Safety Platform for Emergency vACcines

AESI Case Definition Companion Guide

Anaphylaxis Version 2

V1.1 – 19 Oct 2022

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DOCUMENT INFORMATION

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Description of the deliverable	This deliverable replaces an earlier version of the Anaphylaxis Companion Guide (completed Feb 5, 2021) which accompanied the 2007 Anaphylaxis case definition. A new Working Group was formed in 2021 to review and revise the 2007 Anaphylaxis case definition (Anaphylaxis V-1) due to identified issues of the V-1 definition over-calling events with allergic symptoms as anaphylaxis. The new V-2 case definition was completed in September 2022, and this Companion Guide updates the previous one primarily as regards the tools for data abstraction and application to determine level of certainty. No changes were needed for the other sections including risk factors, background rates and ICD9/10-CM & MedDRA codes. This guide should replace the earlier version and can be used by stakeholders to assess the occurrence of anaphylaxis in several settings including as an adverse event following immunization.
Key words	Anaphylaxis, Brighton case definition, risk factors, background rates, ICD-9-CM, ICD-10-CM, MedDRA, case definition level of certainty.

DOCUMENT HISTORY

NAME OF DOCUMENT	DATE	VERSION	CONTRIBUTOR(S)	DESCRIPTION
SO2-D2.5.2.1 Anaphylaxis V-2 Companion Guide	25 September 2022	V 1.1	Barbara Law	

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 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 simplify access to AESI specific tools and resources, companion guides to the Brighton AESI case definition are being prepared for each AESI.

Brighton Collaboration published the Anaphylaxis case definition in 2007[1] and a Companion Guide, structured as noted above, was first prepared for Anaphylaxis in February 2021. In June 2021 a working group was formed to review and revise the Anaphylaxis case definition in response to a long-standing issue with double-counting lip swelling as both a dermatologic and respiratory major criterion as well to new issues with application of the case definition during the COVID-19 mass vaccination campaigns. The issues are fully described in the newly published case definition[2] and won't be repeated here. Throughout the guide, the 2007 version will be referred to as Anaphylaxis V-1 and the updated version as Anaphylaxis V-2. The key changes from V-1 to V-2 are summarized below:

- Removal of the requirement for sudden onset of signs and symptoms – which was never defined in V-1
- Retention of the need for rapid progression of signs and symptoms AND provision of a definition of rapid progression (not included in V-1) as follows: typically, anaphylaxis onset involves symptoms or signs from multiple body systems (skin, mucosa, respiratory, cardiovascular, gastrointestinal) at the same time; the criterion can also be met if there is ≤1 hour from onset involving one body system to involvement of one or more additional body systems.
- Major skin criteria:
    - Both 'urticaria' and 'angioedema' retained as major criteria but no longer described as 'generalized' and must be at a location other than the vaccine administration site
    - Generalized erythema and generalized pruritus with skin rash detailed in V-1 have been combined in V-2 into a single major criterion: generalized erythema of the skin with itch.

- Minor skin criteria:
  - The following three V-1 criteria have been deleted: generalized pruritus without skin rash; generalized prickle sensation; localized injection site urticaria
  - Red and itchy eyes have been retained as a criterion in V-2 with the added requirement that it be bilateral and of new onset
  - V-2 includes a new minor criterion: generalized erythema of the skin without itch
- Major respiratory criteria
  - Wheeze and Stridor have been retained as major criteria but further defined as 'Expiratory wheeze' and 'Inspiratory stridor' and both with the requirement to be documented by a healthcare professional (with or without a stethoscope)
  - Upper airway swelling is retained as a major criterion with the notable difference that lip swelling is no longer included; it still includes swelling of the tongue, pharynx, uvula or larynx but adds the requirement that whatever is present be unequivocally documented by a healthcare profession. Notably this means that they are objective findings as opposed to subjective reporting from a patient.
  - V-2 retains the five indicators of respiratory distress, mentioned in V-1 (tachypnoea, cyanosis, grunting, chest wall retractions, increased use of accessory respiratory muscles) and adds a sixth: measured hypoxia with oxygen saturation <90%. The presence for two or more indicators of respiratory distress being required to meet this major criterion remains unchanged,
- Minor respiratory criteria
  - Two subjective minor criteria in V-1 have been removed: difficulty breathing without wheeze or stridor; and sensation of throat closure.
  - Hoarse voice, a minorcriteria in V-1, has been removed.
  - Persistent dry cough, sneezing and rhinorrhea have been retained but have been reduced to a single minor criterion as follows: cough and/or sneezing and/or runny nose that is new onset and persistent.
- Major cardiac criteria:
  - Measured hypotension remains unchanged from V-1
  - Clinical features of uncompensated shock have been removed as major criteria.
  - Loss of consciousness, one of five possible indicators of uncompensated shock in V-1, is now included as a major criterion with an added caveat that it does not include the 'brief, self-resolving loss of consciousness typical of a vasovagal reaction'.
- Minor cardiac criteria:
  - No minor cardiac criteria are included. The single minor criterion from V-1 (reduced peripheral circulation) has been omitted.
- Gastrointestinal Criteria
  - Diarrhea and vomiting, previously minor criteria in V-1, have been included as major criteria with three caveats:
    - Either must be of new onset
    - For infants <12 months old, there must be two or more episodes.
    - Neither criterion apply to a setting involving an orally administered vaccine; Must be either injected or intranasal vaccine to include the gastrointestinal major criterion.
  - The four minor gastrointestinal criteria in V-1 have been removed.

- Laboratory Criterion
  - An elevated tryptase, included as a minor criterion in V-1, has been included as a major criterion with guidance on the extent of the elevation: ≥upper normal limit for laboratory doing the test, OR 1.2 x baseline tryptase + 2 ng/L.

- **Levels of certainty (LoC):** In general, V-2 is more restrictive than V-1 in terms of the requirements to meet a LoC. Major criteria from at least one system need to be met to reach any Loc with the additional specifications for each Level as follows:
    - **Level 1:** Major criteria from skin and mucosa and from any another system (respiratory, cardiac, gastrointestinal or laboratory) must be met.
    - **Level 2:** Major criteria from two different systems including respiratory and/or cardiac and/or gastrointestinal and/or laboratory should be met. Skin and mucosa are excluded since, if present, this would meet a LoC 1.
    - **Level 3:** Major criteria from one system required plus a minor from a different system (skin/mucosa and/or respiratory systems).

Given these changes, there was clearly a need to update the tools (case report form, algorithms for determining level of certainty) for V-2 Anaphylaxis.

2. Objective of this deliverable

To update the previously completed Companion Guide to the 2007 Brighton case definition for Anaphylaxis[1] to be in line with a 2022 update to the Brighton case definition.[2] The main areas needing updating relate to the data extraction and level of certainty assessment tools, as V-2 uses a modified set of criteria for each of the three levels of certainty.

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
    - SNOMEDCT-US codes were part of the same Codemapper output as the ICD and MedDRA Codes and is described in appendix 6.
- 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 6 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 – unchanged from the February 2021 Guide
2. Anaphylaxis Background Rates – unchanged from the February 2021 Guide
3. Anaphylaxis Diagnostic Codes: ICD-9CM, ICD-10CM, MedDRA: SNOMEDCT-US codes added
4. Anaphylaxis case definition key caveats for diagnosis, data analysis and presentation plus recommendations for real time investigation: updated to changes in Anaphylaxis V-2.

5. Anaphylaxis data abstraction and interpretation forms, including a glossary of terms and algorithms for assessing level of certainty. Completely modified to reflect changes in Anaphylaxis V-2.
6. Summary of methods. Also provides links, as appropriate, to the original deliverable documents with more detailed methodology.

5. Recommendations & discussion.

This guide provides updated tools for use with the new Anaphylaxis V-2 case definition. It also adds SNOMEDCT codes for narrow and broad database searches or coding.

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.

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APPENDIX 1.
Anaphylaxis Risk Factors

1.1. Anaphylaxis Risk Factors

TABLE 1. ANAPHYLAXIS RISK FACTORS [1-11]

Age	• Children[4]: large majority of anaphylaxis triggered by foods; less than 5% by insect venom. • Adults[4]: 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[3,4] (where recognition can be more difficult) and elderly[3,5]
Gender	• Males – more common in those aged <15 years[3] • Females – more common in those aged >15 years[3] • Increased severity of anaphylaxis: pregnancy [4], menses[4]
Genetics	• Atopy[3,4] – multigenic including genes for cytokines and IgE receptor • idiopathic anaphylaxis[4,5] – 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 High Income Countries (Northern latitudes, Australia)[3]
Comorbidity [2,3]	• Increased frequency of anaphylaxis: severe asthma[3] • 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)[7,8] • sedatives, hypnotics and recreational drugs may mask recognition of symptoms[3]
Vaccine	• Institute of Medicine 2011[9] 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[10] 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.[11] 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 (see first bullet above) 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 anaphylaxes. 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) [12 (C)]	1983-1987	**All ages**	**21 [17-25] (133)**		
USA (Minnesota – Olmsted County) [13 (C)]	2001-2010	**All ages**	**42 [38.7-45.3] (631) ***		
USA (Minnesota) [14 (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)[15(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)[16 (D)]	2008 2014	**0-18** **0-18**	**10.1** **24.9**		
USA (New York) [17 (A)]	1990 2006	**All ages**	**1.0** **4.7**		
Chile [18 (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)[19] (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 [20] (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	16.19 18.89 22.37 16.57		

		All ages	**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 [21 (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 [22 (C)]	1995-2000	**All**	**9.9**		
Australia [23 (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 [24 (C)]	1994-1999	All ages	8.4		
UK [25 (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 [26 (A)]	1992 2012	All ages	1.0 7.0		
UK [27 (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 [28 (C)]	1996-1998	All ages	8.9 (249)		
Denmark [29 (A)]	1973-1985	All ages	3.2 [1.9-4.9] (20)		

Denmark [30] (A)	1995-2012	All ages	6.46[6.31-6.62] (6707)		
Finland [31] (A)	1999 2011	0-19	2.7 8.3		
Sweden [31] (A)	1999 2011	0-19	4.3 15		
Spain [32] (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 [33] (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 [34] (A)	2000-2003	0-17	5.9 (203)		

Netherlands[35] **PHARMO Database Network**	2017	All ages	Inpatient: 3.21 [2.85-3.60] GP and inpatient: 10.58 [7.80-14.03]		
Denmark[35] Danish Registries (DCE-AU)	2010	All ages	10.06 [9.26-10.93]		
Spain[35] BIFAP	2017	All ages	GP based: 5.64 [5.17-6.14] GP and inpatient: 8.81 [7.94-9.75]		
Spain[35] **SIDIAP**	2017	All ages	GP based: 11.33 [10.47-12.24] GP and inpatient: 14.96 [13.09-17.06]		
Spain[35] **FISABIO**	2017	All ages	22.07 [20.84-23.37]		
Italy[35] **ARS database**	2017	All ages	7.90 [6.73-9.22]		
Italy[35] **PEDIANET database**	2018	0-14	3.40 [1.11-7.94]		
United Kingdom[35CC] **CPRD & HES**	2017	All ages	19.71 [18.29-21.20]		

* 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 Diagnostic Codes: ICD-9/10-CM and MedDRA

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

TABLE 1. NARROW TERMS FOR ANAPHYLAXIS

UMLS Concept		Diagnostic Coding System Term and Codes				
CUI	Name	Term	MedDRA	ICD9CM	ICD10CM	SNOMEDCT-US
C5549840	Anaphylaxis caused by vaccine product					471351000124102
C0857035	Acute anaphylaxis	Acute anaphylaxis Acute anaphyl Acute anaphylactic reaction	10000664 10000662 10000663			
C0002792	Anaphylaxis	Anaphylactic reaction	10002198			
		Anaphylactic shock	10002199	999.49	T78.2	87467006
		Anaphylaxis	10002218			39579001
		Systemic anaphylactic reaction	10042930			
		Systemic anaphylaxis	10042931			157755003
		Allergic shock	10069526		T78.2	
C3161335	Other anaphylactic reaction			995.0		
C0429892	Type 1 hypersensitivity response					12263007
C0340865	Anaphylactoid reaction					35001004
C0161840	Anaphylactic transfusion reaction		10067113			79337003
C3263932	Anaphylactic reaction due to adverse effect of correct drug or medicament properly administered				T88.6	
C3263869	Anaphylaxis due to serum				T80.5	
C2349793	Anaphylactic reaction due to serum				T80.5	
C3161457	Anaphylactoid reaction due to serum				T80.5	
C3263868	Allergic shock due to serum				T80.5	213320003
C0020523	Immediate hypersensitivity	Immediate hypersensitivity Immediate hypersensitivity reaction Hypersensitivity type 1 Hypersensitivity type 1 NOS	10021413 10021414 10020762 10020763			20671006

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		IgE-mediated allergic disorder				422076005
C4316895	Anaphylactic shock					735173007

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	212995001
		Anaphylactic shock due to serum			T80.5	213320003
		Allergic shock, due to adverse effect of correct medicinal substance properly administered				111737003
		Anaphylactic shock, due to adverse effect of correct medicinal substance properly administered				419042001
C2886701	Anaphylactic shock, unspecified, initial encounter				T78.2XXA	
C2886702	Anaphylactic shock, unspecified, subsequent encounter				T78.2XXD	
C2886703	Anaphylactic shock, unspecified, sequelae				T78.2XXS	
C0391985	Anaphylactic shock, not elsewhere classified		10002212			
C3494642	Anaphylaxis caused by human papillomavirus vaccine					428241000124101
C3494646	Anaphylactic reaction caused by diphtheria and tetanus vaccine					428281000124107
C3494647	Anaphylaxis caused by tetanus, diphtheria and acellular pertussis vaccine					428291000124105
C3494648	Anaphylaxis caused by meningococcal vaccine					428301000124106
C3494649	Anaphylaxis due to Hepatitis B vaccine					428321000124101
C3494650	Anaphylaxis caused by rotavirus vaccine					428331000124103
C3536632	Anaphylaxis due to Hemophilus influenzae type b vaccine					433621000124101

C5549835	Anaphylaxis caused by vaccine product containing Streptococcus pneumoniae antigen					471141000124102
C5549836	Anaphylaxis caused by vaccine product containing Hepatitis A virus antigen					471311000124103
C5549837	Anaphylaxis caused by vaccine product containing human poliovirus antigen					471321000124106
C5549838	Anaphylaxis caused by vaccine product containing Measles morbillivirus and Mumps orthorubulavirus and Rubella virus antigens					471331000124109
C5549839	Anaphylaxis caused by vaccine product containing Human aphaherpesvirus 3 antigens					471341000124104
C5549841	Anaphylaxis caused by vaccine product containing influenza virus antigen					471361000124100
C5549842	Anaphylaxis caused by vaccine product containing alphaherpesvirus 3 recombinant surface glycoprotein E antigen					471371000124107
C5549843	Anaphylaxis caused by vaccine product containing live attenuated human alphaherpesvirus 3 antigens					471381000124105
C0685898	Food anaphylaxis	Anaphylactic reaction due to food Anaphyhlactic reaction to food Food anaphylaxis Anaphylactic reaction due to adverse food reaction	10054843	995.6	T78.0	91941002
		Anaphylactic shock due to adverse food reaction	10002200			
		Food-induced anaphylactoid reaction				212994002

						241946006
C1304184	Anaphylaxis due to ingested food					40239008
C0344159	Anaphylaxis caused by venom		10073013			241930003
C4543744	Anaphylaxis caused by insect venom					735447008
C1304185	Anaphylaxis caused by bite and/or sting					402391007
C5397548	Anaphylaxis caused by insect bite and/or insect sting					871926004
C2315598	Anaphylaxis due to hymenoptera venom					430980000
C0344160	Bee sting-induced anaphylaxis					241931004
C0344161	Wasp sting-induced anaphylaxis					24193006
C0344164	Peanut-induced anaphylaxis					241933001
C0344166	Egg white-induced anaphylaxis					241935008
C1998391	Anaphylaxis due to fish					427903006
C0344165	Seafood-induced anaphylaxis					241934007
C0859880	Anaphylactic shock due to milk products	Anaphylactic shock due to mik products Anaphylactic reaction due to milk products	10002206	995.67		
C0344167	Cow's milk protein-induced anaphylaxis					241936009
C1998404	Anaphylaxis due to fruit					429751004
C2711329	Anaphylaxis due to tree nut					441495001
C1997442	Anaphyalxis due to vegetable					428795003
C2711964	Anaphylaxis due to seed					441492003
C1997452	Anaphylaxis due to mollusk					427833000
C2063647	Anaphylaxis due to shellfish					442052005
C0344178	Non-allergic anaphylaxis caused by drug					241947002
C3697499	Non-allergic anaphylaxis caused by food additive					
C1562287	Anaphylaxis due to substance					417516000
C5397207	Blood product-induced anapylactoid reaction					871554001
C2064633	Anaphylactic reaction to latex	Anaphylaxis caused by latex				441593005
C4543745	Anaphylaxis due to mast cell disorder					7354480003

C4544077	Shock co-occurrent and due to anaphylaxis caused by serum				735955001
C4546212	Anaphylaxis caused by low temperature				762455001
C0859860	Anaphylactic shock due to milk products	10002206	995.67		
C0344168	Drug-induced anaphylaxis				241937000
C0344169	Penicillin-induced anaphylaxis				241938005
C0344170	Insulin-induced anaphylaxis				241930002
C0344183	Exercise anaphylaxis Exercise anaphylaxis Exercise-induced anaphylaxis	10060689			241952007
C5546138	Food-dependent exercise-induced anaphylaxis				1144980001
C1096621	Anaphylactic reaction to chemical	10054845			
C4274489	Anaphylaxis caused by sulfite salt				71588704
C4305004	Anaphylaxis caused by lupin flour				71904004
C4305609	Anaphylaxis caused by sulfur dioxide				716374005
C5547723	Non-allergic anaphylaxis caused by organic phosphorus compound				1155989002
C5547724	Non-allergic anaphylaxis caused by parasympathomimetic agent				1155990006
C1960690	Immune hypersensitivity disorder by mechanism				427439005
C5438739	Anaphylaxis due to Hevea brasiliensis latex protein				1003758002
C0344171	Human protein-induced anaphylaxis				241940000
C0344173	Aeroallergen-induced anaphylaxis				241942008
C1298697	Anaphylactic urticaria				373674001
C0413235	Idiopathic anaphylaxis				241954008
C0812176	Anaphylaxis management				386512002
C0854649	Anaphylaxis treatment	10002222			
C4545321	Anaphylaxis care				737855007

APPENDIX 4

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

4.1. Anaphylaxis Case Definition[2] Key Caveats for Diagnosis, Data Analysis and Presentation

4.1.1 Key elements of Case Definition (CD)

- Case definition criteria predominantly based on clinical signs relying on assessment of dermatologic, cardiovascular, respiratory, gastrointestinal presentations and a single laboratory measurement (mast cell tryptase)
- Anaphylaxis V-2 relies primarily on objective evaluation by health care professionals, as opposed to more subjective reported symptoms
- The CD (LoC 1-3) is not a measure of anaphylaxis severity.
- **Required for all three levels** is an event time course characterized by **'rapid progression'** with the time from first symptom or sign appearance to multi-system involvement required to be within one hour or less.
- The case definition is not intended to be used for clinical diagnosis or management. Treatment (usually with adrenaline/epinephrine) and response to treatment is not included in the case definition. Treatment is often given soon after the onset of symptoms.
- Comprehensive documentation of symptoms and objective signs during the course of presentation is critical to the application of the case definition. A RAPID Assessment form was presented in Gold et al[36] and included a checklist with all the major/minor criteria for anaphylaxis V-1. This is reproduced below, with the appropriate modifications to match Anaphylaxis V-2.

TABLE 1. Rapid assessment of possible post-immunisation cases of Anaphylaxis, based on V-2 of Brighton case definition. (Modified from in Gold et al, Appendix B[36])

• *To be used if anaphylaxis is suspected because of rapid progression of symptoms and signs involving multiple systems including skin, mucosa, respiratory cardiovascular and gastrointestinal systems.* • *Do a RAPiD assessment as described below, using the checklist in the right-hand column to record observations. Check all that are confirmed to be present:*					
R ash and mucosa	***Present at a location other than the vaccine administration site:***	☐ urticaria (hives)	☐ angioedema (skin swelling)		
	☐ Generalized redness of the skin **with itch**	☐ Generalized redness of the skin **without itch**			
	☐ Bilateral red and itchy eyes that is new in onset				
An irway and respiratory	***Signs documented by healthcare professional with or without a stethoscope:***	☐ expiratory wheeze	☐ inspiratory stridor		
	Upper airway swelling observed & documented by a healthcare professional:	☐ tongue	☐ pharynx	☐ uvula	☐ larynx
	☐ Tachypnoea	☐ Cyanosis	☐ Grunting	☐ Chest wall retractions	☐ Increased use of accessory respiratory muscles
	☐ Measured hypoxia with oxygen saturations <90%				
	New (not present before immunization) & persistent (recurring or episode ≥5 minutes:	☐ cough	☐ sneezing	☐ runny nose	
P ressure (blood) and consciousness	☐ Measured hypotension	*Age ≥11 yrs: Systolic <90mmHg or diastolic <60 mm Hg* *Age < 11yrs: Systolic < the sum of: 70mm Hg + 2 times age(yrs)*	☐ Loss of consciousness (do not check if the episode is brief, and self-resolving typical of a vasovagal reaction)		

I nvestigation	☐ Elevated mast cell tryptase *(defined as elevated above upper normal limit for testing lab or >1.2 X baseline mast cell tryptase + 2ng/L)*		
D iarrhoea/vomiting	***New onset (not present prior to immunization). Note if <12 months old must be ≥2 episodes:***	☐ Vomiting	☐ Diarrhoea

4.1.2 Recommendations for real time assessment

- **Objective Assessment of Signs and Symptoms:** Most cases of anaphylaxis occur within minutes to a few hours of immunization. See Table 4.1 above. This provides a 'snapshot' of the major and minor criteria included in Brighton Anaphylaxis V-2. This can be provided to clinical trial immunization providers as an aid for what should be documented in the immunization clinic during the episode. It can be appended to the AEFI report and used to assign a level of diagnostic certainty, following the logic provided in Appendix 5. 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, by a qualified healthcare professional, of urticaria, angioedema, upper airway swelling, expiratory wheeze, inspiratory stridor and hypotension

- **Mast cell tryptase** is a highly specific but insensitive (PPV 93%; NPV 17%)[5] **marker for anaphylaxis.** Given the specificity it has been elevated from a minor criterion in V-1 to a major criterion in V-2. It is important to note, however, that:
  - 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

- **Postmortem findings** – no pathognomonic features of anaphylaxis and therefore not a part of the case definition

4.1.3 Data Collection Guidelines

- Important to document history of allergy including to any prior vaccine, vaccine component or medication; as well as history of food allergy; allergic rhinitis; eczema; asthma.
- See table 4.1 checklist above. Also see appendix 5 for a case report form that could be used for retrospective data collection of possible cases.
- Document date/time of:
  - Onset (time post-immunization when first sign or symptom indicative of anaphylaxis occurred)
  - first observation (date and/or time of first observed sign or symptom)
  - 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

- Document treatment given for anaphylaxis (especially epinephrine, steroids, volume replacement, antihistamines) including date / time given
- Determine whether there were any exposures other than immunization for the 24-hour period before and after immunization (vis a vis other stimulus for anaphylaxis including food, venom, environmental toxins or allergens, drugs)

4.1.4 Data Analysis Guidelines (Primarily for the setting of a clinical trial; but could apply to a large retrospective cohort study or background incidence study)

- 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 case into one of 5 categories:
  - Meets the case definition at:
    1. Level 1 of certainty
    2. Level 2 of certainty
    3. Level 3 of certainty
  - Does not meet the case definition:
    4. Reported as a case of anaphylaxis with insufficient evidence to meet any level of case definition
    5. Not a case of anaphylaxis – (e.g., there is a clear alternate diagnosis such as myocardial infarction)
- If there are many cases, they should be analyzed as the number and percentage that onset in each interval shown below:
  - <30 minutes after immunization
  - 30-≤60 minutes after immunization
  - 60 -≤90 minutes after immunization
  - 90-≤120 minutes after immunization
  - Hourly increments thereafter

4.1.5 **Data Presentation Guidelines** – see section 3.3 of the 2007 Case Definition (V-1) publication.[1]. The V-2 WG did not make any changes to the guidelines for data presentation.

APPENDIX 5

Anaphylaxis Data Abstraction & Interpretation Forms, Level of Certainty Algorithms and Glossary of Terms

5.1. Anaphylaxis Data Abstraction and Interpretation Form for Medical Chart Review

This appendix provides tools that can be used to gather data pertinent to Anaphylaxis V-2 and to use the data to assess the level of certainty based on the published Brighton case definition.[2] These tools can be used in a variety of settings including: medical chart review to validate Anaphylaxis cases; summarize known case information from an AEFI report and guide what supplemental information would be needed to assign a level of certainty; guide data collection and case investigation during a clinical vaccine trial or as part of active surveillance; and to guide data collection for epidemiologic studies of background incidence or to assess causality. Also see the RAPID assessment form in Appendix 4 (Table 4.1) that may be more relevant to the real-time immunization clinic setting.

Five tables and 1 figure are included in this appendix:

- **Table 1** lists all V-2 Brighton case definition[2] criteria for Anaphylaxis and identifies likely sources of information for each.
- **Table 2** is the main data abstraction form that can be used to record data pertinent to Anaphylaxis
- **Table 3** provides a guide for assigning a '**Y**es', '**N**o' or '**U**nknown' status to each case definition criterion based on data entered into table 5.2.
- **Table 4** is a brief summary of the final value for each criterion. As per table 5.3
- **Table 5** provides the formulae used to assign level of certainty for Anaphylaxis V-2 based on criterion values summarized in Table 5.4.
- **Table 6** provides a glossary of terms used in the case definition.
- **Figures 1 and 2** show pictorial algorithms for determining level of certainty for Anaphylaxis V-2

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

Criterion	Criterion category	Likely sources of information	Actual sources of information
A	Rapid progression	• Immunization clinic notes • EMT/ambulance attendant notes • Emergency room MD + RN notes • Hospital admitting/progress notes • Hospital discharge summary • Vital signs (Blood pressure, respiratory rate, Oxygen saturation)	
B	Skin symptoms/signs		
C	Cardiac symptoms/signs		
D	Respiratory symptoms/signs		`
E	GI symptoms/signs		

F	Mast cell tryptase	Laboratory studies (including orders for mast cell tryptase to be done)	

TABLE 2. CRITERIA FOR MEETING BRIGHTON CASE DEFINITION OF ANAPHYLAXIS

Step 1. Complete the case data entry form

Record date and time of onset of the first symptom or sign of anaphylaxis:		
1. Criterion A. Rapid progression of symptoms and signs	**i. *Read this statement carefully:*** *From the start of symptoms or signs of possible anaphylaxis, there were multiple body systems involved (≥2 of skin, respiratory, cardiovascular or gastrointestinal)* ***OR*** *what started out involving 1 system spread to involve at least 1 other system within 1 hour of onset.*	**ii. Statement 'i 'is (choose the one best answer):** ☐ 1. TRUE ☐ 2. FALSE ☐ 3. UNABLE TO CONFIRM AS EITHER TRUE OR FALSE
2. Criteria B. SKIN Symptoms or signs	*Check all that were present of 1,2,3,4 or 5, OR choose only 6 or 7 depending on which is most accurate*	☐ 1 Urticaria (hives) at a location other than the vaccine administration site ☐ 2 Angioedema (skin swelling) at a location other than the vaccine administration site ☐ 3 Generalized (widespread) erythema (redness) of the skin WITH pruritis (itchiness of the skin) ☐ 4 Generalized (widespread) erythema (redness) of the skin WITHOUT pruritis (itchiness of the skin) ☐ 5 Bilateral red and itchy eyes that was new in onset ☐ 6 None of the above present ☐ 7 Unknown if any of 1-5 present
3. Criteria C CARDIAC symptoms or signs	*Check one or both of 1 or 2 if present; OR choose either 3 or 4 depending on which is most accurate.*	☐ 1 Measured hypotension (Defined *by Age as shown below:* IF Age: *≥11 yrs: Systolic <90 mm Hg OR Diastolic <60 mm Hg OR > 30% decrease from the person's baseline systolic BP* *< 11yrs: Systolic < the sum of: 70mm Hg + 2 times age(yrs)* ☐ 2 Loss of consciousness ☐ 3. Neither 1 nor 2 were present ☐ 4. Unknown if 1 or 2 were present

4. Criteria D. RESPIRATORY symptoms or signs	**D-1** *Check all that were present of 1, 2, 3 and 4; OR choose either 5 or 6 depending on which is most accurate.*	☐ **1 Expiratory wheeze** (when breathing out) documented by a healthcare professional, with or without a stethoscope ☐ **2 Inspiratory stridor** (when breathing in) documented by a healthcare professional, with or without a stethoscope ☐ **3 Upper airways swelling of the tongue, pharynx (throat), uvula or larynx -** unequivocally documented by a healthcare professional. *Note: isolated lip swelling, if present, is angioedema (see B2 above) not upper airway swelling* ☐ **4. Cough or sneezing or runny nose that is new in onset and** persistent (lasts ≥ 5 minutes or occurs repeatedly) ☐ **5. None of 1, 2, 3 or 4** were present ☐ **6. Unknown if any of 1, 2, 3 or 4** were present		
	D-2 *Check all that were present of 1, 2, 3, 4, 5 and 6; OR choose either 7 or 8 depending on which is most accurate.*	☐ 1. Tachypnoea ☐ 2. Cyanosis ☐ 3. Grunting	☐ 4. Chest wall retractions ☐ 5. Increased use of accessory respiratory muscles ☐ 6. Measured hypoxia: oxygen saturation <90%	☐ 7. None of 1, 2, 3, 4, 5 or 6 presents ☐ 8. Unknown if any of 1, 2, 3, 4, 5 or 6 presents
5. Criterion E GI symptoms	*Check one or both of 1, 2 if present; OR choose either 3 or 4 depending on which is most accurate. NOTE: these count towards anaphylaxis, ONLY in the context of an intranasally administered or injected vaccine. They are not relevant for oral vaccines.*	☐ 1 New onset vomiting (at least 2 episodes in infants <12 months of age) ☐ 2 New onset diarrhoea (at least 2 episodes in infants < 12 months of age) ☐ 3. Neither 1 nor 2 were present ☐ 4. Unknown if 1 or 2 were present		
6. Criterion F Mast cell tryptase	*Check the one best option*	☐ 1 Mast cell tryptase > upper limit of normal for lab doing test OR 1.2 times baseline measurement + 2ng/L ☐ 2 Mast cell tryptase not elevated, or not tested, or unknown if tested or results not available		

TABLE 3. INTERPRETATION FORM FOR ARDS CRITERION VALUES: Based on clinical data entered into Table 5.2, assign a value to each criterion using the rules in the Criterion Options columns. *(Ne stands for not equal to)*

CRITERIA			OPTIONS FOR CRITERION VALUE			Criterion Value
			YES (Y) IF:	NO (N) IF:	UNKNOWN(U) IF:	
Criterion A	Rapid progression		__A = 1	__A = 2	__A = 3	A = Y N U
Criterion B	Skin:	Major B-1	__B = 1 or 2 or 3	__B = 4 or 5 or 6 AND B ne (1 or 2 or 3)	__B = 7	B-1 = Y N U
		Minor B-2	__B = 4 or 5	__B = 1 or 2 or 3 or 6 AND B ne (4 or 5)	__B = 7	B-2 = Y N U
Criterion C	Cardiac Major:		__C = 1 or 2	__C = 3	__C = 4	C = Y N U
Criterion D	Respiratory:	Major D-1	__D-1 = (1 or 2 or 3) OR __D-2 = ≥2 of (1, 2, 3, 4, 5 or 6)	__D-1 = 5 AND D-2 = 7 OR __D-1 = 5 AND D-2 = ≤1 of (1,2,3,4,5or6)	__D-1 = 6 & D-2 = 8	D-1 = Y N U
		Minor D-3	__D-1 = 4	__D-1 ne 4 OR D-1 = 5	__D-1 = 6	D-2 = Y N U
Criterion E	GI Major:		__E = 1 or 2	__E = 3	__E = 4	E = Y N U
Criterion F.	Laboratory Major:		__F = 1	Not applicable	__F = 2	F = Y N U

TABLE 4. SUMMARY OF ARDS CRITERION VALUES Record the final value for each Criterion from Table 5.3.

Criterion	A	B-1	B-2	C	D-1	D-3	E	F
Final Value								

TABLE 5. TABULAR ALGORITHM TO DETERMINE ANAPHYLAXIS V-2 LEVEL OF CERTAINTY (LOC) BASED ON CRITERION VALUES

Use final values of all criteria recorded in Table 5.4 to determine LOC based on the formulae below. The highest row in the table where **all criteria are met** =LOC.

Level of Certainty	ANAPHYLAXIS V-2
Level 1	A = Yes AND B-1 = Yes AND ≥1 OF (C or D-1 or E or F) = Yes
Level 2	A = Yes AND B-1 = (No or Unknown) AND ≥2 of (C or D-1 or E or F) = Yes
Level 3	A = Yes AND B-1 = (No OR Unknown) AND either of the following : ○ 1 of (D-1) = Yes AND (B-2) = Yes ○ 1 of (C or E or F) = Yes AND (B-2 or D-2) = Yes
Level 4	Unable to meet any level of certainty (1, 2 or 3) because of insufficient information
Level 5	A = No OR only a single system is involved (B or C or D or E or F)

FIGURE 1. PICTORIAL ALGORITHM FOR DETERMINING ANAPHYLAXIS V-2 LEVEL OF CERTAINTY

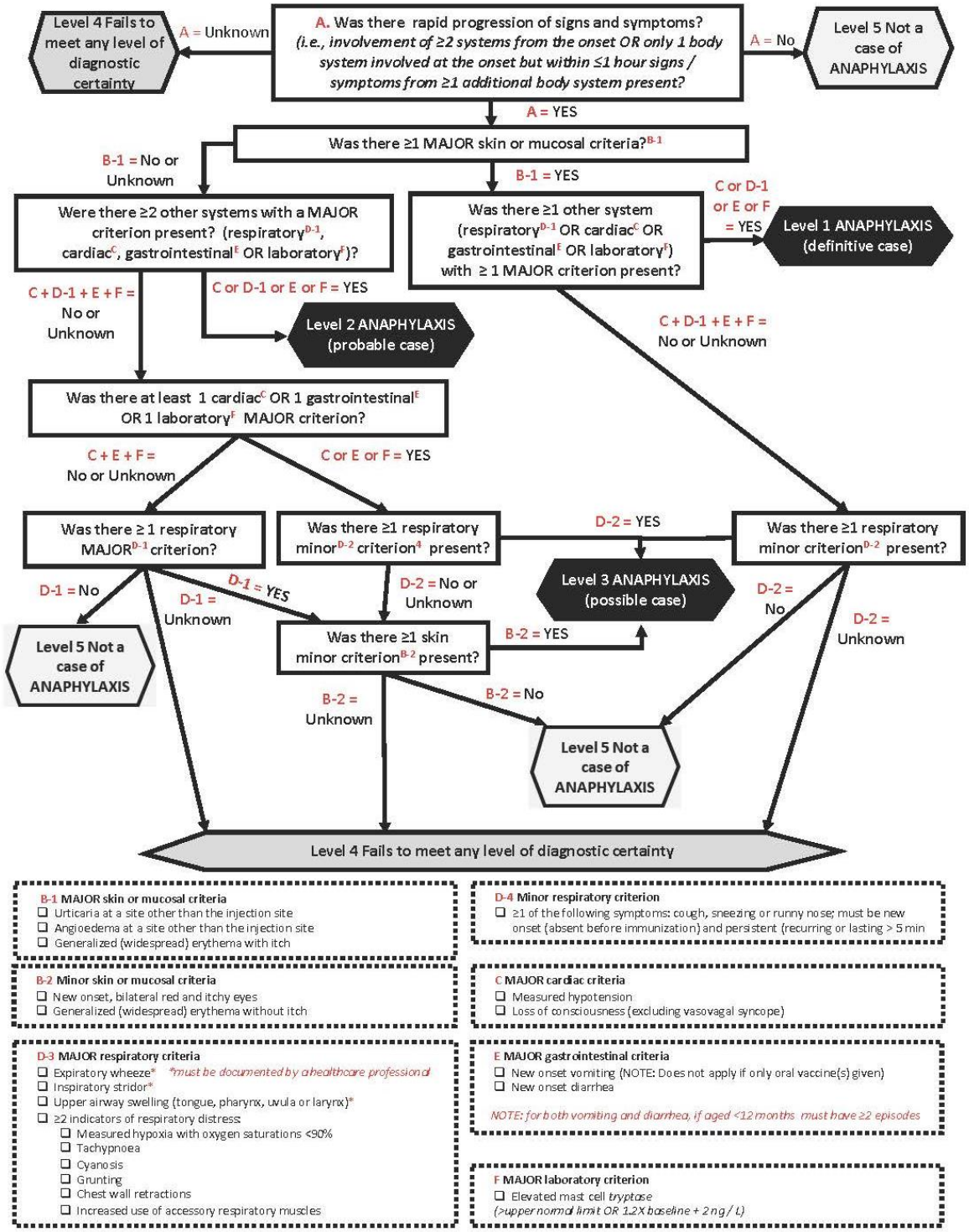

TABLE 6. GLOSSARY OF TERMS [36]

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 or mucosal tissues which may not be well circumscribed and usually not itchy. NOTE: hereditary angioedema, usually with a history of recurrent episodes of swelling, should be excluded (affects 1 in 50,000)
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. Synonym = widespread
Grunting	A sudden and short noise with each breath when breathing out
Hypotension	An abnormally low blood pressure (BP) documented by appropriate measurement. Age dependent as follows: • **<11 years:** Systolic < the sum of: 70mm Hg + 2 times age in years • **≥11 years:** Systolic <90 mm Hg OR Diastolic <60 mm Hg OR > 30% decrease from the person's baseline systolic BP
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).
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.
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 from the nose
Sneezing	An involuntary (reflex), sudden, violent, and audible expulsion of air through the mouth and nose.
Stridor	A harsh and continuous sound made on inspiration (breathing in)
Tachypnoea	Faster than normal respiratory rate. Age (in yrs) specific upper normal limits for breaths/min: <1=60; 1-<2=40; 2-<5=35; 5-<12=30; >12=16
Urticaria (hives)	Localized redness of superficial layers of skin that is itchy, raised, sharply demarcated and transient (usually lasts <12 hours)
Wheezing	A whistling, squeaking, musical or puffing sound made on expiration (breathing out)

APPENDIX 6.

Methodology: Brief Summary

6.1. Anaphylaxis Risk Factors [1-11]

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

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

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

The published Brighton Case definition[1] for 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]

6.2. Anaphylaxis Background Incidence [12-35]

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.

6.3. Anaphylaxis Case Definition key caveats for diagnosis, data analysis and presentation [2,36]

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.

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

An initial set of codes were retrieved through the Codemapper tool that was developed in the IMI-ADVANCE project. Subsequently they were reviewed and classified into narrow or broad codes by the authors.

CodeMapper [37] builds upon information from the Metathesaurus of the Unified Medical Language System (UMLS). The Metathesaurus is a compendium of many medical vocabularies, which have been integrated by assigning equivalent codes and terms from different source vocabularies to the same concepts. Each concept in the UMLS is identified by a CUI. A CUI is a Concept Unique Identifier for a Metathesaurus concept to which strings with the same meaning are linked. The Metathesaurus contains more than one million concepts connected to codes from 201 vocabularies. Each concept is assigned to one or more of 127 semantic types, which define broad conceptual categories like Disease or syndrome, Finding, or Substance.[38] Codemapper was built on the version 2016AA of the UMLS. The automatic concept identification of CodeMapper is based on lexical information from the Metathesaurus. The lexical information of a concept consists of terms that can be used in free text to refer to that concept. We compiled a dictionary for the concepts in the semantic groups Anatomy, Chemicals & Drugs, Disorders, Genes & Molecular Sequences, Living Beings, Phenomena, Physiology, and Procedures of non-suppressible, English terms from several vocabularies including ICD-9 CM, ICD-10 CM, and MedDRA.[39,40] A text-indexing engine Peregrine uses this dictionary to identify medical concepts in the case definition.[41] Of note, while SPEAC focused on ICD-9/10-CM and MedDRA codes, the CodeMapper concepts shown in the table can be used to search for codes in other systems including SNOMED-CT, MeSH, ICPC-2 and Read-CTv3.

CodeMapper has three screens.

1. The first displays the free text entered by the user – in this case the Brighton case definition. Medical concepts are automatically identified in the text and highlighted inline.
2. The second displays the mapping as a table with one row for each medical concept, and one column for each targeted vocabulary. Each cell contains the names of the codes that are used to represent the medical concept of the row in the targeted vocabulary of the column. The codes are displayed when the names are hovered over with the mouse. Several user operations are available for revising the mapping. The user can remove concepts from the mapping, search and add concepts, or retrieve more general and more specific concepts. The retrieved concepts are shown in a list and can be selected by the user for inclusion in the mapping. The user can also add or remove vocabularies that should be targeted by the mapping. After every operation, the codes are automatically updated and displayed in the table.
3. The third shows a list of all operations that have been made, for later traceability of the mapping process. When the user saves the mapping, he has to provide a summary of the modifications, which is incorporated into the mapping

history. The user can download the mapping as a spreadsheet file to incorporate the codes into extraction queries. The spreadsheet file comprises the original free-text case definition, the concepts of the mapping, the codes for the targeted vocabulary, and the full history of the mapping process.

Codemapping was conducted by MS. The output of the Codemapper concepts was reviewed by a medical expert (BL) familiar with the 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.

6.5. Tabular Checklist and Algorithms for Level of Certainty Determination [2,42]

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 algorithms were developed for each case definition. For one, formulae based on the logic in the case definition were put into tables with each row representing a level of certainty. For the second a more visual decision tree algorithm was developed based on a published algorithm. [42] Both however, were based on the logic inherent in the published case definition.[2]

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.