Safety Platform for Emergency vACcines

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

Anaphylaxis

Work Package: WP2 Standards and tools

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DEFINITIONS & ACRONYMS

AESI	Adverse Events of Special Interest
BC	Brighton Collaboration
CEPI	Coalition for Epidemic Preparedness and Innovation
CUI	Concept Unique Identifier
ICD	International Classification of Diseases
MedDRA	Medical Dictionary for Regulatory Activities
SPEAC	Safety Platform for Emergency Vaccines
UMLS	Unified Medical Language System

INTRODUCTION

1. Background

CEPI has contracted with the Brighton Collaboration (BC), through the Task Force for Global Health, to harmonize the safety assessment of CEPI-funded vaccines via its Safety Platform for Emergency vACcines (SPEAC) Project.
A key aspect of this harmonization has been creation of lists of priority potential adverse events of special interest (AESI) that are relevant to vaccines targeting CEPI target diseases.

SPEAC Work Package 2 is creating resources and tools for the AESI including:

1. Tabular summaries of risk factors and background rates for each AESI.
2. Guidance on AESI real time investigation, data collection, analysis and presentation.
3. Spreadsheet summaries of ICD9/10 and MedDRA codes for each AESI.
4. Tools to facilitate capturing the specific clinical data needed to meet AESI case definitions across a variety of settings applicable to clinical trials, epidemiologic studies and individual case causality assessment. These include:
    a. Data abstraction and interpretation forms to facilitate capturing data from medical charts and applying it to determine a given AESI case definition level of certainty.
    b. Tabular checklists that are a stand-alone tool useful for summarizing key clinical data needed to determine the level of diagnostic certainty for a given case definition.
    c. Tabular logic and pictorial decision tree algorithms, also stand-alone tools, to facilitate correct application of key clinical data to determine the level of diagnostic certainty for each AESI.
    d. Glossary of terms relevant to anaphylaxis and the neurologic AESI.

To guide timelines for the activities above, the AESIs have been prioritized into 4 tiers as shown in the Table below (process described in SO1-D2.0 Addendum to SO1-D2.2 & 2.3 Landscape Analyses Priority Tiers for All CEPI Vaccine Development AESI). This is available in the Developers Toolbox and on the Brighton Collaboration website.

TABLE 1. AESI PRIORITIZED BY TIER

Tier 1	Tier 2	Tier 3	Tier 4
Anaphylaxis	Vaccine associated enhanced disease	Sensorineural hearing loss	Acute/Chronic inflammatory rheumatism
Thrombocytopenia	Acute respiratory distress syndrome	Anosmia/ageusia	Total/partial loss of vision
Generalized convulsion	Acute cardiovascular injury	Chilblain like lesions	Optic neuritis
Aseptic meningitis	Coagulation disorder	Erythema multiforme	Alopecia
Encephalitis	Acute kidney injury	Acute aseptic arthritis	Neonatal sepsis
Myelitis	Acute liver injury	Single organ cutaneous vasculitis	Neonatal encephalopathy
Acute disseminated encephalomyelitis	Stillbirth	Maternal death	Neonatal neuro-developmental delay
Guillain Barré & Miller Fisher Syndromes	Spontaneous abortion and ectopic pregnancy	Neonatal death	
Peripheral facial nerve palsy	Pathways to Preterm birth & Preterm birth		

To simplify access to AESI specific tools and resources, companion guides to the Brighton AESI case definition are being prepared for each AESI. That is the purpose of this deliverable, which focuses on Anaphylaxis.

2. Objective of this deliverable

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

3. Methods

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

- Anaphylaxis risk factors and background rates: SO1-D2.4 Tier 1 AESI: Risk Factors and Background Rates
- Anaphylaxis Case definition key caveats for diagnosis, data analysis and presentation: SO1-D2.7 Guidance for CEPI Developers
- Anaphylaxis Diagnostic Codes: SO2-D2.3 Tier 1 AESI: ICD-9/10-CM and MedDRA Codes
- Anaphylaxis Tabular checklist and Level of Certainty algorithms: SO2-D2.5.1.1-Tools for Tier 1 AESI Data Collection and Interpretation

The methods are briefly described in Appendix 7 of this Guide along with links to source documents which have more detailed methodology.

4. Results

The outputs are provided as separate appendices to simplify printing as needed. These are provided as appendices shown below.

1. Anaphylaxis Risk Factors
2. Anaphylaxis Background Rates
3. Anaphylaxis Case Definition key caveats for diagnosis, data analysis and presentation
4. Anaphylaxis Diagnostic Codes: ICD-9CM, ICD-10CM, MedDRA
5. Anaphylaxis Tabular checklist for key case definition criteria and level of certainty algorithm
    - Unlike most other AESI, there is no Data abstraction and interpretation form for anaphylaxis mainly because anaphylaxis is primarily seen in an outpatient setting. Further the content of what would be needed to abstract from a medical chart is provided in either the tabular checklist (Appendix 5) or pictorial algorithm (Appendix 6) either of which can be used to assist in collecting data from medical charts.
6. Anaphylaxis Pictorial level of certainty algorithm
7. Summary of methods. Also provides links, as appropriate, to the original deliverable documents with more detailed methodology.

5. Recommendations & discussion

This guide brings together many resources and tools related to the AESI of Anaphylaxis including risk factors, background rates, guidance for real time investigation, ICD-9/10-CM and MedDRA codes for data entry or database searching and provides tools for collecting and interpreting clinical data to apply the Brighton Anaphylaxis case definition and determine the level of diagnostic certainty.

The choice of tabular or pictorial algorithm is up to the user in terms of what is best suited to the situation and the assessor. SPEAC recommends that the tools be used in order to assign level of certainty for all identified AEFI with features of Anaphylaxis. This standard, harmonized approach will facilitate signal detection and assessment as well as the capacity to combine data across trials for meta-analyses.

6. References

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APPENDIX 1.
Anaphylaxis Risk Factors

1.1. Anaphylaxis Risk Factors

TABLE 1. ANAPHYLAXIS RISK FACTORS [1-10]

Age	• Children[3]: large majority of anaphylaxis triggered by foods; less than 5% by insect venom. • Adults[3]: relative to children, medication triggered anaphylaxis more common (about 1/3), food triggered anaphylaxis less common (about 1/3), insect venom more common (close to 20%) • Increased severity of anaphylaxis: infants[2,3] (where recognition can be more difficult) and elderly[2,4]
Gender	• Males – more common in those aged <15 years[2] • Females – more common in those aged >15 years[2] • Increased severity of anaphylaxis: pregnancy [3], menses[3]
Genetics	• Atopy[2,3] – multigenic including genes for cytokines and IgE receptor • idiopathic anaphylaxis[3,4] – most common in females with known atopy history. ○ Recurrent reaction with no consistent trigger. Approximately 2/3 have 5 or less episodes per year; remainder have >5 episodes / year.
Geography	• More common in Northern latitudes[2]
Comorbidity [2,3]	• Increased frequency of anaphylaxis: severe asthma[2] • Increased severity of anaphylaxis: asthma, pulmonary disease, mastocytosis, thyroid disease, coronary artery disease, ischemic dilated cardiomyopathy
Medication	• increased severity of anaphylaxis: antihypertensive medications (beta-adrenergic blockers, calcium channel blockers, ACE inhibitors, angiotensin receptor blockers, direct renin inhibitors) • polyethylene glycol (PEG)[6,7] • sedatives, hypnotics and recreational drugs may mask recognition of symptoms[3]
Vaccine	• Institute of Medicine 2011[8] concluded that evidence convincingly supports an association between MMR, VZV, influenza, Hepatitis B, meningococcal and tetanus toxoid vaccines and anaphylaxis; they also concluded that evidence favors acceptance of a causal relationship between HPV vaccine and anaphylaxis. In all instances the evidence that contributed to the conclusion was mechanistic consisting of multiple case reports. • Updated review[9] of evidence published since 2011 IOM report agreed with and did not add any additional vaccine – anaphylaxis associations. They noted the attributable risk was 1 in 100,000 to 1 in 1,000,000 doses. • The US Vaccine Safety Datalink studied the rate of anaphylaxis, confirmed using the Brighton case definition, following child and adult vaccination.[10] A total of 33 confirmed (Brighton level 1 or 2) cases of anaphylaxis occurred after 25,173,965 doses for a rate of 1.31 (95% Confidence Interval, 0.90-1.84) per million vaccine doses. There was a total of 17,606,500 vaccination visits for a rate of 1.87 (95% CI 1.29-2.63) per million visits. 85% of cases had a history of atopy. The implicated vaccines involved all those considered as causal by IOM and in addition: pneumococcal polysaccharide 23 valent (1 given alone, 1 with influenza vaccine), Herpes Zoster vaccine (1 given alone, 1 with allergy shot), rabies (1 given alone), Hepatitis A (1 given alone, 3 given with concomitant vaccines) Time to onset was: ○ <30 minutes - 8 (24.2%)

	○ 30-<120 minutes – 8 (24.2%) ○ 2 - <4 hours – 10 (30.3%) ○ 4 – 8 hours – 2 (6.1%) ○ Next day – 1 (3%) ○ Not documented – 4 (12.1%)

APPENDIX 2.
Anaphylaxis Background Rates

2.1 Anaphylaxis Background Rates

TABLE 1. ANAPHYLAXIS BACKGROUND RATES

All types of anaphylaxis. Variation in rates dependent in part on case ascertainment method shown in brackets next to citation number and coded as follows: A=hospital admission; B=epinephrine prescriptions; C=community based including specialty clinics; D = Emergency department

Country reference (case ascertainment method)	Study years	Population (age in years)	Incidence rate per 100,000 patient years [95% confidence interval] (total cases)		
			All	Males	Females
AMERICAs					
USA (Minnesota – Olmsted County) [11] (C)	1983-1987	**All ages**	**21 [17-25] (133)**		
USA (Minnesota – Olmsted County) [12] (C)	2001-2010	**All ages**	**42 [38.7-45.3] (631)***		
USA (Minnesota) [13] (C)	1990-2000	0-9 10-19 20-29 30-39 40-49 50-59 80+ **All ages**	75.1 65.2 38.8 53.3 49.1 40.4 28.0 **49.8[45.0-54.5](211)**	89.6 63.4 29.8 40.3 44.7 24.6 24.7 **45.6[39.0-52.1](93)**	59.6 67.0 47.0 66.1 53.3 54.9 30.1 **53.7[46.7-60.6](118)**
USA (Washington)[14] (C)	1991-1997	0-4 5-9 10-14 15-17 **0-17**	9.9 7.4 11.2 14.5 **10.5 (67)**	**12.2 [8.7,16.6] (40)**	**8.7 [5.7,12.6] (27)**
USA(National)[15] (D)	2008 2014	**0-18** **0-18**	**10.1** **24.9**		
USA(New York) [16] (A)	1990 2006	**All ages**	**1.0** **4.7**		
Chile [17] (A)	2001-2010	0-9 10-19 20-29 30-39 40-49 50-59 60-69 70-79 80-99 **All ages**	0.6 [0.5-0.7] (166) 1 [0.9-1.1] (294) 1.1 [1.0-1.2] (278) 1.4 [1.3-1.6] (347) 1.7 [1.5-1.8] (382) 2.3 [2.1-2.6] (374) 2.4 [2.2-2.8] (254) 2.6 [2.2-3.0] (158) 2.4 [1.9-3.0] (63) **1.41[1.36-1.47](2316)**	**1.3 [1.2-1.4] (1093)**	**1.5 [1.4-1.6] (1223)**

ASIA					
China (Hong Kong)[18 (C)]	2001-2 2002/3 2003/4 2004/5 2005/6 2006/7 2007/8 2008/9 2009/10 2010/11 2011/12 2012/13 2013/14 2014/15	0-18 years	2.46 [1.76-3.42] (35) 1.23 (17) 1.85 (25) 2.43 (32) 1.86 (24) 1.57 (20) 2.96 (37) 2.64 (32) 3.03 (36) 3.01 (35) 2.61 (30) 2.95 (33) 4.59 (51) 6.63 [5.27-8.32] (74)		
Korea [19 (C)]	2008-2014	**All ages**	**22.01 (76)**	**23.85**	**20.06**
	2008	0-19 20-39 40-69 ≥70 **All ages**	6.03 12.27 15.35 14.73 **16.02 (7716)**	**17.54 (4261)**	**14.48 (3455)**
	2009	0-19 20-39 40-69 ≥70 **All ages**	7.61 13.19 25.67 20.66 **17.9 (8703)**	**19.73 (4836)**	**16.04 (3867)**
	2010	0-19 20-39 40-69 ≥70 **All ages**	11.56 14.64 17.38 13.69 **19.42 (9496)**	**N/A (5101)**	**18.12 (4395)**
	2011	0-19 20-39 40-69 ≥70 **All ages**	11.14 14.76 17.82 15.97 **19.65 (9687)**	**20.7 (5140)**	**18.58 (4395)**
	2012	0-19 20-39 40-69 ≥70 **All ages**	12.26 17.27 32.08 26.59 **23.31 (11578)**	**25.35 (6333)**	**21.26 (5245)**
	2013	0-19 20-39 40-69 ≥70 **All ages**	16.19 18.89 22.37 16.57 **25.09 (12540)**	**27.04 (6799)**	**23.1 (5741)**

	2014	0-19 20-39 40-69 ≥70 **All ages**	21.26 24.23 28.47 29.49 **32.19 (16198)**	**35.41 (8958)**	**28.93 (7249)**
AUSTRALIA/OCEANIA					
Australia [20(B)]	2008-2009	<1 1-4 5-11 12-16 **All (0-16)**	2.8 18.4 9.5 11.8 **11.8**		
	2015-2016	< 1 1-4 5-11 12-16 **All (0-16)**	53.5 48.2 29.2 42.2 **38.7**		
Australia [21(C)]	1995-2000	**All**	**9.9**		
Australia [22(A)]	2005-2006	0-4 5-14 15-29 ≥30 **All ages**	26.4 9.0 12.4 11.3 **12.2**		
	2011-2012	0-4 5-14 15-29 ≥30 **All ages**	35.1 17.8 18.8 15.4 **17.7**		
EUROPE					
UK [23(C)]	1994-1999	All ages	8.4		
UK [24(C)]	2001 2002 2003 2004 2005	All ages	6.7 [5.7-7.7] 6.6 [5.7-7.6] 6.8 [5.9-7.9] 8.5 [7.5-9.6] 7.9 [7.0-9.0]		
UK [25(A)]	1992 2012	All ages	1.0 7.0		
UK [26(D)]	2012	< 16 ≥ 16 All ages	35.9 [27.0,46.3](105) 34.1[29.6,39.1] (321) 34.5[30.4,38.9] (426)		
Switzerland [27(C)]	1996-1998	All ages	8.9 (249)		
Denmark [28(A)]	1973-1985	All ages	3.2 [1.9-4.9] (20)		
Denmark [29(A)]	1995-2012	All ages	6.46[6.31-6.62] (6707)		

Finland [30(A)]	1999 2011	0-19	2.7 8.3		
Sweden [30(A)]	1999 2011	0-19	4.3 15		
Spain [31(A)]	1998 1999 2000 2001 2002 2003 2004 2005 2006 2007 2008 2009 2010 2011	All ages	1.35 [1.35-1.36] (528) 1.44 [1.44-1.44] (572) 1.42 [1.42-1.43] (569) 1.54 [1.54-1.55] (628) 1.55 [1.55-1.56] (646) 1.61 [1.60-1.61] (683) 1.66 [1.66-1.66] (717) 1.71 [1.70-1.71] (755) 1.79 [1.78-1.79] (807) 1.69 [1.68-1.69] (771) 1.86 [1.86-1.86] (874) 2.03 [2.03-2.04] (971) 2.43 [2.42-2.43] (1181) 2.38 [2.38-2.39] (1180)	1.41 (270) 1.54 (299) 1.60 (314) 1.65 (329) 1.67 (341) 1.79 (375) 1.79 (382) 1.73 (378) 1.93 (431) 1.82 (410) 1.95 (454) 2.22 (527) 2.63 (631) 2.61 (638)	1.30 (258) 134 (273) 1.25 (255) 1.44 (299) 1.44 (305) 1.43 (308) 1.53 (335) 1.69 (377) 1.65 (376) 1.56 (361) 1.77 (420) 1.85 (444) 2.23 (550) 2.16 (542)
Spain [32(C)#]	2004-2005#	0-4 5-9 10-14 15-19 20-24 25-29 30-34 35-39 40-44 45-49 50-54 55-59 60-64 65-69 70-74 75-79 80-84 85+ All ages	313.6[230.5,416.8] 74.4 [35.7, 136.8] 112.5 [61.5, 188.7] 124.5 [73.8, 196.7] 124.5 [83.4, 178.8] 84.1 [57.2, 119.4] 72.9 [48.0, 106] 94.2 [62.1, 137] 153.4 [105.6, 215.3] 53.1 [24.3, 100.8] 86.1 [50.1, 137.8] 65.5 [38.2, 104.8] 104.8 [66.5, 157.3] 91.6 [47.3, 159.9] 71.8 [28.9, 147.9] 78 [25.3, 181.8] 87.6 [23.9, 224.2] 153.1 [56.2, 332.8] 103.4 [92.6, 115] (336)	98.8[84.1,115.4] (159)#	107.8[92.5,124.9] (177)#
Italy [33(A)]	2000-2003	0-17	5.9 (203)		

* Rates are available for each year of the study in the Anaphylaxis Background Rate spreadsheet.

Rates are available separately for each year of the study as are gender specific rates for each age group in the Anaphylaxis Background Rate spreadsheet (see link above).

APPENDIX 3
Anaphylaxis Case Definition Key Caveats for Diagnosis, Data Analysis and Presentation

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

- Key elements of Case Definition (CD)
  - Predominantly a clinical diagnosis relying on objective assessment of dermatologic, cardiovascular, respiratory and gastrointestinal presentations which make up the major and minor case definition criteria.
  - 3 levels of diagnostic certainty which have nothing to do with severity.
  - **Required for all 3 levels** is an event time course that involves '**sudden onset'** (meaning "the event occurred unexpectedly and without warning leading to a marked change in a subject's previously stable condition" and 'rapid progression'(no exact timeframe specified).
  - A response to treatment is specifically not included in the case definition. To this extent, since treatment is often given very early in the course of presentation, emphasis on rapid documentation of objectives signs as opposed to subjective symptoms is very important – i.e. observation of swollen tongue rather than a patient history of a sensation of tongue swelling. A RAPID Assessment form was presented in Gold et al[34] and included a checklist with all the major/minor criteria for anaphylaxis:
    1. Rash and mucosa
    2. Airway and respiratory:
    3. Pulse and cardiovascular:
    4. Investigation:
    5. Diarrhoea and GI tract:
- Duration of Surveillance for Anaphylaxis:
  - Relevant biologic characteristics of the study subjects/controls may help to define this including: history of atopy, past episodes of anaphylaxis, nutrition, underlying disease.
  - Reports of anaphylaxis should be collected throughout the study period regardless of the time elapsed between immunization and adverse event. If not feasible, the study periods during which safety data are collected on anaphylaxis should be clearly defined.
- Recommendations for real time assessment
  - Appendix 5 provides a symptom/sign checklist corresponding with the case definition major and minor criteria. This can be provided to clinical trial immunization providers as an aid for what should be documented and to append to the AEFI report. It also provides the rules for assigning level of certainty – which could be included or reserved for use of the site investigator or study monitor. This is not meant to guide treatment. Many of the criteria can rapidly be assessed by one staff member as others are providing treatment. It is especially important to have objective documentation rather than historical report of urticaria, angioedema, and upper airway swelling.
  - Laboratory
    1. **mast cell tryptase** is a highly specific but insensitive (PPV 93%; NPV 17%)[4] **marker for anaphylaxis.** As such it is rated a minor criterion only.
       - Levels peak between 15 and 120 minutes from onset
       - Samples need to be taken within 6 hours of the event onset
       - Recommendation: determine which study sites are able to measure mast cell tryptase and include it if feasible in the early assessment of anaphylaxis

2. IgE levels – not included in the case definition because anaphylaxis may be non-IgE mediated. That said the working group noted that its role in causality assessment is undisputed
3. Postmortem findings – no pathognomonic features of anaphylaxis and therefore not a part of the case definition

- Data Collection Guidelines
  - Important to document history of allergy including to vaccines, vaccine components or medications; food allergy; allergic rhinitis; eczema; asthma; absence of anaphylaxis following prior vaccines also important to document.
  - See appendix 5 checklist for all the major and minor anaphylaxis criteria, by body system. Where possible distinguish those features, which were medically confirmed (i.e. seen by a physician).
  - Document date/time of:
    1. Onset (time post-immunization when first sign or symptom indicative of anaphylaxis occurred)
    2. first observation (date and/or time of first observed sign or symptom)
    3. diagnosis (when the event first met the anaphylaxis case definition at any level of certainty)
    4. end of episode (when event no longer meets the case definition at the lowest level of certainty)
    5. final outcome - choose the most accurate:
       - recovery to pre-immunization health status
       - spontaneous resolution
       - resolution with therapeutic intervention
       - persistence of the event
       - recurrence of the event (biphasic anaphylaxis; recurrence may be from 1–72 hours after initial event; wide range of frequency (<1%-20%[4]) depending on study
       - sequelae (specify)
       - death
  - Treatment given for anaphylaxis (especially epinephrine, steroids, volume replacement, antihistamines) including date / time given
  - Determine exposures other than immunization for the 24-hour period before and after immunization (foods, environmental)

- Data Analysis Guidelines
  - If few cases are reported in the trial the concrete time course should be analyzed for each including interval from immunization to onset
  - Classify each even into one of 5 categories:
    1. Meets level 1 of certainty
    2. Meets level 2 of certainty
    3. Meets level 3 of certainty
    4. Reported as a case of anaphylaxis with insufficient evidence to meet any level of case definition
    5. Not a case of anaphylaxis
  - If there are many cases, they should be analyzed as the number and percentage in each interval:
    - <30 minutes after immunization
    - 30-≤60 minutes after immunization
    - 60 -≤90 minutes after immunization
    - 90-≤120 minutes after immunization
    - Hourly increments thereafter

- Data Presentation Guidelines – see section 3.3 of the Case Definition publication.[1]

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

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

TABLE 1 NARROW TERMS FOR ANAPHYLAXIS

UMLS Concept		Diagnostic Coding System Term and Codes			
CUI	Name	Term	MedDRA	ICD9CM	ICD10CM
C0002792	Anaphylaxis	Anaphylactic reaction (ICD9CM other anaphylactic reaction; ICD10CM anaphylactic shock, unspecified, initial encounter)	10002198	995.0	T78.2XXA
		Anaphylactic shock	10002199		
		Anaphylaxis	10002218		
		Systemic anaphylactic reaction	10042930		
		Systemic anaphylaxis	10042931		
		Allergic shock	10069526		T78.2
C0161840	Anaphylactic transfusion reaction	Anaphylactic transfusion reaction	10067113		
C3263932	Anaphylactic reaction due to adverse effect of correct drug or medicament properly administered	Anaphylactic reaction due to adverse effect of correct drug or medicament properly administered			T88.6
C3263869	Anaphylaxis due to serum	Anaphylaxis due to serum			T80.5
C2349793	Anaphylactic reaction due to serum	Anaphylactic reaction due to serum			T80.5
C3161457	Anaphylactoid reaction due to serum	Anaphylactoid reaction due to serum			T80.5
C0161840	Anaphylactic transfusion reaction	Anaphylactic shock due to serum			T80.5
C3263868	Allergic shock due to serum	Allergic shock due to serum			T80.5
C0274304	Anaphylactic shock, due to adverse effect of correct medicinal substance properly administered	Anaphylactic shock due to adverse effect of correct drug or medicament properly administered			T88.6
C2886703	Anaphylactic shock, unspecified, sequela	Anaphylactic shock, unspecified, sequela			T78.2XXS

TABLE 2 BROAD SEARCH TERMS FOR ALLERGIC REACTIONS

Diagnostic Coding System Term and Codes					
CUI	Name	Term	MedDRA	ICD9CM	ICD10CM
C0002994	Angioedema	Angio-edema	10002394		
		Angio-oedema	10002395		
		Angioedema	10002424		
		Angioedemas	10002425		
		Angioedema and urticaria	10002426		
		Giant hives	10018257		
		Giant urticaria	10018259		
		Hives giant	10020198		
		Urticaria giant	10046744		
C0149526	Allergic urticaria	Allergic urticaria	10001734	708.0	L50.0
C0020517	Hypersensitivity	Allergic reaction	10001718		
		Allergic reaction NOS	10001719		
		Allergy	10001738		
		Allergy NOS	10001741		
		Hypersensitivity	10020751		
		Hypersensitivity NOS	10020755		
		Hypersensitivity reaction	10020756		
		Hypersensitivity reaction (NOS)	10020757		
		Hypersensitivity symptom	10020759		
		HYSN	10021150		
		Reaction allergic (NOS)	10037932		
		Reaction hypersensitivity (NOS)	10037948		
		Allergic reaction (NOS)	10048495		
		Allergy, unspecified			T78.40
C1527304	Allergic Reaction	Allergic reaction NOS			T78.40
C2886707	Other and unspecified allergy	Other and unspecified allergy			T78.40

TABLE 3 CONCEPTS THAT COULD BE CONFUSED WITH VACCINE-ASSOCIATED ANAPHYLAXIS (MAY BE INCLUDED FOR BACKGROUND INCIDENCE RATE PURPOSES)

UMLS Concept		Diagnostic Coding System Term and Codes			
CUI	Name	Term	MedDRA	ICD9CM	ICD10CM
C0685898	Food anaphylaxis	Anaphylactic shock due to adverse food reaction	10002200		
		Anaphylactic reaction to food	10054843		
		Anaphylactic reaction due to food		995.6	
		Anaphylactic reaction due to adverse food reaction			T78.0

APPENDIX 5

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

5.1 Anaphylaxis Tabular Checklist for Key Case Definition Criteria and Level of Certainty Algorithm*

STEP 1: USE AVAILABLE CLINICAL DATA TO COMPLETE PARTS 1 AND 2 OF TABLE 1, CHECKING ALL MAJOR AND MINOR CRITERIA THAT WERE PRESENT FOR EACH BODY SYSTEM.
STEP 2: USE TABLE 2 TO DETERMINE LEVEL OF CERTAINTY (LOC) BASED ON THE NUMBER AND TYPE OF CRITERIA PRESENT

TABLE 1 CRITERIA FOR MEETING BRIGHTON CASE DEFINITION OF ANAPHYLAXIS

1. COURSE OF ILLNESS: must be able to check both 1.1 AND 1.2 to meet any level of certainty for anaphylaxis	
☐ **1.1 SUDDEN ONSET of signs & symptoms** *Working group defines this as "an event that occurred unexpectedly and without warning leading to a marked change in a subject's previously stable condition"*	☐ **1.2 RAPID PROGRESSION of signs & symptoms** *Working group did not define this and further noted that "Using an arbitrarily restrictive setpoint might bias future data collection unnecessarily." Accordingly, it is open to judgement.*

2. ≥ 2 body systems involved: check all symptoms/signs present by checking appropriate boxes in rows below. Ideally these should be documented in writing (E.G. AEFI report, clinical record in immunization clinic, Emergency room, or other clinical setting. Alternatively, a verbal report from a professional (R.N., M.D, Pharmacist) who witnessed the event.

Body System	B. MAJOR CRITERIA	C. MINOR CRITERIA	
SKIN **excluding hereditary angioedema*	☐ Generalized urticaria (hives) ☐ Generalized erythema ☐ Angioedema* (general or localized including lip) ☐ Generalized pruritus WITH skin rash	☐ Localized injection site urticaria ☐ Red AND itchy eyes ☐ Generalized prickle sensation ☐ Generalized pruritus WITHOUT skin rash	
RESPIRATORY (RESP)	☐ Bilateral wheeze (bronchospasm; by stethoscope) ☐ Stridor ☐ Upper airway swelling (tongue, throat, uvula, larynx) ☐ ≥ 2 indicators of respiratory distress: ○ Tachypnea ○ Cyanosis ○ Grunting ○ Chest wall retractions ○ Increased use of accessory respiratory muscles	☐ Persistent dry cough ☐ Hoarse voice ☐ Sensation of throat closure ☐ Sneezing OR rhinorrhea ☐ Difficulty breathing WITHOUT wheeze or stridor	
CARDIO-VASCULAR (CV)	☐ Measured hypotension ☐ ≥ 3 signs of uncompensated shock: ○ Tachycardia ○ Capillary refill >3 seconds ○ Reduced central pulse volume ○ Decreased level or loss of consciousness	☐ ≥ 2 signs of reduced peripheral circulation ○ Tachycardia ○ Capillary refill >3 seconds ○ Decreased level of consciousness	
GASTRO-INTESTINAL (GI)	NONE	☐ Nausea ☐ Abdominal pain	☐ Vomiting ☐ Diarrhea
LABORATORY	NONE	☐ Elevated mast cell tryptase (> upper normal limit for laboratory doing test)	

TABLE 2 CRITERIA FOR MEETING BRIGHTON CASE DEFINITION OF ANAPHYLAXIS

1. COURSE OF ILLNESS: must be able to check both 1.1 AND 1.2 to meet any level of certainty for anaphylaxis	
☐ **1.1 SUDDEN ONSET of signs & symptoms** *Working group defines this as "an event that occurred unexpectedly and without warning leading to a marked change in a subject's previously stable condition"*	☐ **1.2 RAPID PROGRESSION of signs & symptoms** *Working group did not define this and further noted that "Using an arbitrarily restrictive setpoint might bias future data collection unnecessarily." Accordingly, it is open to judgement.*

2. ≥ 2 body systems involved: check all symptoms/signs present by checking appropriate boxes in rows below. Ideally these should be documented in writing (E.G. AEFI report, clinical record in immunization clinic, Emergency room, or other clinical setting. Alternatively, a verbal report from a professional (R.N., M.D, Pharmacist) who witnessed the event.			
Body System	**B. MAJOR CRITERIA**	**C. MINOR CRITERIA**	
SKIN **excluding hereditary angioedema*	☐ Generalized urticaria (hives) ☐ Generalized erythema ☐ Angioedema* (general or localized including lip) ☐ Generalized pruritus WITH skin rash	☐ Localized injection site urticaria ☐ Red AND itchy eyes ☐ Generalized prickle sensation ☐ Generalized pruritus WITHOUT skin rash	
RESPIRATORY (RESP)	☐ Bilateral wheeze (bronchospasm; by stethoscope) ☐ Stridor ☐ Upper airway swelling (tongue, throat, uvula, larynx) ☐ ≥ 2 indicators of respiratory distress: ○ Tachypnea ○ Cyanosis ○ Grunting ○ Chest wall retractions ○ Increased use of accessory respiratory muscles	☐ Persistent dry cough ☐ Hoarse voice ☐ Sensation of throat closure ☐ Sneezing OR rhinorrhea ☐ Difficulty breathing WITHOUT wheeze or stridor	
CARDIO-VASCULAR (CV)	☐ Measured hypotension ☐ ≥ 3 signs of uncompensated shock: ○ Tachycardia ○ Capillary refill >3 seconds ○ Reduced central pulse volume ○ Decreased level or loss of consciousness	☐ ≥ 2 signs of reduced peripheral circulation ○ Tachycardia ○ Capillary refill >3 seconds ○ Decreased level of consciousness	
GASTRO-INTESTINAL (GI)	NONE	☐ Nausea ☐ Abdominal pain	☐ Vomiting ☐ Diarrhea
LABORATORY	NONE	☐ Elevated mast cell tryptase (> upper normal limit for laboratory doing test)	

TABLE 3 LOGIC TO DETERMINE LEVEL OF DIAGNOSTIC CERTAINTY

Level of Certainty	Logic to reach level of certainty for Anaphylaxis
Level 1, 2 & 3	**Must meet both of the following criteria (if one or both not met, it is not a case – level 5):** ___Sudden onset of symptoms/signs ___Rapid progression of symptoms/signs
Use the pattern of MAJOR and minor criteria met for skin, respiratory, cardiac and gastrointestinal (GI) systems and laboratory result from the table above to determine the highest level of diagnostic certainty (with level 1 > level 2 > level 3).	
Level 1	≥1 Skin MAJOR AND [≥ 1 Respiratory MAJOR AND / OR ≥ 1 Cardiac MAJOR]
Level 2 *NOTE: 4 different ways to meet level 2*	1. ≥ 1 Skin MAJOR AND [≥ 1 Respiratory minor AND / OR ≥ 1 Cardiac minor]
	2. ≥ 1 Respiratory MAJOR AND ≥ 1 Cardiac MAJOR
	3. ≥ 1 Respiratory MAJOR AND ≥ 1 minor from a different system (Skin, Cardiac, GI, lab)
	4. ≥ 1 Cardiac MAJOR AND ≥ 1 minor from a different system (Skin, Respiratory, GI, lab)
Level 3 *NOTE: 2 different ways to meet level 3*	1. ≥ 1 Respiratory minor AND ≥ 1 minor from each of 2 different systems (Skin, Cardiac, GI, lab)
	2. ≥ 1 Cardiac minor AND ≥ 1 minor from each of 2 different system (Skin, Respiratory, GI, lab)
Level 4	Reported anaphylaxis with insufficient evidence to meet any of levels of diagnostic certainty
Level 5	**Not a case of anaphylaxis:** if unable to check 1.1 and 1.2 (i.e., onset not sudden and did not progress rapidly)

TABLE 4 GLOSSARY OF TERMS [34]

Accessory muscles	Muscles, primarily in the neck (sternocleidomastoid which elevates sternum; scalene group which elevates upper ribs) which assist but don't play a primary role in breathing. When used at rest they indicate a level of respiratory distress or increased work of breathing.
Angioedema	Areas of deeper swelling of the skin and/or mucosal tissues in either single or multiple sites which may not be well circumscribed and usually not itchy. (Reported symptoms of "swelling of the tongue" or "throat swelling" should not be documented as angioedema unless there is visible skin or mucosal swelling). NOTE: hereditary angioedema, usually with a history of recurrent episodes of swelling, should be excluded (affects 1 in 50,000)
Capillary refill time	The time required for normal skin colour to reappear after a blanching pressure is applied for 5 seconds. Usually assessed by pressing on the nail bed to cause blanching and then counting the time it takes for the blood to return to the tissue indicated by a pink colour returning to the nail. It normally takes < 3 seconds.
Cyanosis	A dark bluish or purplish discolouration of the skin and/or mucous membranes due to lack of oxygen in the blood
Dry cough	Rapid expulsion of air from the lungs and not accompanied by expectoration/sputum (a non-productive cough)
Erythema	Abnormal redness of the skin without any raised skin lesions
Generalized	Involving >1 body site – that is each limb is counted separately as is the abdomen, back, head and neck
Grunting	A sudden and short noise with each breath when breathing out
Hoarse voice	An unnaturally harsh cry in an infant or vocalisation in and adult or child

Hypotension	An abnormally low blood pressure (BP) documented by appropriate measurement. For infants and children: age specific systolic BP <3-5th percentile OR >30% decrease from that person's baseline; For adults: Systolic BP of <90mm Hg or >30% decrease from that person's baseline.
In-drawing or retractions	Inward movement of the muscles between the ribs (inter-costal), in the lower part of the neck (supra-clavicular or tracheal tug) or below the chest (sub-costal). The movements are usually a sign of difficulty with breathing which results in increased use of 'accessory respiratory muscles' (sternocleidomastoid and intercostal).
Injection site urticaria	Urticaria which is continuous with the injection site or involves other aspects of the injected limb
Localised	Involving one body site only
Loss of consciousness	Total suspension of conscious relationship with the outside world as demonstrated by an inability to perceive and respond to verbal, visual or painful stimulus
Mast cell tryptase	Inflammatory mediator released by mast cells during acute anaphylaxis. Typically levels peak between 15 and 120 minutes after onset; samples for measurement should be taken within 6 hours of onset of signs/symptoms.
Prickle sensation	An unpleasant skin sensation that provokes the desire to run and/or scratch to obtain relief
Pruritus	Itchiness
Red and itchy eyes	Redness of the whites of the eyes (sclera) with sensation that provokes the desire to rub and/or scratch to obtain relief.
Retractions	Indrawing of skin while breathing in (implies an obstruction to breathing); may be supraclavicular (above the collarbone), suprasternal (above the sternum), intercostal (between the ribs), substernal (below the sternum) or subcostal (abdomen just below the rib cage)
Rhinorrhea	Discharge of thin nasal mucus
Sensation of throat closure	Feeling or perception of throat closing with a sensation of difficulty breathing
Sneezing	An involuntary (reflex), sudden, violent, and audible expulsion of air through the mouth and nose.
Stridor	A harsh and continuous sound made on breathing in
Tachycardia	Faster than normal heart rate which varies by age – see table below
Tachypnoea	Faster than normal respiratory rate which varies by age – see table below
Urticaria	Localized redness of superficial layers of skin that is itchy, raised, sharply demarcated and transient (that is skin changes at any location are usually present for less than 12 hours)
Wheezing	A whistling, squeaking, musical or puffing sound made on breathing out

TABLE 5 AGE-RELATED UPPER LIMITS FOR RESPIRATORY AND HEART RATE. NOTE: THESE SHOULD BE COMPARED TO NORMS FOR STUDY POPULATION AND ANY DIFFERENCES RELEVANT TO THE LOCAL POPULATION CAPTURED.[34]

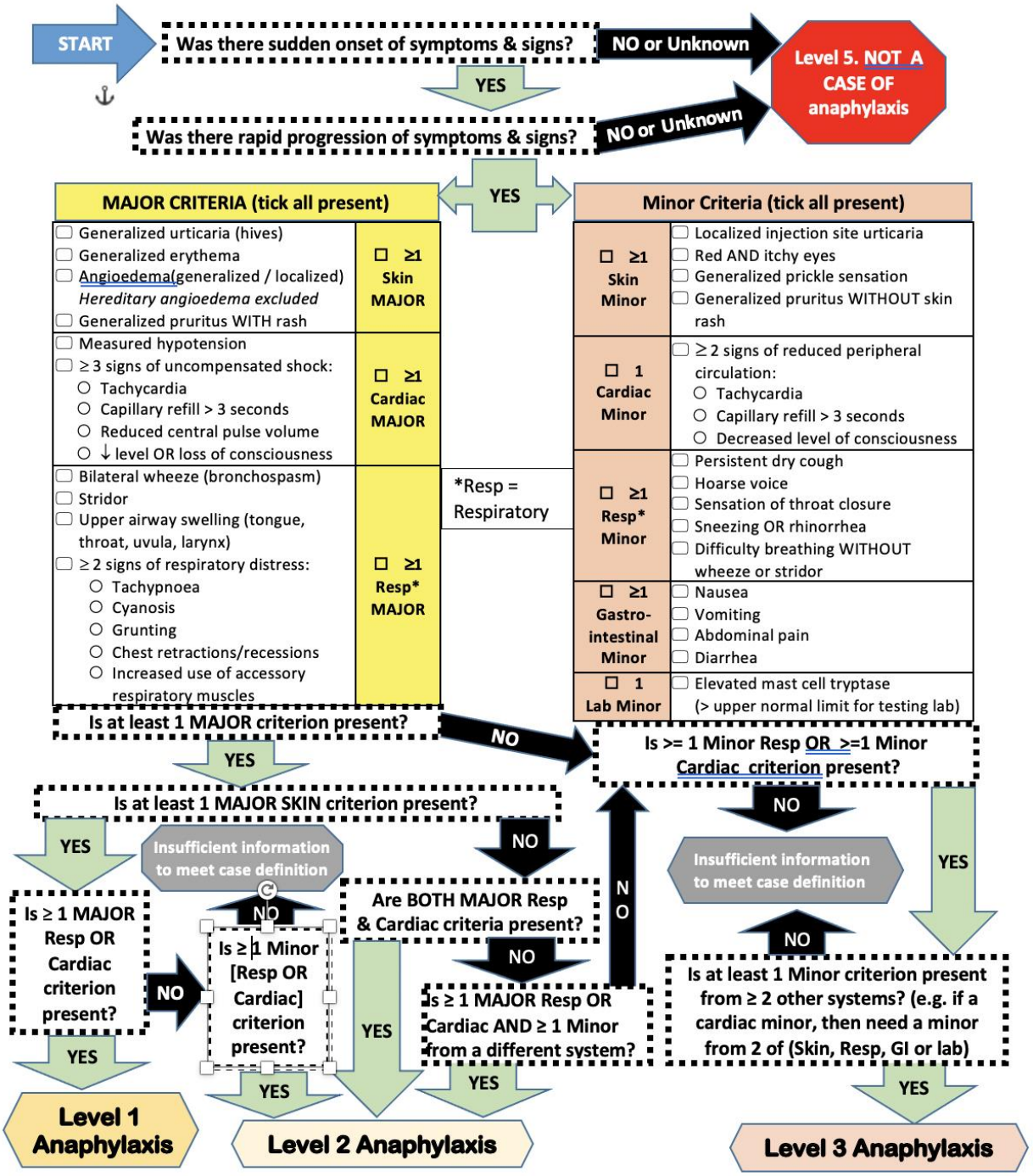
Age in years	Respiratory rate: upper limit in breaths / minute	Heart rate: upper limit in beats/minute
<1 year	60	160
1 – 2 years	40	150
2 – 5 years	35	140
5 – 12 years	30	120
>12 years	16	100

APPENDIX 6

Anaphylaxis Pictorial Level of Certainty Algorithm

6.1 Pictorial level of certainty algorithm for anaphylaxis (adapted from Joshi *et al* [40])

Use available clinical history, examination & laboratory results to determine level of diagnostic certainty for Anaphylaxis



APPENDIX 7.

Methodology: Brief Summary

7.1. Anaphylaxis Risk Factors [1-10]

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

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

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

The published Brighton Case definition[1] for Anaphylaxis 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 Anaphylaxis.[2-10]

7.2. Anaphylaxis Background Incidence [11-33]

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

("Anaphylaxis"[Mesh:noexp] OR "anaphylaxis"[ti] OR "anaphylactic"[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 Anaphylaxis were

extracted. Anaphylaxis 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 reviewed and relevant data abstracted for inclusion in the background rate table (MRV) when novel articles were found from systematic reviews, these were included. The spreadsheet with all extracted background incidence data is available on the Brighton Collaboration website.

7.3. Anaphylaxis Case Definition key caveats for diagnosis, data analysis and presentation [1,34]

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

- Anaphylaxis Diagnostic Codes: Anaphylaxis

For a more detailed description of methodology see SO1-D2.7 Guidance for CEPI Developers which is available in the CEPI Developers' Toolbox.

7.4. Anaphylaxis ICD-9/10-CM and MedDRA Codes [35-39]

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 [35] builds upon information from the Metathesaurus of the Unified Medical Language System (UMLS). The Metathesaurus is a compendium of many medical vocabularies, which have been integrated by assigning equivalent codes and terms from different source vocabularies to the same concepts. Each concept in the UMLS is identified by a CUI. A CUI is a Concept Unique Identifier for a Metathesaurus concept to which strings with the same meaning are linked. The Metathesaurus contains more than one million concepts connected to codes from 201 vocabularies. Each concept is assigned to one or more of 127 semantic types, which define broad conceptual categories like Disease or syndrome, Finding, or Substance.[36] Codemapper was built on the version 2016AA of the UMLS. The automatic concept identification of CodeMapper is based on lexical information from the Metathesaurus. The lexical information of a concept consists of terms that can be used in free text to refer to that concept. We compiled a dictionary for the concepts in the semantic groups Anatomy, Chemicals & Drugs, Disorders, Genes & Molecular Sequences, Living Beings, Phenomena, Physiology, and Procedures of non-suppressible, English terms from several vocabularies including ICD-9 CM, ICD-10 CM, and MedDRA.[37,38] A text-indexing engine Peregrine uses this dictionary to identify medical concepts in the case definition.[39] 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 Anaphylaxis Brighton case definitions for all Tier 1 AESI. The concepts identified for Anaphylaxis were considered relevant for background incidence rate determination as well as to study hypotheses related to Anaphylaxis 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.

7.5. Tabular Checklist and Algorithms for Level of Certainty Determination [1,40]

The Brighton Collaboration case definition for Anaphylaxis[1] was thoroughly and repeatedly reviewed by one individual (Barbara Law) to identify all clinical, laboratory and other criteria (e.g., temporal course of disease) used to define each and every case definition level of certainty.

The Anaphylaxis criteria were displayed in a tabular format to enable recording of all relevant clinical data (based on history, physical examination, laboratory investigation and temporal criteria as relevant to each case definition) needed to meet each criterion.

Algorithms were developed for each level of diagnostic certainty based on the values of each criterion as described in the published case definition. Two types of algorithm were developed for each case definition. For one, formulae based on the logic in the case definition were put into tables with each row representing a level of certainty (Appendix 5). For the second a more visual decision tree algorithm (Appendix 6). was developed based on a published algorithm. [40] Both however, were based on the logic inherent in the published case definition.[1]

For a more detailed description of methodology see Tabular checklist and Level of Certainty algorithms: SO2-D2.5.1.1-Tools for Tier 1 AESI Data Collection and Interpretation which is available in the CEPI Developers' Toolbox.