,620
Other Studies (n=2)									

Petousis-Harris, 2012[363]	New Zealand	2010 - 2011	36 months	Febrile seizure	3	IIV3	Incidence Rate per 10,000 doses	35	Case ascertainment= BC Risk period = 0-1 day Number of doses = 865
Kelly, 2010[364]	Australia	2010	6 months - 4 years	Febrile seizure	55	Fluvax or Fluvax junior	Estimated risk (%) (Upper limit of 95% CI)	0.39% (0.51%)	Case ascertainment= BC Risk period = 0-24 Number of doses: Fluvax or Fluvax junior= >10,000

TABLE 3.7 Studies reporting on risk of Seizure after vaccination with HPV containing vaccines, by study type

Author, year	Location	Study Years	Age Group	Type of seizures	Number of Seizure cases	Specific Vaccine	Risk Estimate	Risk estimate value	Relevant Additional Study Details
Cohort studies (n=1)									
Gee, 2011[239]	USA	2006 - 2009	9 - 17 years	Seizure	47	HPV4	Relative risks (95% CI), compared to expected rate	1.02	Case ascertainment= ICD-9 Risk period = 0-42 days Number of doses = 9-17 years: 351,706, 18-26 years: 150,603
			18 - 26 years		22			1.13	
Pharmacovigilance Studies (n=6)									
Hu, 2021[365]	China	2018 - 2020	-	Seizure	6	HPV4	Reporting rate per 10,000 doses	0.07	Case ascertainment= ICD-10
Neha, 2020[366]	USA	2006 - 2017	-	Convulsion	763	HPV	ROR-1.96SE, versus all other events	2.01	-
				Seizure	124			2.655	
Donahue, 2019[367]	USA	2015 - 2017	9 - 17 years	Seizure	44	HPV9	RR, MaxSPRT	0.4	Case ascertainment= ICD-10-CM Risk period = 0-42 days Number of doses = 304,384

Mauro, 2019[368]	Brazil	2014 - 2016	9-29 years	Seizure	25	HPV4	Reporting rate per 100,000 doses	0.7	Case ascertainment= BC
Harris, 2014[369]	Canada	2007 - 2011	-	Seizure	2	HPV4	Rate per 100,000 doses	0.3	-
Crawford, 2011[370]	Australia	2007 - 2009	8-26 years	Syncopal seizure	31	HPV4	Reporting rate per 100,000 doses	2.6	Number of doses = 1.2 million

TABLE 3.8 Studies reporting on risk of Seizure after vaccination with Pneumococcal containing vaccines, by study type

Author, year	Location	Study Years	Age Group	Type of seizures	Number of Seizure cases	Specific Vaccine	Risk Estimate	Risk estimate value	Relevant Additional Study Details
SCCS (n=7)									
Duffy, 2016[332]	USA	2006 - 2011	-	Febrile seizure	22	PCV7/PCV 13	Adjusted IRR (95% CI); p-value	1.81 (0.97, 3.39)	Case ascertainment= ICD-9 Risk period = 0-1 days
Hambidge, 2014[241]	USA	2004 - 2010	38 - 730 days	Febrile seizure	Age at receipt 38-92 days =9	Pneumococcal	IRR (95% CI)	1.12 (0.56, 2.24)	Case ascertainment= ICD-9 Risk period = 0-2 days
					93-730 days =1			1.33 (0.16, 10.84)	
Tse, 2012[335]	USA	2010 - 2011	6 - 59 months	Febrile seizure	8	PCV13	IRR (95% CI), adjusted for concomitant TIV	2.5 (1.3, 4.7)	Case ascertainment= BC, ICD-9 Risk period = 0-1 days
Kim, 2024[371]	South Korea	2018 - 2022	Mean (SD): 9.8 weeks (3.1)	Febrile seizure	116	PCV13	IRR (95% CI), adjusted for age	0.95 (0.74, 1.23)	Case ascertainment= ICD-10 Vaccinated n = 8,661

Baker, 2020[337]	USA	2013 - 2015	6 - 23 years	Febrile seizure	35	PCV13	IRR (95% CI), adjusted for age and calendar time	1.54 (1.04, 2.28)	Case ascertainment= Current Procedural Terminology (CPT), Healthcare Common Procedure Coding System (HCPCS), National Drug Codes (NDC), and ICD-9-CM Risk period = 0-1 days Vaccinated n= 581,868
Wang, 2018[253]	USA	1995 - 2015	11 - 23 months	Seizure	6	PCV7	IRR (95% CI); p-value	2.1 (0.9, 5.0); 0.097	Case ascertainment= ICD-9 Risk period = 7-10 days vs control window (14-56 days)
Kawai, 2015[340]	USA	2010 - 2011	-	Febrile seizure	10	PCV13	aIRR (95% CI)*	1.61 (0.91 - 2.82)	Case ascertainment= Seizure and fever documentation Risk period = 0-1 *Adjusted for age, seasonality, TIV and DTaP
Cohort studies (n=1)									
Tseng, 2013[372]	USA	2010 - 2012	1<4 months	Febrile seizure	12	PCV13	RR vs PVC7	1.29	Case ascertainment= ICD-9-CM Number of doses = 599,229
			4<6 months		9			0.91	
			6<12 months		12			1.04	
			12-24 months		10			0.99	
Pharmacovigilance Studies (n=3)									
Wang, 2024[373]	China	2020 - 2023	-	Febrile seizure	1	PCV13	Reporting rate per 10,000 doses	0.02	Risk period = 9
Autret-Leca, 2011[374]	France	2004 - 2007	1-108 months	Febrile seizure	13	PCV7	Incidence/100,000 doses (95% CI) for all cases	0.34 (0.24, 0.46)	Number of doses = 7,836,151
				Afebrile or unspecif	14				

				ied Seizures					
Hu, 2022[375]	China	2017 - 2020	-	Febrile seizure	5	PCV13	Reporting rate per 10,000 doses	0.03	-
Other Studies (n=1)									
Artama, 2018[376]	Finland	2010 - 2014	-	Febrile seizure	-	PCV10	IRR (95% CI) for target cohort - all first-only diagnosis	0.99 (0.93, 1.05)	Case ascertainment= ICD-10 Ecologic before–after study

TABLE 3.9 Studies reporting on risk of Seizure after vaccination with Diphtheria, Tetanus or Pertussis containing vaccines, by study type

Author, year	Location	Study Years	Age Group	Type of seizures	Number of Seizure Cases	Specific Vaccine	Risk Estimate	Risk estimate value	Relevant Additional Study Details
SCCS (n=12)									
Duffy, 2016[332]	USA	2006 - 2011	-	Febrile seizure	22	DTaP	Adjusted IRR (95% CI); p-value	1.04 (0.47, 2.28)	Case ascertainment= ICD-9 Risk period = 0-1 days
Hambidge, 2014[241]	USA	2004 - 2010	-	Febrile seizure	Age at receipt 38-92 days =10	DTaP	IRR (95% CI)	1.26 (0.65, 2.45)	Case ascertainment= ICD-9 Risk period= 0-2 days
					93-730 days =1			1.56 (0.19, 12.92)	
Kelly, 2010[364]	UK	2003 - 2006	-	Seizure	0 day =3	DTaP-IPV/Hib	Relative Incidence (95% CI)	2.05 (0.65, 6.46)	Case ascertainment= READ or OXMIS codes from UK General Practice Research Database (GPRD) Risk period = 0-7 days Number of doses: DTaP-IPV/Hib= 177,600, DTwP/Hib= 162,600
					1-3 days =2			0.45 (0.11, 1.83)	
					4-7 days =2			0.34 (0.08, 1.38)	
					0 day =7	DTwP/Hib		4.14 (1.92, 8.92)	
					1-3 days =7			1.37 (0.63, 2.95)	
					4-7 days =7			1.02 (0.47, 2.20)	
	USA		-	Seizure	Dose 1 =28	DTaP		1.02 (0.70, 1.50)	Case ascertainment= ICD-9-CM

Huang, 2010[377]		1997 - 2006			Dose 2 =20 Dose 3 =24 Dose 4 =40		Adjusted IRR (95% CI)	0.75 (0.48, 1.17) 0.90 (0.60, 1.35) 0.95 (0.69, 1.29)	Number of doses = dose 1: 388,335
Gold, 2010[249]	Australia	1997 - 2002	0-7 years	Febrile seizure	323	DTP	IRR (95% CI), p-value	Risk interval: 0 to 3 days=0.59 (0.24, 1.45), 0.25 4 to 7 days=0.94 (0.46, 1.91), 0.86 8 to 14 days=0.93 (0.54, 1.62), 0.80	Case ascertainment= ICD Vaccinated n = 125,560
Dodd, 2020[378]	Multiple	1990 - 2015	0-6 years	Febrile seizure	-	aP	IRRs (95% CI)	SSI database: 0.24 (0.18, 0.31) BIFAP database: 2.23 (0.77, 6.47) SIDIAP database: 0.40 (0.13, 1.27) RCGP RSC database: 1.93 (0.66, 5.65) THIN database: 0.31 (0.10, 0.98)	Case ascertainment= BC Risk period = 0-3 days Vaccinated n = 2.6 million
Weibel, 2020[379]	Multiple Denmark UK Spain	1990 - 2015	-	Febrile and afebrile seizures	- 137 453 87 30 26	wP and aP	Incidence rate per 1000 PY (95% CI)	8.9 (8.3; 9.5) AUH database: 2.7 (1.8, 4) SSI database: 7.2 (6, 8.6) THIN database: 5 (3.3, 7.1) RCGP RSC database: 3 (2.4, 3.7) BIFAP database: 4 (0.1, 22.1)	Case ascertainment= ICD9, ICD10, READ-CTV3, READ-v2, ICPC Risk period = 0-72 hours Vaccinated n = 5,048,286 total

					126			SIDIAP database: 25 (21, 29.5)	
	Italy				1			PEDIANET database: 15.8 (14.4, 17.3)	
Wang, 2018[253]	USA	1995 - 2015	11 - 23 months	Seizure	14	DTaP	IRR (95% CI); p-value	1.3 (0.8, 2.3); 0.307	Case ascertainment= ICD-9 Risk period = 7-10 days vs control window (14-56 days)
Hawken, 2012[380]	Canada	1994 - 1996	-	Convulsion	10	wP	RIR (95% CI) vs Acellular pertussis at 2-months	8.80 (0.99, 78.11)	Case ascertainment= ICD-9 Risk period = 0-3 days Vaccinated n: 297,043
Xu, 2023[381]	China	2016 - 2019	Median (IQR): 516 days (415-615)	Febrile seizure	Dose 1 =7	DTaP containing vaccines	RI (95% CI) within 0-7 days after dose	0.63 (0.20, 1.97)	Case ascertainment= ICD-10 Risk period = 0-7 days Vaccinated n = 3,394
					Dose 2= 4			0.69 (0.31, 1.56)	
					Dose 3= 8			0.60 (0.28, 1.28)	
					Dose 4= 71			1.16 (0.92, 1.47)	
Zerbo, 2022[255]	USA	1995 - 2012	-	Febrile seizure	39	DTaP	Rate ratio (95% CI) vs control interval (14-28 days)	2.36 (1.58 – 3.52)	Case ascertainment= ICD-9-CM and ICD-10-CM Risk period = 0-3 days Vaccinated n = 1,427,265
Sun, 2012[382]	Denmark	2003 - 2009	-	Febrile seizure	Dose 1 =17	DTaP-IPV-Hib	Adjusted relative incidence (95% CI)	1.65 (0.94-2.90)	Case ascertainment= ICD-10 Risk period = 0-7 days Number of doses = Dose 1: 329,521, Dose 2: 339,288, Dose 3: 320,049
					Dose 2 =32			1.32 (0.90-1.92)	
					Dose 3 =201			0.99 (0.86-1.15)	
Cohort studies (n=14)									
Izadi, 2023[383]	Iran	2019	2-10 months	Febrile seizure	1	DTP-HB-Hib	Calculated rate per 100,000 individuals	89.37	Case ascertainment= WHO Risk period = 3 days Vaccinated n = 1,119

Layton, 2018[384]	USA	2006 - 2014	Mean (SD): 11.2 weeks (5.0)	Seizure	Dose 1 =498	DTaP + RV	Adjusted Hazard ratio (95% CI)	0.83 (0.65, 1.07)	Vaccinated n = 833,657
					Dose 2 =346			1.14 (0.84, 1.56)	
					Dose 3 =267			0.68 (0.51, 0.90)	
				Febrile seizure	Dose 1 =72			1.22 (0.62, 2.38)	
					Dose 2 =88			1.36 (0.75, 2.49)	
					Dose 3 =122			0.67 (0.43, 1.02)	
Tartof, 2014[259]	USA	2003 - 2011	6 months - 3 years	Febrile seizure	-	DTaP	RR (95% CI) compared to non-vaccine associated (NVA) person-time	1.4 (1.2, 1.6)	Case ascertainment= ICD-9 Vaccinated n = 265,275
Huang, 2010[377]	USA	1997 - 2006	-	Seizure	Dose 1 =28	DTaP	Adjusted incidence rate ratio (95% CI)	0.99 (0.68, 1.44)	Case ascertainment= ICD-9-CM Number of doses = Dose 1: 388,335
					Dose 2 =20			0.72 (0.46, 1.12)	
					Dose 3 =24			0.87 (0.58, 1.30)	
					Dose 4 =40			0.89 (0.65, 1.22)	
Yih, 2009[385]	USA	2005 - 2008	10 - 64 years	Seizure	34	DTaP	Relative risk	0.84	Case ascertainment= ICD-9 Risk period = 0-7 days Number of doses = 624,813
Davis, 2005[386]	USA	1995 - 2000	-	Seizure	40	DTPw	Calculated rate per 100,000 doses	18.8	Case ascertainment= ICD-9-CM Number of doses: DTPw vaccine= 212,634 DTPa vaccine= 63,367
					11	DTPa		17.4	
Jackson, 2002[387]	USA	1997 - 2000	0 - 7 years	Febrile seizure	Dose 2 =1	DTaP	Rate per 10,000 doses	1.4	Case ascertainment= Internal definitions - clinical criteria Risk period = 0-7 days Number of doses = 76,133
					Dose 3 =1			1.4	
					Dose 4 =4			2.4	
Barlow, 2001[266]	USA	1991 - 1993	-	Febrile seizure	Day 0 =5	DTP	RR compared to non-vaccinated (95% CI)	5.70 (1.98, 16.42)	Case ascertainment= ICD-9 Number of doses = 340,386
					1-7 days =9			1.16 (0.53, 2.56)	
					8-14 days =10			1.12 (0.53, 2.33)	
					15-30 days =18			1.43 (0.82, 2.50)	
					0-7 days =4			1.94 (0.62, 6.12)	
					8-14 days =2			0.77 (0.16, 3.67)	

				Nonfebrile seizures	15-30 days =4			1.05 (0.32, 3.37)	
Huang, 2020[388]	China	2012 - 2017	0-24 years	Seizure	2	DTaP	Incidence rate per 100,000 doses	0.6 (0.2–1.3)	Case ascertainment= ICD-10 Risk period = 7 days Number of doses = DTaP: 365,707, DTaP-IPV-Hib: 53,573
					1	DTaP-IPV-Hib		1.9 (-1.8–5.3)	
Jackson, 2018[389]	USA	2005 - 2015	-	Seizure	-	Tdap	Adjusted RR, vs Td	0.8	Vaccinated n: Tdap= 61,394, Td= 7,521
Hansen, 2016[390]	USA	2008 - 2010	Mean (SD): 2.0 months (1.2)	Seizure	4	DTaP-IPV/Hib	Calculated rate per 100,000 individuals	7.12	Risk period = 0-3 days Vaccinated n = 14,042
Nelson, 2013[391]	USA	2008 - 2011	-	Seizure	9	DTaP-IPV-Hib	Relative risk (95% CI) - observed vs expected	1.04	Number of doses = 72,651
Martins, 2007[392]	Brazil	2004	-	Convulsions	4	DTwP/Hib	Rate per 10,000 (95% CI)	1.9 (0.5, 4.9)	Vaccinated n = 20,925 Number of doses = 20,925
Kharbanda, 2016[393]	USA	2007 - 2013	14-49 years	Seizure	1	Tdap	Rate per 10,000	<1	Risk period = 0-3 days Vaccinated n = 53,885
Pharmacovigilance Studies (n=11)									
Sturkenboom, 2020[394]	Denmark	1990 - 2015	0-1 years	Febrile seizure	-	wP or aP	Incidence rate per 1000 person years*	AUH: 3.1 (3.1, 3.2)	Case ascertainment= BC * Additional data available
					-			SSI: 14.9 (14.8, 15.1)	
	Spain				-			BIFAP: 3.9 (3.7, 4)	
					-			SIDIAP: 4.5 (4.4, 4.6)	
	Italy				-			Val Padana: 5.6 (5.1, 6.1)	

					-			Tuscany: 4.8 (4.7, 5)	
	UK				-			THIN: 4.5 (4.4, 4.7)	
					-			RCGP: 5.1 (4.9, 5.3)	
Aagaard, 2011[279]	Denmark	1998 - 2007	-	Febrile seizure	-	DTaP-IPV-Hib	Reporting rates per 100,000 doses	0.95	Case ascertainment= MedDRA Vaccinated n = 1,685
Monteiro, 2010[395]	Brazil	2003 - 2004	Mean: 3.8 months	Convulsion	Dose 1 =455 Dose 2 =426 Dose 3 =203	DTwP-Hib	Incidence rates per 100,000 doses	7.2 7.0 3.2	Number of doses = 18,700,000
Zieliński, 2008[396]	Poland	2001 and 2005	≤ 5 years	Febrile seizure	108	DTwP	Relative risk (95% CI), vs DTaP	3.41 (1.50-7.76)	Number of doses: DTwP= 7,037,929 DTaP= 1,334,143
					6	DTaP	Relative risk (95% CI), vs children aged <2 years	0.19 (0.02-1.65)	
Kuno-Sakai, 2004[397]	Japan	1981 - 2003	-	Seizure	16	DTwP	Rate per 10 million	6.4	Case ascertainment= clinician-developed diagnostic criteria
				Febrile seizure	35			13.9	Number of doses: DTwP=
				Seizure	1	DTaP		0.2	25,100,000, DTaP= 40,300,000
				Febrile seizure	4			1	*Age at initiation: 3 months
LeSaux, 2003[281]	Canada	1995 - 2001	-	Febrile seizure	50	DTaP	Monthly Rate (1998-2001)	0.25	Case ascertainment= Investigator-developed definitions
				Seizure	28			0.19	
Pan, 2022[398]	China	2015 - 2020	-	Febrile seizure	13	DTaP-IPV-Hib	Calculated rate per 100,000 doses	0.45	Number of doses = 2,860,884
				Seizure	1			0.03	

Elas, 2021[399]	El Salvador	2019	-	Febrile seizure	24	DTaP-IPV-Hib-HBV	Rate per 100,000 doses	8.2	Case ascertainment= BC Number of doses = 355,824
Li, 2020[400]	China	2011 - 2017	-	Convulsion	3	DTaP-IPV/Hib	Rate for convulsions per 100,000 doses	0.6	Number of doses = 516,158
Chang, 2013[401]	USA	2005 - 2007	Median: 22 years	Seizure	9	Tdap	Rate per 100,000 dose	0.14	Case ascertainment= BC
Sato, 2018[402]	Brazil	2000 - 2013	-	Seizure	Dose 1 =2	DTPw, DTPw-Hib, DTPw-Hib-Hepatitis B	Rate per 10,000 doses	0.5	Number of doses = 42,082
					Dose 2 =7			1.7	
					Dose 3 =7			1.7	
					Booster dose = 9			2.3	
RCT Studies (n=2)									
Kerdpanich, 2008[403]	Multiple	2003 - 2005	-	Febrile seizure	5	DTPw-HBV/Hib-MenAC	Proportion of participants (95% CI)	0.126% (0.041-0.294)	Number of doses = 3,967
Tregnaghi, 2012[404]	Argentina	2006	-	Nonfebrile convulsion	1	DTaP-IPV-Hep B-PRP-T	Calculated proportion	0.44%	Vaccinated n = 231
Other Studies (n=2)									
David, 2008[405]*	Netherlands	2003 - 2007	-	Febrile seizure	2	wP combination	Proportion of participants (95% CI)	0.056% (0.007%, 0.2%)	Number of doses: wP-vaccine = 3,562 aP-vaccine = 4,317 aP without Pneumococcal vaccine= 2,775 * Survey
					1	aP combination		0.02% (0.001% - 0.1%)	

					1	aP without pneumococcal		0.01% (0.00, 0.06%)	
Khazaei, 2020[406]*	Iran	2015	-	Febrile seizure	186 287	DTP DTwP-HepB-Hib	Calculated rate per 100,000	4.38 6.8	Vaccinated n: DTP = 4,249,050, Pentavalent = 4,230,870 * Cross-sectional study

TABLE 3.10 Studies reporting on risk of Seizure after vaccination with Meningococcal vaccines, by study type

Author, year	Location	Study Years	Age Group	Type of seizures	Number of Seizure cases	Specific Vaccine	Risk Estimate	Risk estimate value	Relevant Additional Study Details
Cohort studies (n=2)									
Stehr-Green, 2008[407]	New Zealand	2004 - 2005	6 months - 2 years	Febrile seizure	Dose 1	Meningococcal B	RR (95% CI), compared to outside risk period	1.43 (0.71, 2.87)	Case ascertainment= BC Risk period = 7 days Number of doses = 63,000
					Dose 2			0.37 (0.09, 1.47)	
					Dose 3			0.20 (0.03, 1.42)	
Phan, 2019[408]	Vietnam	2016	-	Febrile seizure	1	MenACWY-D	Calculated rate per 100,000 individuals	446.4	Case ascertainment= MedDRA, International Conference on Harmonization E2A guideline Risk period = 7 days Vaccinated n = 224
Pharmacovigilance Studies (n=5)									
Levi, 2014[409]	Italy	2005 - 2012	-	Non febrile seizure	4	Meningococcal C	Calculated rate per 100,000 individuals	0.88	Number of doses = 451,570
				Unspecified convulsion	3			0.66	

Ouandaogo, 2012[410]	Burkina Faso	2010	1 - 29 years	Convulsion	32	MenAfriVac™	Attack Rate (95% CI)	29.76 (19.44, 40.07)	Case ascertainment= National Experts Committee (NEC) for causality assessment Vaccinated n = 107,493
Bentsi-Enchill, 2007[411]	Burkina Faso	2003	-	Seizure	2	Meningococcal	Calculated rate per 100,000 individuals	0.14	Case ascertainment= WHO guideline Number of doses = 1,469,013
Stefanizzi, 2022[412]	Italy	2018 - 2020	11-13 years	Seizure	1	Meningococcal B	Reporting rate per 10000 doses	2.3	Case ascertainment= WHO Number of doses = 43,061
Bryan, 2018[413]	UK	2015 - 2017	-	Seizures	-	Meningococcal B	Age-adjusted observed vs expected ratio (95% CI)	0.13 (0.10, 0.17)	-
RCT Studies (n=1)									
Vesikari, 2013[414]	Multiple	2008 - 2010	-	Febrile seizure	2	Meningococcal B	Calculated proportion	0.08%	Risk period = 24 hours Vaccinated n = 2481

Table 3.11 Studies reporting on risk of Seizure after vaccination with Malaria vaccines, by study type

Author, year	Location	Study Years	Age Group	Type of seizures	Number of Seizure cases	Specific Vaccine	Risk Estimate	Risk estimate value	Relevant Additional Study Details
SCCS (n=1)									
Guerra Mendoza, 2019[415]	Multiple	2009 - 2014	5-17 months	Febrile seizure	FS	Malaria RTS,S/AS01	SCCS Risk Ratio (95%CI)	4 doses: 3.8 (1.7–8.7) 3 doses plus 1 dose of control vaccine: 2.3 (0.8–6.0)	Case ascertainment= BC Risk period = 0-6 days

RCT Studies (n=8)									
Oneka, 2021[416]	Kenya	2017 - 2018	5-12 months	Febrile & afebrile seizure	25	Malaria	Proportion of participants (95% CI)	9.9%	Vaccinated n = 336
Agnandji, 2011[353]	Multiple	2009 - 2011	5-17 months	Generalized convulsive seizure	7	Malaria RTS,S/AS01	Incidence per 1,000 doses (95% CI)	1.04 (0.62 - 1.64)	Case ascertainment= BC Risk period = 7 days Vaccinated n = 5,949
Owusu-Agyei, 2009[417]	Ghana	2006 - 2008	Mean (SD): 10.7 months (3.5)	Febrile seizure	1	Malaria RTS,S/AS01E	Calculated proportion	1.11%	Case ascertainment= BC Risk period = 14 Vaccinated n = 90 Number of doses = Dose 1: 90
Chandramohan, 2021[418]	Multiple	2017	-	Febrile seizure	5	Malaria RTS,S/AS01E	Calculated proportion	0.11%	Risk period = 1 day Vaccinated n = 4,574
Guerra Mendoza, 2019[415]	Multiple	2009 - 2014	6-12 weeks	Febrile seizure	-	Malaria RTS,S/AS01	Incidence (95%CI)	0.2 (0.0–0.6)	Case ascertainment= BC Risk period = 0-7 days
			5-17 months					1.0 (0.6–1.6)	
Otieno, 2016[419]	Kenya	2010 - 2013	-	Febrile seizure	10	Malaria RTS,S/AS01	Proportion of participants	10.1%	Case ascertainment= BC Risk period = 0-7 days Vaccinated n: Malaria= 99, Rabies= 101
				Convulsion	2			2.0%	
Vekemans, 2011[420]*	Multiple	2008	6 weeks – 4 years	Febrile seizure	32	Malaria RTS,S/AS	Relative Risk (95 %CI) vs control	0.73 (0.44, 1.22)	Case ascertainment= BC Number of doses = 8,868 * Pooled analysis of RCTs
RTS, 2015[421]	Multiple	2009 - 2014	6-12 weeks	Seizure	-	Malaria RTS,S/AS01	Incidence per 1,000 doses	2.2	Case ascertainment= BC Risk period = 7 days
			5-17 months					2.5	

TABLE 3.12 Studies reporting on risk of Seizure after vaccination with Other vaccines, by study type

Author, year	Location	Study Years	Age Group	Type of seizures	Number of Seizure cases	Specific Vaccine	Risk Estimate	Risk estimate value	Relevant Additional Study Details
SCCS (n=5)									
Macartney, 2015[248]	Australia	2012 - 2013	-	Febrile seizure	15	Varicella	Relative incidence (95% CI) compared to background rates with 1 month intervals, p-value	5-12 days: 0.64 (0.34, 1.19), 0.158	Case ascertainment= ICD-10 AM Risk period = 5-30 days
								13-30 days: 0.71 (0.47, 1.08), 0.109	
Hambidge, 2014[241]	USA	2004 - 2010	-	Febrile seizure	38-92 days =10	IPV	IRR (95% CI)	1.26 (0.65, 2.45)	Case ascertainment= ICD-9 Risk period Rotavirus: 0-7 days All other vaccines: 0-2 days
					93-730 days =1			1.56 (0.19, 12.92)	
					38-92 day =10	Rotavirus		1.17 (0.57, 2.39)	
					93-730 days =1			0.70 (0.08, 5.99)	
					361-488 days =61	Varicella		2.75 (2.05, 3.70)	

					489-730 days =13			3.64 (1.86, 7.12)	
					38-92 days=8	Haemophilus influenza type B		1.04 (0.50, 2.16)	
					93-730 days =1			1.56 (0.19, 12.92)	
Hoffman, 2018[242]	USA	2008 - 2013	-	Convulsion	Dose 1 =27	Rotavirus	IRR (95% CI), vs 15-30 days control period	2.40 (0.73– 7.86)	Case ascertainment= BC Risk period = 0-7 days
Wang, 2018[253]	USA	1995 - 2015	11 - 23 months	Seizure	12	Hep A	IRR (95% CI); p-value	1.0 (0.6, 1.8); 0.979	Case ascertainment= ICD-9 Risk period = 7-10 days vs control window (14-56 days)
					5	Varicella		1.9 (0.7, 5.0); 0.172	
					1	HiB		0.9 (0.1, 6.7); 0.898	
Sun, 2022[422]	China	2016 - 2019	6-71 months	Febrile seizure	Manufacturer A =4	EV71	Adjusted IRR (95% CI), vs control interval (14-21 days), adjusted for age and season	1.18 (0.37, 3.77)	Risk period = 0-7 days Vaccinated n: EV71 - Manufacturer A= 24,989 EV71 - Manufacturer B= 39,772 EV71 - Manufacturer C= 172,145
					Manufacturer B=11			0.85 (0.38, 1.87)	
					Manufacturer C=32			1.09 (0.75, 1.59)	
Cohort studies (n=5)									

Lewis, 2001[423]	USA	1991 - 1994	0 - 21 days	Seizure	Within 1 day of birth	Hepatitis B	Relative risk (95% CI) vs nonvaccinated	0.18 (0.02-1.6); 0.17	Vaccinated n = Within 1 day of birth: 3,302, Within 1 day of birth: 2,718
					Within 21 days of birth			0.22 (0.02-1.9); 0.19	
Huang, 2020[388]	China	2012 - 2017	0-24 years	Seizure	3	OPV	Incidence rate per 100,000 doses	1.1 (0.1– 2.3)	Case ascertainment = ICD- 10 Risk period = 7 days Number of doses = OPV: 280,531, Hib: 108,823
					5	Hib		4.6 (0.6– 8.6)	
Hoffman, 2018[242]	USA	2008 - 2013	-	Convulsion	Any dose =43	Rotavirus	IRR (95% CI)*	1.62 (1.12, 2.36)	Case ascertainment = BC LOC 1 or 2 Risk period = 0-59 days Vaccinated n : 57,931 *Adjusted for age at specific vaccination, gender, dose-specific calendar quarter of vaccination, and database
					Dose 1 =27			2.05 (1.24, 3.38)	
					Dose 2 =16			1.24 (0.69, 2.21)	
De Alwis, 2014[424]	Sri Lanka	2006	-	Seizure	6	JEV	Cumulative incidence rate per 100 immunizations per 2 weeks (95% CI)	0.06 (0.01, 0.11)	Case ascertainment = BC Number of doses = 422
Sun, 2022[422]	China	2016 - 2019	-	Febrile seizure	Manufacturer A=4	EV71	Calculated rate per 100,000 individuals	16.0	Risk period = 0-7 days Vaccinated n : EV71 - Manufacturer A= 24,989 EV71 - Manufacturer B= 39,772 EV71 - Manufacturer C= 172,145
					Manufacturer B=11			27.66	
					Manufacturer C=32			18.59	

Pharmacovigilance Studies (n=8)									
Nyombayire, 2023[425]	Rwanda	2019 - 2021	-	Febrile seizure	10	Ad26.ZEBOV	Calculated rate per 100,000 individuals	23.83	Case ascertainment= Clinical Vaccinated n: 41,959
Sejvar, 2005[426]	USA	2002 - 2004	-	Seizure	8	Smallpox	Incidence per 100 000 Vaccinations	1.2	-
Shaum, 2022[427]	Zimbabwe	2019	Median (IQR): 3 years (2, 9)	Febrile and Afebrile Seizure	20	Typhoidconjugate	RR per 100,000 doses	6.27	Case ascertainment= BC Number of doses = 318,698
Wu, 2017[240]	China	2008 - 2013	-	Febrile seizure	83	JE-L (live-attenuated)	Reporting rates (per million doses)	0.3	Vaccinated n = 34,879
					33	JE-L (inactivated)		0.4	
Lv, 2022[428]	China	2016 - 2020	-	Febrile seizure	11	IPV Sabin-Strains	Reporting rate per 10,000 doses	0.1	Case ascertainment= National AEFI guidance Number of doses =Sabin-Strains= 3,861,758, Salk-Strains= 1,018,604
					3	IPV Salk-Strains		0.08	
Walker, 2018[163]	USA	2012 - 2016	Median: 32 years	Seizure	2	JE-VC	Reporting rate per 100,000 doses distributed	0.2	Case ascertainment= BC + FDA regulatory definition Risk period = 14 days Number of doses = 802,229
DallaValle, 2024[429]	Italy	-	≥ 9 years	Generalized convulsive seizure	3	HPV4v	Reporting rate per 100,000 doses (95% CI)	0.45	Case ascertainment= BC
					1	HPV9v		0.27	
Huang, 2012[430]	Taiwan	2009 - 2010	-	Convulsion	-	H1N1	Estimated to expected ratio (95% CI)	0.94 (0.60, 1.48)	Case ascertainment: BC
RCT Studies (n=2)									

Groome, 2020[431]	South Africa	2016 - 2017	-	Febrile seizure	1	Rotavirus	Calculated proportion	0.30%	Vaccinated n = 327
Otieno, 2016[419]	Kenya	2010 - 2013	-	Febrile seizure	13	Rabies	Proportion of participants	12.9%	Case ascertainment= BC Risk period = 0-7 days Vaccinated n: Malaria= 99, Rabies= 101

APPENDIX 4

Generalized Convulsive Seizure Case Definition: Key Caveats for Diagnosis, Data Analysis and Presentation

4.1. Generalized convulsive seizure Case Definition[432] Key Caveats for Diagnosis, Data Analysis and Presentation

4.1.1 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.

4.1.2 Duration of Surveillance for Generalized convulsive seizure

- 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.

4.1.3 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](#)

4.1.4 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 convulsive seizure 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.

4.1.5 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 convulsive seizure occurs intermittently base the analysis on the value corresponding to the longest seizure.

- Classify each case into one of five categories:
 - Meets level 1 as specified in the case definition
 - Meets level 2 as specified in the case definition
 - Meets level 3 as specified in the case definition
 - Reported case of generalized convulsive seizure with insufficient evidence to meet the case definition (Level 4)
 - Not a case of generalized convulsive seizure (Level 5)
- The prevalence and incidence of cases should be presented and for each case definition level of certainty (1-5) the numerator/denominator should be presented for febrile, afebrile, unknown fever episodes.

APPENDIX 5

Generalized Convulsive Seizure: Data Abstraction and Interpretation Forms With Algorithms for Assessing Level of Diagnostic Certainty and Glossary of Terms

5.1. Generalized Convulsive Seizure Data Abstraction and Interpretation Form with algorithms for assessing level of certainty

The form is organized in a series of Steps presented as tables.

- **Step 1** guides the collection of data needed to meet the case definition criteria for Generalized Convulsive Seizure. Depending on the specific criterion, data are collected using two formats:
 - i. as mutually exclusive answers of YES, NO or UNKNOWN to a series of questions
 - ii as a checklist of specific things that were noted to be present (i.e. YES) like signs or symptoms, or lab test results.

Relatively simple criteria used in the case definition may be defined directly in step 1. Others may require formulae to define – as done in Step 2.

- **Step 2** uses some or all of the data entered in Step 1 to assign values (YES, NO or UNKNOWN) to selected case definition criteria, as necessary..
- **Step 3** is a small tabular summary of the assigned value (YES, NO or UNKNOWN) for each criterion in the case definition.
- **Step 4** provides a tabular algorithm to assign the Level of certainty that meets the case definition (Level 1, 2 or 3) or that does not meet the case definition (Levels 4 and 5).
- A Pictorial algorithm is presented that presents, in a single page, all the relevant criteria needed to meet the case definition and a flow diagram that shows the path to each level of diagnostic certainty depending on the criterion values.
- A Glossary of Terms is also included. Any terms defined in the glossary are **yellow highlighted** in the Step 1 data form.

Digital Transformation: For the digital version, in the Automated Brighton Classification (ABC) Tool users need to enter data into the online form for Step 1 only and an LOC will be provided (based on the information in Steps 2-4 which operate in the background of the Tool) along with a summary of the data entered. In addition, the pictorial algorithm will be provided so users can see how the LOC was derived based on data entered. In contrast, for the analog version, as here in the Companion Guide, users must complete all 4 steps in order to reach the LOC.

The data abstraction form (analog or digital versions) can be used in several settings:

- **Epidemiologic research:** As a case report form for data abstraction from a hospital/other institutional chart as part of epidemiologic studies or hypothesis testing studies for causal association between vaccine (s) and Generalized Convulsive Seizure.
- **Real world evidence studies:** Guide data collection for case validation (all or a subset) in studies where electronic health data were used for case identification based on selected medical codes (ICD9/10, SNOMEDCT, MedDRA).

- **Clinical vaccine trials:** Serve as a supplement to a clinical trial case report form that does not capture information specific to Generalized Convulsive Seizure; i.e., when generalized convulsive seizure is not part of solicited safety information in the clinical trial. In such settings it may also serve as a guide for the type of data to be collected and investigations to be done should generalized convulsive seizure occur as an unsolicited adverse event.
- **Pharmacovigilance:** Most AEFI report forms, including the CIOMS form, allow for free text to describe an adverse event but are not set up to collect specific information that would facilitate applying a standard Brighton case definition. In the event of a possible safety signal involving Generalized Convulsive Seizure, the abstraction form could be used to gather the information needed to assess individual cases to see if they meet the Brighton case definition. In the absence of a signal, where Generalized Convulsive Seizure is considered an AESI (such as in the COVID-19 pandemic campaign), the data abstraction form can be used to guide selection of critical criteria needed to meet the case definition, that could then be added to a special AEFI report form for use in a mass campaign setting.

TABLE 5.1. GENERALIZED CONVULSIVE SEIZURE 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 (witnessed or not)	<ul style="list-style-type: none">• 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 (in particular neurology)	
B	Generalized motor movements		
C	Seizure motor manifestations		
D	Conditions which exclude atonic movements from being part of a seizure episode		

Step 1. Complete the case data entry form choosing the most appropriate answer as defined below:

- 'YES' means there was written or verbal evidence that the criterion was present.
- 'NO' means there was written or verbal evidence that the criterion was not present.
- 'UNKNOWN' means there was uncertainty in interpreting whether the criterion was present or absent, OR nothing was documented about the criterion.

Terms with a glossary definition

Criterion	Question	Possible Answers		
Criterion A: Documentation that loss of consciousness was associated with the seizure episode				
A1: <u>Loss of consciousness*</u>	Did <u>loss of consciousness</u> occur just prior to or during the seizure episode?	<input type="checkbox"/> YES	<input type="checkbox"/> NO	<input type="checkbox"/> UNKNOWN
A2: <u>Witnessed loss of consciousness*</u>	Did someone see the patient lose consciousness just prior to or during the seizure episode?	<input type="checkbox"/> YES	<input type="checkbox"/> NO	<input type="checkbox"/> UNKNOWN
Criterion B: Generalized motor movements				
B: <u>Generalized motor movements*</u>	Did the seizure movements involve both right and left limbs (i.e., right and left arms, right and left legs, or all four limbs)?	<input type="checkbox"/> YES	<input type="checkbox"/> NO	<input type="checkbox"/> UNKNOWN
Criterion C: Seizure motor manifestations Types of motor movements that accompanied the seizure				
C1: <u>Tonic, clonic or tonic-clonic movements*</u>	During the seizure were there tonic, clonic or tonic-clonic motor movements?	<input type="checkbox"/> YES	<input type="checkbox"/> NO	<input type="checkbox"/> UNKNOWN
C2: <u>Atonic movements*</u>	During the seizure were there atonic movement? (e.g., sudden loss of postural tone; part or all of the body became limp; fell down) If C2 = YES, Answer D 1, 2 and 3. If C2 = NO or UNKNOWN skip D1, 2 and 3.	<input type="checkbox"/> YES	<input type="checkbox"/> NO	<input type="checkbox"/> UNKNOWN
C3: <u>Other movements*</u>	During the seizure were there motor manifestations other than tonic, clonic, tonic-clonic or atonic movements?	<input type="checkbox"/> YES	<input type="checkbox"/> NO	<input type="checkbox"/> UNKNOWN
Criterion D Conditions which exclude atonic movements from being part of a seizure episode. If C2 answered YES, answer 1, 2 and 3 below:				
1: <u>Hypotonic hyporesponsive episode</u>	Were the atonic movements part of a hypotonic hyporesponsive episode (only applies to ages ≤2 years old)?	<input type="checkbox"/> YES	<input type="checkbox"/> NO	<input type="checkbox"/> UNKNOWN
2: <u>Myoclonic jerks</u>	Were the atonic movements accompanied by myoclonic jerks?	<input type="checkbox"/> YES	<input type="checkbox"/> NO	<input type="checkbox"/> UNKNOWN
3: <u>Syncope</u>	Were the atonic movements part of a fainting (syncope) episode?	<input type="checkbox"/> YES	<input type="checkbox"/> NO	<input type="checkbox"/> UNKNOWN

Step 2. Based on clinical data entered in Step 1, assign a value to Criteria **D and **C2.1** using the rules in the Criterion Options column**

CRITERION		CRITERION VALUE: compare data entered in step 1 table to formulae in the YES, NO and UNKNOWN columns to determine FINAL VALUE for each criterion.				
CLINICAL CATEGORY	Name	FINAL VALUE (Circle/Highlight)			YES (Y) IF:	NO (N) IF: UNKNOWN (U) IF:
Conditions which exclude atonic movements from being part of seizure	D	Y	N	U	D (1, 2 OR 3) = YES	D (1 AND 2 AND 3) = NO D(1 AND 2 AND 3) = NO OR Unknown*
Atonic Movements were part of the seizure episode	C2.1	Y	N	U	C2 = YES AND D = NO or UNKNOWN	(C2 = YES AND D = YES) OR C2 = NO C2 = UNKNOWN

* NOTE: choose UNKNOWN if there is a combination of NO and unknown (e.g. if D1 and D2=NO and D3=UNKNOWN, then Criterion D = UNKNOWN)

Step 3. Record the final value for Criteria **A1, A2, B, C1 and **C2.1** from step 1 and Criterion **C2.1** from step 2 in the 2nd row of the table below.**

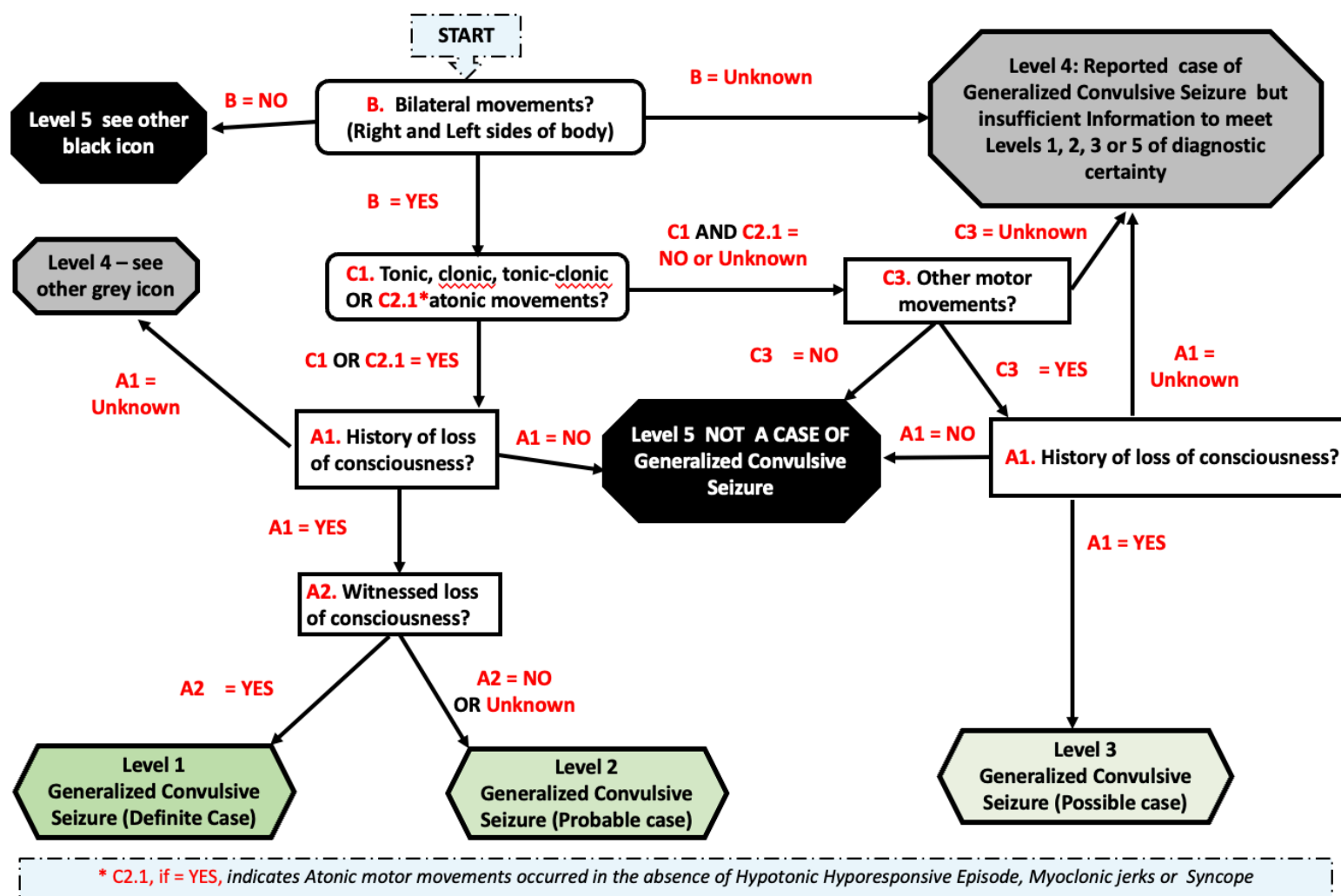
Criterion	A1	A2	B	C1	C2.1	C3
Final Value						

Step 4. Use the values of the Generalized Convulsive Seizure criteria recorded in the Step 2 above to determine the level of certainty based on the formulae below. Start with Level 1 (criteria **A1, A2, B, C, C2.1**). If Level 1 not met, then move to Level 2 (criteria **A1, A2, B, C1, C2.1**), and, if not met try Level 3 (**A1, B, C1, C2.1, C3**). If none of Levels 1, 2 or 3 met, try Level 5 (criteria **A1, B, C1, C2.1, C3**). If Levels 1, 2, 3 and 5 not met, then assign Level 4.

Level of Certainty	GENERALIZED CONVULSIVE SEIZURE
Level 1	A1 AND A2 = YES AND B = YES AND (C1 OR C2.1 = YES)
Level 2	A1 = YES AND A2 = NO or Unknown AND B = YES AND (C1 OR C2.1 = YES)
Level 3	[A1 = YES]* AND B = YES AND (C1 AND C2.1 = NO or Unknown) AND C3 = YES
Level 4	Reported as Generalized Convulsive Seizure but fails to meet any level of certainty
Level 5	[A1 = NO OR B = NO OR [(C1 AND C2.1 = NO or Unknown) AND C3 = NO]]

* For Level 3, it doesn't matter if the convulsion was witnessed (A2 can be YES, NO or Unknown) so long as there was a history of loss of consciousness.

Figure 5.1 Pictorial algorithm for determining GENERALIZED CONVULSIVE SEIZURE level of diagnostic certainty



5.2 GLOSSARY OF TERMS

TERM	DEFINITION
Atonic movements	sudden loss in tone of postural muscles; may be preceded by a myoclonic jerk (see myoclonus); can be precipitated by hyperventilation in setting of syncope; may reflect a seizure but not in conjunction with a hypotonic hyporesponsive episode, myoclonic jerk or syncope.
Clonic (movements)	sudden, brief (<100 milliseconds) involuntary contractions of the same muscle groups, regularly repetitive at a frequency of about 2-3 contractions / second
EEG (Electroencephalogram)	Test used to record spontaneous electrical activity of the brain
Generalized Motor Movements	bilateral and more than minimal muscle involvement (also see tonic, clonic, tonic-clonic, atonic seizure manifestations/movements)
Hypotonic Hyporesponsive Episode	sudden onset of two of the following: hypotonia (muscle limpness), change in skin color (pallor or cyanosis), change in responsiveness (hyporesponsiveness – i.e., reduced responsiveness; or unresponsiveness). If all 3 are present it meets Brighton Collaboration case definition level 1 of certainty.(case definition available here) HHE typically affects children <2years old. A similar triad may be seen in older individuals but this is usually recognized as vasovagal syncope (see definition below).
Loss of consciousness	Temporary state in which a person appears unresponsive and is unable to respond to external stimuli (e.g. verbal commands, pain). May occur just prior to, or at same time, as the seizure.
Myoclonic jerks	quick involuntary muscle contractions that results in visible movement; can involve a single muscle group or several; also, can present as hiccups.
Other movements	Not defined by the case definition working group but could include: myoclonic movements (sudden twitches or lightning quick jerking movements), twitching of the corners of the mouth or rhythmic protrusion of the lips.
Syncope	Fainting or passing out. Multiple causes but most common in immunization setting is vasovagal syncope – see definition below.
Tonic (movements)	sustained increase in muscle contraction lasting seconds to minutes
Tonic-clonic (movements)	sequence of tonic movement followed by clonic phaseal
Vasovagal reflex	The vagus nerve is a cranial nerve originating in the brain. The reflex involves the vagal nerve, peripheral nerves and the heart and blood vessels. The reflex causes a sudden drop in blood pressure and heart rate and may lead to pooling of blood in the legs which adds to the low blood pressure and results in lower blood flow to the brain. Common stimuli that lead to the reflex include emotional stress or fear which may be the result of immunization anxiety at the time of being immunized.
Vasovagal syncope	Fainting due to a sudden drop in blood pressure and heart rate. May be caused by anxiety or prolonged standing especially in a hot environment. There may be prodromal symptoms seconds to minutes before the faint, such as light-headedness, ringing or buzzing in the ears, visual disturbances (e.g. sensation of shimmering or tunnel vision), nausea or sweating. May be accompanied by jerky seizure-like movements due to lack of oxygen to the brain. Once lying down, blood flow is restored and consciousness rapidly returns. The greatest risk of harm is if the fall is in an unsafe environment with risk of head injury.

Witnessed loss of consciousness	One or more persons reported seeing the patient lose consciousness just before or at the same time as the seizure. The person could be a parent, a friend, a bystander, a health care professional or combination thereof. For the seizure event to have been witnessed the person(s) should have been physically present in the same space as the patient AND observed a change from their baseline state to an unconscious state in conjunction with the seizure.
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APPENDIX 6.

Methodology: Brief Summary

6.1. Generalized Convulsive Seizure ICD-9/10-CM, MedDRA Codes and SNOMEDCT Codes [433-437]

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[434] builds upon information from the Meta-thesaurus of the Unified Medical Language System (UMLS). The Meta-thesaurus 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 Meta-thesaurus concept to which strings with the same meaning are linked. The Meta-thesaurus 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.[433] Codemapper was built on the version 2016AA of the UMLS. The automatic concept identification of CodeMapper is based on lexical information from the Meta-thesaurus. 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.[435, 436] A text-indexing engine Peregrine uses this dictionary to identify medical concepts in the case definition.[437] 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 convulsive seizure Brighton case definitions for all Tier 1 AESI. The concepts identified for generalized convulsive seizure were considered relevant for background incidence rate determination as well as to study hypotheses related to generalized convulsive seizure 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](#).

6.2. Generalized convulsive seizure Background Incidence

What follows is the methodology used for V1.0 of the Companion Guide. It is kept here because most of the references found in that search have been kept for this guide. Details of the search done for the updated background incidence are provided in the Methods section on page 6.

A systematic literature search to estimate the incidence of acute generalized convulsive seizure 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 convulsive seizure were extracted. Generalized convulsive seizure 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 [SPEAC website](#) and the SPEAC Safety Portal.

6.3. Generalized convulsive seizure Risk Factors [93, 94, 184, 235, 238, 432, 438-440]

What follows is the methodology used for V1.0 of the Companion Guide. It is kept here because most of the references found in that search have been kept for this guide. Details of the search done for the updated background incidence are provided in the Methods section on page 6.

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. Attributes include genetic makeup, age, gender, ethnicity, social status, occupation. Behavior includes smoking, drinking, other substance abuse, sexual practices, and 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[432] for generalized convulsive seizure 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 convulsive seizure.[93, 94, 184, 235, 238, 438-440]

6.4. Generalized convulsive seizure Case Definition[432] key caveats for diagnosis, data analysis and presentation

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

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

The Brighton Collaboration case definition for generalized convulsive seizure[432] 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.

A data abstraction form was developed to capture information relevant to the Generalized Convulsive Seizure case definition criteria. The form uses a standard format developed to ensure harmonized approaches between paper forms (as here in the Companion Guide) and digital forms used online. The questions in the form are designed to enable one of three possible answers:

- 'YES' means there was written or verbal evidence that the criterion was present.
- 'NO' means there was written or verbal evidence that the criterion was absent or not present.
- 'UNKNOWN' means there was uncertainty in interpreting whether the criterion was present or absent OR nothing was documented about the criterion

Step 1 involves completing the data abstraction form. Most of the criteria used to determine Level of diagnostic Certainty (LOC) are determined by the evidence provided in Step 1. However, for some criteria further manipulation of the data entered in Step 1 is needed to define one or more specific criteria. This is done in Step 2. A small summary table of all the final criterion values from the first two steps is done as Step 3. Step 4 involves a tabular algorithm that uses the values of

the Case Definition Criteria (YES, NO or UNKNOWN) to determine the highest achievable LOC with Level 1 being the highest, most specific level (Definite Case). A one-page pictorial algorithm is created to show the stepwise pathway to each defined LOC based on the criterion values. This algorithm is designed for use as a stand-alone tool for LOC calculation since in addition to the pathway it also provides defines the data needed for each criterion.

A glossary of terms relevant to the case definition criteria was developed based initially on the published case definition. Where possible, the term definition was taken directly from the published case definition (often from the footnotes provided within each published case definition). If there was no definition in the Brighton publication, then an on-line search was done to obtain definitions based on available medical dictionaries or other on-line resources. The glossary is provided for use by data-abstractors without a medical background.

5. REFERENCES

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