Safety Platform for Emergency vACcines

AESI Case Definition Companion Guide
Vaccine-associated enhanced disease (VAED)

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In case you have used this or any other Brighton Collaboration case definition companion guide, please take 3 minutes to respond to this survey, it will help us to improve our tools.

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DOCUMENT INFORMATION

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Description of the deliverable	This deliverable collates into a single document the SPEAC Vaccine-associated enhanced disease tools (data abstraction & interpretation form, tabular summary of key case definition criteria and algorithm for level of certainty determination, pictorial level of certainty algorithm) and guidance (real time investigation, data collection, analysis and presentation). This guide can be used by stakeholders to assess the occurrence of Vaccine-associated enhanced disease in clinical trials or epidemiologic studies. Unlike all other Brighton case definitions, this one cannot be applied to individual case reports in a pharmacovigilance setting. It is designed for use in controlled clinical trials or settings where the frequency of cases can be compared to that seen in naturally infected, unvaccinated individuals.
Key words	Vaccine-associated enhanced disease, Brighton case definition, case definition level of certainty.

DEFINITIONS & ACRONYMS

AESI	Adverse Events of Special Interest
α	alpha
APACHE II	Acute physiologic assessment and chronic health evaluation II
ARDS	Acute respiratory distress syndrome
BC	Brighton Collaboration
BNP	B-Natriuretic peptide
BUN	Blood urea nitrogen
CD	Case definition
CEPI	Coalition for Epidemic Preparedness and Innovation
CRP	C-reactive protein
CSF	Cerebrospinal fluid
dL	deciliter
ECG	Electrocardiogram
FiO2	Inspired fraction of Oxygen (expressed as a decimal – e.g., 21% O_2 = 0.21)
γ	Gamma
ICU	Intensive care unit
IL	Interleukin
INF	Interferon
INR	International normalized ratio
LDH	Lactate dehydrogenase
MAP	Mean arterial pressure
mg	milligram
NEWS	National Early Warning Score
NK	Natural killer
PALICC	Pediatric Acute Lung Injury Consensus Conference
PaO2	Partial pressure of arterial oxygen (measured in mm Hg)
PCR	Polymerase chain reaction
PELOD	Pediatric organ logistic dysfunction
PEWS	Pediatric early warning score
P-MODS	Pediatric multiple organ dysfunction
pSOFA	Pediatric sequential organ failure assessment
PT	Prothrombin time
PTT	Partial thromboplastin time
RBD	Receptor binding domain
SD	Standard deviation
SIRS	Severe inflammatory response syndrome
SOFA	Sequential organ failure assessment
SpO2	Hemoglobin oxygen saturation (expressed as a percentage - %)

SPEAC	Safety Platform for Emergency Vaccines
TNF	Tumor necrosis factor
VAED	Vaccine -associated enhanced disease
VAERD	Vaccine-associated enhanced respiratory disease
VPD	Vaccine preventable disease
WBC	White blood cell

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.

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 Vaccine-associated enhanced disease.

2. Objective of this deliverable

To collate SPEAC & BC tools, resources and guidance that have been developed for Vaccine-associated enhanced disease, hereinafter abbreviated as VAED.

3. Methods

3.1 VAED Case Definition key caveats for real time investigation, data collection, data analysis and presentation

The published Brighton case definition for VAED[1] was reviewed and key aspects identified with particular relevance to real time assessment of VAED in the context of a clinical trial or epidemiologic study. In addition, the supplemental guideline section for the VAED case definition was reviewed, and key recommendations identified for data collection, analysis and presentation (Guideline section available online by following the doi link to the publication). Recommended severity scores, also published as a supplement to the publication, were also reviewed for inclusion in the key caveats section.

3.2 Tabular Checklist and Algorithms for Level of Certainty Determination

The Brighton Collaboration case definition for VAED was thoroughly and repeatedly reviewed 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 VAED 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.

3.3 VAED background rates, risk factors and codes (ICD-9/10, MedDRA, SNOMEDCT)

These resources are usually included in Companion Guides but at this point it is not possible for VAED. The working group developed the case definition to apply to any vaccine preventable disease where infection following vaccination is more severe or more frequent than what occurs in unvaccinated individuals. Thus, for this particular guide, it is impossible to include background rates, risk factors or codes for an entire spectrum of vaccine preventable diseases.

4. Results

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

1. VAED Case Definition key caveats for diagnosis, data analysis and presentation
2. VAED Case report and interpretation forms with level of certainty algorithms

5. Recommendations & discussion

This guide brings together many guidelines and tools for studying VAED in the context of clinical vaccine trials or epidemiologic studies. It is important to note that while individual suspect cases may be assessed to determine level of certainty, the full case definition cannot be met on a case-by-case basis. Rather a comparison of case frequency is also required in the context of clinical vaccine trials (where there is a comparator control group) or large epidemiologic studies where the frequency of severe outcomes in vaccinated individuals who become infected after receiving vaccine can be compared to unvaccinated individuals who had natural infection. With this constraint, the VAED case definition cannot be applied in the pharmacovigilance setting unless in the context of evaluating a possible signal.

6. References

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APPENDIX 1.

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

1.1. Vaccine associated enhanced disease Case Definition[1] Key Caveats for Diagnosis, Data Analysis and Presentation

1.1.1 Key elements of Case Definition (CD)

- There is no level 1 (highest specificity and certainty) for VAED because of current lack of knowledge regarding the pathogenic mechanisms and also of any definitive diagnostic test(s).
- Both Levels 2 and 3 have sub-levels based on knowledge of the serostatus prior to vaccination:
    - Vaccinated individual known to have been seronegative, prior to vaccination, for the infection the vaccine is designed to prevent.
    - Vaccinated individual has no prior history of infection by the vaccine-targeted pathogen and serostatus prior to vaccination is unknown.
- Level 2 requires evidence of immunopathology in target organs. This is the only difference between Level 2 and Level 3.
- Criteria common to both Levels 2 and 3 include clinical findings of disease involving one or more organ systems, documented severe disease using a clinical severity index/score (described below) and no identified alternative etiology.
- NOTE: A unique additional criterion for both Levels 2 and 3 of the case definition is "increased frequency of severe outcomes (including severe disease, hospitalization and mortality) when compared to a non-vaccinated population (control group or background rates). While the criteria mentioned above can be applied to individuals, the frequency criterion requires large populations of vaccinated individuals where VAED frequency in the vaccinated group can be statistically compared to equally large populations of unvaccinated controls. Alternatively, the VAED incidence can be compared to unvaccinated populations undergoing natural infection. In either case it will be important to be aware of and try to control for any risk factors (e.g., age, sex, comorbidities, geographic location) that impact on the incidence of severe disease.

- Duration of Surveillance
    - The Working Group recommended a minimum period of 1 year surveillance for VAED in vaccine clinical trials where it is potential AESI. For any pathogens with a seasonal distribution, it is recommended to continue follow-up through at least two years in case there is variation in strains from year to year which could impact on natural disease severity.

Guidelines for Data Collection, analysis and presentation of VAED and VAERD

- A severity score is a required criterion for the case definition. Ideally the same system for assessing severity should be used for all cases.
- Interval from vaccination to presentation
    - <6 months post-vaccination

- 6-<12 months post-vaccination
- 12-<24 months post-vaccination
- 12 month increments thereafter

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APPENDIX 2

VAED Case Report and Interpretation Forms with Level of Certainty Algorithms

2.1. Vaccine-associated enhanced disease Data Abstraction and Interpretation Form for Medical Chart Review

Instructions are provided with each table. The focus is on the specific data needed to meet and/or exclude VAED based on the Brighton case definition.[1] This form will be most applicable to active surveillance or situations where a hospital/other institutional chart is available and used retrospectively to gather the information needed to validate that a case coded as VAED meets or does not meet the Brighton case definition (with the exception of the requirement for increased frequency of severe outcomes or of acquisition of infection, which can only be determined by analysis of multiple cases with a control group or known background incidence among naturally infected, non-vaccinated populations).

Five tables and 1 figure are included in this appendix:

- **Table 2.1** lists all Brighton case definition[1] criteria for VAED and identifies likely sources of information for each.
- **Table 2.2** is the main data abstraction form that can be used to record data pertinent to VAED
- **Table 2.3** 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 2.4** is a brief summary of the final value for each criterion. As per table 5.3
- **Table 2.5** provides the formulae used to assign level of certainty for VAED based on criterion values summarized in Table 2.4
- **Figure 2.1** shows pictorial algorithms for determining level of certainty for VAED cases

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

Criterion	Criterion category	Likely sources of information	Actual sources of information
A	Laboratory confirmed VPD	• Laboratory test results (culture, antigen detection, nucleic acid detection, paired acute and convalescent serology)	
B	VPD Serostatus prior to vaccination	• Pre-vaccination serology results • Absence of a history of infection by the targeted pathogen.	
C	Multisystem disease	• Emergency room notes; • admission (hospital or ICU) history and physical examination; • sub-specialty consultations; • laboratory tests indicating organ injury (e.g., cardiac troponin; elevated liver enzymes);	`
D	VPD severity index/score		
E	Alternative etiologies		`

		• physiologic tests of system function (e.g., cardiac function by echocardiography; renal function by determination of glomerular filtration rate).	
F	VPD target organ immunopathology	• Immunology consultation • Immunopathology report (tissue biopsy or autopsy) • Measures of complement, cytokines, immune complex deposition in tissue	
G	Increased frequency of severe VPD outcomes	• Epidemiologic data on severe outcomes in naturally infected, unvaccinated populations or controls	

TABLE 2. VAED DATA ABSTRACTION FORM: Complete all rows in the table to the extent possible. Red font identifies specific VAED criteria. Note that the form below is generic since multiple vaccines directed against a range of pathogens could potentially lead to VAED. This form can be used to develop a specific CRF that would identify more specifically the tests used to detect infection by the pathogen or assess serostatus.

1.Date of illness onset	
2.Hospital admission?	
3.Admitting diagnosis	
4.Discharge diagnosis	
5. Criterion A **Laboratory confirmed infection with pathogen targeted by vaccine**	*Choose the single best option from 1-3 below:* ☐ 1. There was definitive laboratory confirmation of infection by the pathogen targeted by the vaccine ☐ 2. Valid tests to detect the pathogen targeted by the vaccine were done and were negative. ☐ 3. It is unknown if valid tests to detect the pathogen targeted by the vaccine were done, or tests were done but results unknown
6. Criterion B **Patient VPD serostatus prior to vaccination or past history of VPD**	*Choose the single best option from 1, 2 and 3 below:* ☐ 1. Seronegative status against the pathogen targeted by the vaccine confirmed prior to vaccination. ☐ 2. Serostatus against the pathogen targeted by the vaccine not measured prior to vaccination or status unknown. Individual had no history of prior infection with the pathogen at the time of vaccination. ☐ 3. Serostatus and history of infection by the pathogen targeted by the vaccine unknown

7. Criterion C **Evidence for multisystem clinical illness** Choose all clinical and testing options that apply for each system, and if at least 1 clinical	**System**	Clinical and features	Radiologic, Physiologic or Laboratory Testing
	☐ **C-1 Respiratory**	☐ Respiratory distress ☐ Respiratory failure ☐ Lower respiratory tract disease ☐ Pulmonary hemorrhage	☐ Hypoxemia or increased oxygen requirement ☐ Decreased PaO2 ☐ PaO2/FiO2 or SpO2/FiO2 ratio ☐ Aa gradient ☐ Chest radiographic abnormalities
	☐ **C-2 Cardiovascular**	☐ Tachycardia ☐ Hypotension ☐ Heart failure	☐ Elevated cardiac Troponin (s) ☐ Elevated NTproBNP ☐ Abnormal EKG

or lab feature present, check the System box. ***Note:*** *This is not meant to be an exhaustive list and it should be adapted based on the severe clinical manifestations of the target pathogen infection. The requirement is that at least 2 systems be involved, but no specific system signs, symptoms or labs are required. This is just a guide that was included in the case definition publication.*		☐ Myocarditis ☐ Vasculitis / vasculopathy ☐ Cardiogenic shock	☐ Abnormal echocardiogram
	☐ **C-3. Hematopoietic & Immune**	☐ Coagulopathy ☐ DIC ☐ Abnormal bleeding ☐ Thrombotic / Thromboembolic events	☐ Leukopenia or Lymphopenia or Thrombocytopenia ☐ Altered coagulation parameters (PT, PTT, D-dimer, INR) ☐ Elevated inflammatory markers (CRP, procalcitonin, ferritin, LDG) ☐ Elevated cytokines
	☐ **C-4 Renal**	☐ Acute kidney injury ☐ Acute renal failure ☐ Needed renal replacement therapy	☐ Elevated serum creatinine ☐ Decreased urine output ☐ Decreased glomerular filtration rate
	☐ **C-5 Gastrointestinal & Hepatic**	☐ Vomiting, diarrhea or abdominal pain ☐ Hematochezia / M\melena ☐ Hepatitis ☐ Acute liver failure	☐ Electrolyte abnormalities ☐ Elevated liver enzymes (SGOT, SGPT) ☐ Elevated bilirubin
	☐ **C-6 Central Nervous System**	☐ Altered mental status ☐ Seizure(s) ☐ Cranial nerve palsies ☐ Loss of consciousness	☐ Elevated intracranial pressure ☐ Abnormal cerebrospinal fluid parameters
	☐ **C-7 Other**	☐ Fatigue ☐ Myalgia ☐ Myositis / myonecrosis ☐ Arthralgia / arthritis ☐ Multiorgan failure ☐ Death	☐ Viral load (PCR tests) ☐ Antibody titers
8. Criterion D	*Check any severity index or score applied during the case illness. Record actual score calculated, choosing the one that indicated the highest degree of severity*		

Clinical severity index or score *There should be at least 1 severity score applied. These are the ones mentioned in the VAED CD publication. The WG did not recommend a specific scoring system, but noted that the same system should be used across all cases*	**Adult Severity Scores (see section 2.2 below)** ☐ 1. National Early Warning Score (NEWS) ☐ 2. APACHE II ☐ 3. Sequential Organ Failure Assessment (SOFA) ☐ 4. Glasgow Coma Score. ☐ 5. Other adult score (describe)	**Pediatric Severity Scores (see section 2.3 below)** ☐ 6.Pediatric Early Warning Score (PEWS) ☐ 7. Pediatric SOFA ☐ 8. Pediatric Glasgow Coma Score. ☐ 9. Pediatric Logistic Organ Dysfunction Score (PELOD) 2 ☐ 10. Pediatric Multiple Organ Dysfunction Score (P-MODS) ☐ 11. Other Pediatric score (describe)
9. Criterion E. **Alternate etiology**	☐ 1. Yes, there was an alternate explanation for the illness ☐ 2. There was no alternate explanation for the illness (including if no testing done for alternate diagnosis)	
10. Criterion F **Target organ immunopathology**	*Choose all that apply for options 1 – 5; If unable to choose any of 1-5, select 6* ☐ 1. Presence or elevation of eosinophils in tissue (relative to what would be expected for the specific tissue location) ☐ 2. Elevated pro-inflammatory Th2 cytokines in tissue (IL-4, IL-5, IL-10, IL-13) ☐ 3. C4d tissue deposition (evidence of immune complex deposition) ☐ 4. C1q assessments of immune complexes in fluid ☐ 5. Low C3 levels (evidence of complement consumption) ☐ 6. Some or all of tests mentioned above done, and all that were done were negative for target organ immunopathology or none of the tests 1-5 were done, or unknown if done, or done but results unknown.	

TABLE 3. Based on the information recorded in Table 2 above, record the value of each of the listed criteria

CRITERIA		OPTIONS FOR CRITERION VALUE			Criterion Value
		YES (Y) IF:	NO (N) IF:	UNKNOWN (U) IF:	
Criterion A Confirmed infection by vaccine-targeted pathogen		__A = 1	__A = 2	__A = 3	A = Y N U
Criterion B Target pathogen serostatus prior to vaccination or no history of prior infection	B-1	__B = 1	Not applicable	__B = 3	B-1 = Y U
	B-2	__B = 2 and not equal to 1	Not applicable	__B = 3	B-2 = Y U
Criterion C Multiorgan involvement		__C = ≥ 2 systems involved (C-1, C-2, C-3, C-4, C-5, C-6 or C-7)	__C = 0-1 system involved (C-1, C-2, C-3, C-4, C-5, C-6 or C-7)	Not applicable	C = Y N
Criterion D Clinical Severity Index / Score applied to assess severity		__D = any of 1 - 11	Not applicable	__D = none of 1 – 11 checked	D = Y N
Criterion E Alternate etiology		__E = 1	__E = 2	Not applicable	E = Y N
Criterion F Demonstration of target organ immunopathology		__F = ≥1 of (1, 2, 3, 4 or 5)	__F = 6	Not applicable	F = Y N

TABLE 4. SUMMARY OF VAED CRITERION VALUES Record the final value for each Criterion from Table 3.

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

TABLE 5. TABULAR ALGORITHM TO DETERMINE VAED LEVEL OF CERTAINTY (LOC) BASED ON CRITERION VALUES Use final values of all criteria recorded in Table 4 to determine LOC based on the formulae below. The highest row in the table where **all criteria are met** will be the LOC.

Level of Certainty		
Level 1		There is no Level 1 of certainty for VAED due to lack of evidence on mechanism or diagnostic tests
Level 2	2-A	(A & B-1 & C & D & F = Yes) AND (E = No or Unknown)
	2-B	(A & B-2 & C & D & F = Yes) AND (E = No or Unknown) AND (B-1 & F = No)
Level 3	3-A	(A & B-1 & C & D = Yes) AND (E = No or Unknown) AND (F = No)
	3-B	(A & B-2 & C & D = Yes) AND (E = No or Unknown) AND (B-1 & F = No)
Level 4		Fails to meet any level of certainty (2-A, 2-B, 3-A, 3-B or 5) because insufficient data
Level 5		(A or B-2 or C or D = No) OR E = Yes

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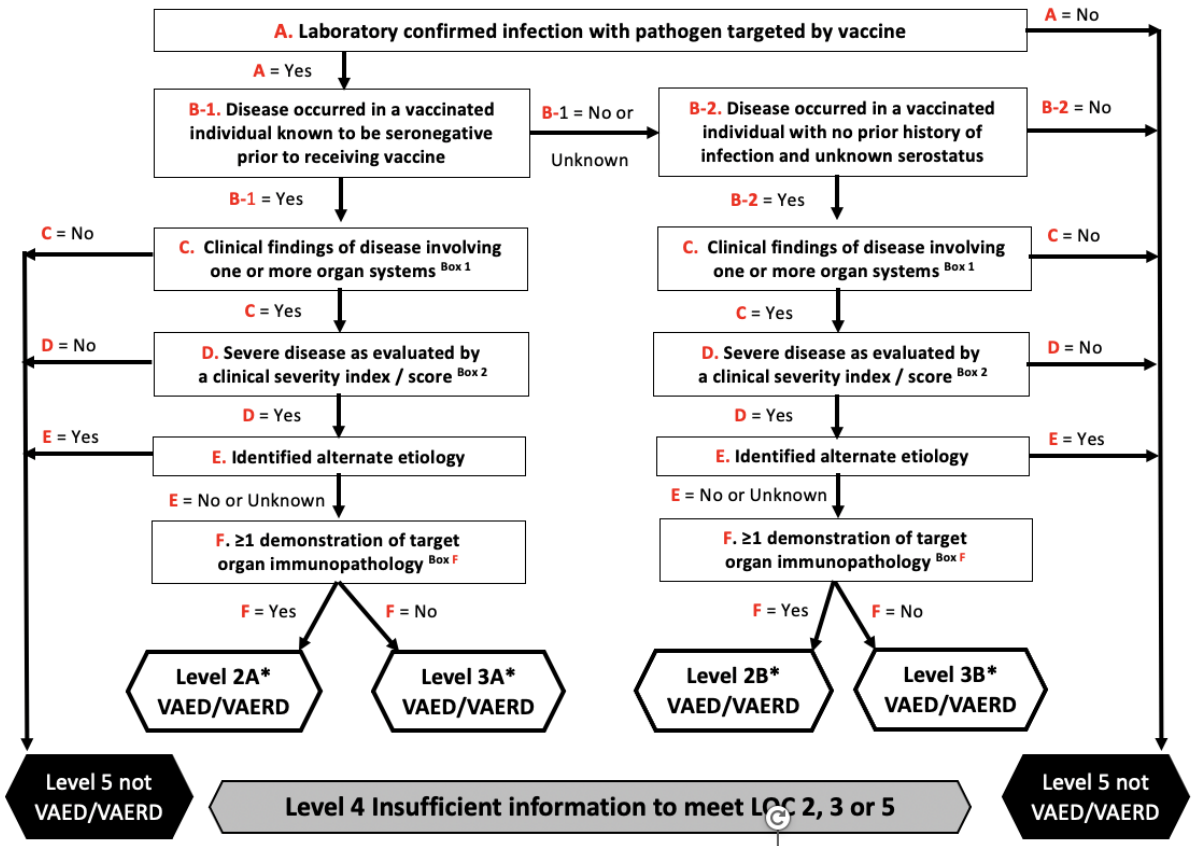
FIGURE 1. PICTORIAL ALGORITHM FOR DETERMINING VAED LEVEL OF CERTAINTY IN ADULTS



C.. Organ system involvement (guide only; not exhaustive)

i. Respiratory (VAERD) ≥1 :
- ❑ Clinical - respiratory distress / failure; Lower respiratory tract disease; pulmonary hemorrhage; Radiolographic abnormalities
- ❑ Lab – hypoxemia, oxygen requirement; PaO2; Aa gradient; PaO2/FiO2 ratio

ii. Cardiovascular ≥1:
- ❑ Clinical: tachycardia; hypotension; heart failure; myocarditis; vasculitis/vasculopathy; cardiogenic shock
- ❑ Lab – elevated NTproBNP or Troponin; abnormal EKG; abnormal echocardiogram

iii Hematopoietic & Immune system - ≥1:
- ❑ Clinical: coagulopathy; DIC; bleeding/thrombotic events
- ❑ Lab – leukopenia; lymphopenia; thrombocytopenia; B and t cell functioin assays; altered coagulation parameters (PT, PTT, D-Dimer, INR); elevated inflammatory markers (CRP, procalcitonin, ferritin, LDH); elevated cytokines

iv. Renal - ≥1:
- ❑ Clinical: renal dysfunction; acute kidney injury; need for renal replacement therapy
- ❑ Lab – decreased urine output; elevated serum creatinine; decreased GFR

v. Gastrointestinal and Hepatic systems - ≥1:
- ❑ Clinical: emesis/diarrhea; abdominal pain; hematochezia/Melena; hepatitis; acute liver failure
- ❑ Lab – electrolyte abnormalities; elevated liver enzymes / bilirubin

vi. Central Nervous System
- ❑ Clinical: altered mental status, seizures; cranial nerve palsies; loss of consciousness
- ❑ Lab: elevated ICP; abnormal CSF parameters

vii. Other
- ❑ Clinical: fatigue; myalgia/myositis/myonecrosis;arthralgia / arthritis; multiorgan failure; death
- ❑ Lab – viral load (PCR Ct value); antibody titers

NOTE: There is no Level 1 for VAED/VAERD due to lack of evidence for establishing a definite case

***G. Increased frequency of severe outcomes (including severe disease, hospitalization and mortality) when compared to a non-vaccinated population (control group or background rates)**

Criteria A, B-1, B-2, C, D, E and F must be applied to individuals. However, to meet the case definition of VAED/VAERD at any level of certainty , it is necessary to confirm that the frequency of identified cases exceeds that in a control group or the background rate of severe outcomes following infection in unvaccinated persons

F. Evidence of immunopathology in target organs - ≥1:
- ❑ Present or elevated eosinophils in tissue
- ❑ Elevated pro-inflammatory Th2 cytokines in tissue (IL4, IL5, IL10, IL13)
- ❑ C4d tissue deposition (evidence of immune complex deposition)
- ❑ C1q assessments of immune complexes in fluids
- ❑ Low C3 levels (evidence of complement consumption)

2.2 Adult severity scores

2.2.1 National Early Warning Score[2] (NEWS) 2.

Use primarily in ambulatory care setting to standardize assessment and response to acute illness.
Not suited for assessment of systemic multiorgan dysfunction (see SOFA score below)

TABLE 6. National Early Warning Score[2] (NEWS) 2

Physiologic parameter	SCORE						
	3	2	1	0	1	2	3
Respiration rate/minute	≤8		9-11	12-20		21-24	≥25
SpO2 Scale 1 (%)	≤91	92-93	94-95	≥96			
SpO2 Scale 2 (%)	≤83	84-85	86-87	88-92 ≥93 on air	93-94 on oxygen	95-96 on oxygen	≥97 on oxygen
Air or Oxygen		Oxygen		Air			
Systolic blood pressure (mmHg)	≤90	91-100	101-110	111-219			≥220
Pulse (per minute)	.≤40		41-50	51-90	01-110	111-130	≥131
Consciousness				Alert			CVPU
Temperature (°C)	≤35.0		35.1-36.0	36.1-38.0	38.1-39.0	≥39.1	

NEW Score	Clinical Risk	Response
Aggregate score 0-4	Low	Ward-based response
Red score – 3 in any individual parameter	Low-medium	Urgent ward-based response*
Aggregate score 5-6	Medium	Key threshold for urgent response*
Aggregate score 7 or more	High	Urgent or emergency response**

* Response by a clinician or team with competence in assessment and treatment of acutely ill patients and in recognizing when the escalation of care to a critical care team is appropriate

** The response team must also include staff with critical care skills, including airway management

Score interpretation:

- **Low clinical risk:** aggregate score 0-4
- **Low to medium clinical risk:** Score of 3 in any individual parameter
- **Medium clinical risk:** Aggregate score of 5-6
- **High clinical risk:** Aggregate score of ≥7

2.2.2 APACHE (Acute Physiologic Assessment and Chronic Health Evaluation) II Scoring System.3

- Used to predict mortality, not guide management.
- Assess on first day in ICU; choose worst value of all measured.
- APACHE II score is sum of the 12 individual parameters
- Add points for age: 0 for <44 years; 2 for 45-54 years; 3 for 55-64 years; 5 for 65-74 years; 6 for ≥75 years
- Add points for chronic health status, which must have preceded current admission: 2 for elective postoperative patient with immunocompromise or history of severe organ insufficiency; 5 points for nonoperative patient or emergency postoperative patient with immunocompromise or severe organ insufficiency.

TABLE 7. APACHE (Acute Physiologic Assessment and Chronic Health Evaluation) II Scoring System.3

PARAMETER	SCORE								
	+4	+3	+2	+1	0	+1	+2	+3	+4
Temperature, core (^{APACHE}C)	≥41°	39-40.9°		38.5-38.9°	36-38.4°	34-35.9°	32-33.9°	30-31.9°	≤29.9°
Mean arterial pressure (mmHg)	≥160	130-159	110-129		70-109		50-69		≤49
Heart rate	≥180	140-179	110-139		70-109		55-69	40-54	≤39
Respiratory rate	≥50	35-49		25-34	12-24	10-11	6-9		≤5
Oxygenation									
If FIO2≥0.5 use A-aDO2	≥500	350-499	200-349		<200				
If FIO2 <0.5 use PAO2 (mmHg)					>70	61-70		55-60	≤55
Arterial pH	≥7.7	7.6-7.69		7.5-7.59	7.33-7.49		7.25-7.32	7.15-7.24	<7.15
Serum sodium (mmol/L)	≥180	160-179	155-159	150-154	130-149		120-129	111-119	≤110
Serum potassium (mmol/L)	≥7	6-6.9	---	5.5-5.9	3.5-5.4	3-3.4	2.5-2.9	---	<2.5
Serum creatinine (mg/dL) Double point score if acute renal failure	≥3.5	2-3.4	1.5-1.9	---	0.6-1.4	---	<0.6	---	---
Hematocrit (%)	≥60	---	50-59.9	42-49.9	30-45.9	---	20-29.9	---	<20
WBC (in 1000s)	≥40	---	20-39.9	15-19.9	3-14.9	---	1-2.9	---	<1
Glasgow Coma Score (GCS) (see table below)	Assigned score =15 – calculated GCS								
(Serum bicarbonate (venous-mmol/L)*	≥52	41-51.9		32-40.9	23-31.9		18-21.9	15-17.9	<15

** Use this to score ONLY if arterial blood gas measurements are unavailable.*

2.2.3 SOFA (Sequential Organ Failure Assessment) [4]

TABLE 8. SOFA (Sequential Organ Failure Assessment) [4]

System	Parameter	SOFA SCORE			
		1	2	3	4
Respiratory	PaO1/FiO2(mmHg)[1] SaO2/FIO2	<400 221-301	<300 142-220	<220 67-141	<100 <67
Coagulation	Platelet count (X 10^3/mm^3)	100-<150	50-<100	20-<50	<20
Liver	Bilirubin (mg/dL)	1.2-1.9	2.0-5.9	6.0-11.9	≥12.0
Cardiac	Mean arterial pressure (MAP)	MAP <70	Dopamine ≤ 5 or dobutamine (any)[2]	Dopamine >5 or norepinephrine ≤0.1[2]	Dopamine >15 or norepinephrine >0.1[2]
CNS	Glasgow Coma Score[3]	13-14	10-12	6-9	<6
Renal	Creatinine (mg/dL) OR Urine output (mL/day)	1.2-1.9 NA	2.0-3.4 NA	3.5-4.9 OR <500	>5.0 OR <200

[1] PaO_2/FIO_2 value preferred but if not available use SaO_2/FIO_2 ratio

[2] Requiring vasoactive medications as shown, administered for at least 1 hour. Values refer to nanograms/kilogram body weight/minute

[3] See 2.2.3 below

2.2.4 Glasgow coma score for adults[5]

TABLE 8. Glasgow coma score for adults[5]

Score	Best Eye Response (E)	Best Verbal Response (V)	Best Motor Response (M)
6			__Obeys commands
5		__Oriented	__Localising pain
4	__Eyes open spontaneously	__Confused	__Withdrawal from pain
3	__Eye opening to verbal command	__Inappropriate words	__Flexion to pain
2	__Eye opening to painful stimulus	__Incomprehensible sounds	__Extension to pain
1	__No eye opening	__No verbal response	__No motor response
Score	___E + ____V + ____M = ____total Glasgow Coma Score (GCS)		

2.3 Pediatric severity scores

2.3.1 Pediatric Early Warning Signs[6] (PEWS) Scores – identifies acutely ill patients at risk for deterioration
Many different scoring systems which are not validated so no specific one recommended. The Working Group cited a systematic review of 33 scoring systems which may be helpful to identify a suitable severity score.[7]

2.3.2 Pediatric Sequential Organ Failure Assessment Score (pSOFA)[8]

TABLE 9. Pediatric Sequential Organ Failure Assessment Score (pSOFA)[8]

	Score[a]				
Variables	0	1	2	3	4
Respiratory					
Pao_2:Fio_2[b] or Spo_2:Fio_2[c]	≥400	300-399	200-299	100-199 With respiratory support	<100 With respiratory support
	≥292	264-291	221-264	148-220 With respiratory support	<148 With respiratory support
Coagulation					
Platelet count, $\times 10^3/\mu L$	≥150	100-149	50-99	20-49	<20
Hepatic					
Bilirubin, mg/dL	<1.2	1.2-1.9	2.0-5.9	6.0-11.9	>12.0
Cardiovascular					
MAP by age group or vasoactive infusion, mm Hg or μg/kg/min[d]					
<1 mo	≥46	<46	Dopamine hydrochloride ≤5 or dobutamine hydrochloride (any)	Dopamine hydrochloride >5 or epinephrine ≤0.1 or norepinephrine bitartrate ≤0.1	Dopamine hydrochloride >15 or epinephrine >0.1 or norepinephrine bitartrate >0.1
1-11 mo	≥55	<55			
12-23 mo	≥60	<60			
24-59 mo	≥62	<62			
60-143 mo	≥65	<65			
144-216 mo	≥67	<67			
>216 mo[e]	≥70	<70			
Neurologic					
Glasgow Coma Score[f]	15	13-14	10-12	6-9	<6
Renal					
Creatinine by age group, mg/dL					
<1 mo	<0.8	0.8-0.9	1.0-1.1	1.2-1.5	≥1.6
1-11 mo	<0.3	0.3-0.4	0.5-0.7	0.8-1.1	≥1.2
12-23 mo	<0.4	0.4-0.5	0.6-1.0	1.1-1.4	≥1.5
24-59 mo	<0.6	0.6-0.8	0.9-1.5	1.6-2.2	≥2.3
60-143 mo	<0.7	0.7-1.0	1.1-1.7	1.8-2.5	≥2.6
144-216 mo	<1.0	1.0-1.6	1.7-2.8	2.9-4.1	≥4.2
>216 mo[e]	<1.2	1.2-1.9	2.0-3.4	3.5-4.9	≥5

2.3.3 Pediatric Version of Glasgow Coma Scale[9]

TABLE 10. Pediatric Version of Glasgow Coma Scale[9]

Score	Eyes Open	Best Verbal Response	Best Motor Response
5		Orientated	Obeys command
4	Spontaneously	Words	Localizes pain
3	To speech	Vocal sounds	Flexion to pain
2	To pain	Cries	Extension to pain
1	None	None	None
Score	___E + ____V + ____M = ____total Glasgow Coma Score (GCS)		

TABLE 11. Best achievable normal scores for age: (13+ = mild brain injury; 9-12=moderate; <=8=severe

	Best verbal response	Best motor response	Normal aggregate score
0-6mos	Cry = 2	Flexion to pain = 3	9
6-12mos	Vocal sound = 3	Locates pain = 4	11
12-24 mos	Words = 4	Locates pain = 4	12
2-5 yrs	Words = 4	Obeys command = 5	13
>5 yrs	Orientated = 5	Obeys command = 5	14
Adult	Orientated=5	Obeys command=6	15

2.3.4 Pediatric Logistic Organ Dysfunction Score (PELOD) 2 [10]

TABLE 12. Pediatric Logistic Organ Dysfunction Score (PELOD) 2 [10]

System and Related Parameter	Age	SCORE						
		0	1	2	3	4	5	6
Neurologic								
Glasgow Coma Score	All ages	≥11	5-10			3-4		
Pupillary reaction	All ages	Both reactive					Both fixed	
Cardiovascular								
Lactatemia (mmol/L)	All ages	<5.0	5.0-10.9			>11.0		
MAP (mmHg)	0-<1mo 1-11mo 12-23mo 24-59mo 60-143mo ≥144 mo	≥46 ≥55 ≥60 ≥62 ≥65 ≥67		31-45 39-54 44-59 46-61 46-64 52-66	17-30 25-28 31-43 32-44 36-48 38-51			≤16 ≤24 ≤30 ≤31 ≤35 ≤37
Renal: Creatinine (umol/L)	0-<1mo 1-11mo 12-23mo 24-59mo	≥69 ≥22 ≥34 ≥50		≥70 ≥23 ≥55 ≥51				

	60-143mo ≥144 mo	≥58 ≥92		≥59 ≥93				
Respiratory								
PaO2/FiO2	All ages	≥61		≤60				
PacO2(mmHg)		≥58	58-94		≥95			
Invasive ventilation		No			Yes			
Hematologic								
WBCs (X 10^9/L)	All ages	>2		≤2				
Platelets (X 10^9/L)		≥142	77-141	≤76				

TABLE 13. Relationship between number of organ dysfunctions, PELOD-2 score and mortality

Number of Organ Dysfunctions	PELOD-2 mean score (SD)	Mortality Rate (%)
0	0 (0.0)	0.4
1	2.3 (0.8)	0.3
2	4.9 (1.3)	1.2
3	7.5 (2.0)	7.1
4	11.5 (4.4)	30.5
5	16.8 (5.2)	59.0

2.3.5 Pediatric Multiple Organ Dysfunction Score (P-MODS)[11]

MODS defined as concurrent dysfunction of ≥2 organ systems. Strongly correlates with PICU mortality.

TABLE 14. Pediatric Multiple Organ Dysfunction Score (P-MODS)[11]

Parameter	SCORE				
	0	1	2	3	4
Lactic acid (mmol/L)	<1	1-2	2-5	5-7.5	>7.5
PaO2/FIO2	>150	100-150	75-100	50-75	<50
Bilirubin					
µmol/L	<8.5	8.5-34.2	34.2-85.5	85.5-171	>171
mg/dL	<0.5	0.5-2.0	2.0-5.0	5.0-10.0	>10
BUN					
µmol/L	<7.10	7.10-14.3	14.3-21.4	21.4-28.5	>28.5
mg/dl	<20	20-40	40-60	60-80	>80