CONSULTATION DOCUMENT FOR CASE DEFINITIONS

Adverse Events of Special Interest, and Adverse Events Following Immunization during COVID-19 Vaccine Introduction

Second Edition

PAHO
Pan American Health Organization
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REGIONAL OFFICE FOR THE Americas

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Washington, D.C., 2022

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ABBREVIATIONS AND ACRONYMS

AAA	acute aseptic arthritis
ACCESS	vACCine covid-19 monitoring readinESS
ACE	angiotensin-converting-enzyme
ADEM	acute disseminated encephalomyelitis
AEFI	adverse event following immunization
AESI	adverse event of special interest
AF	atrial fibrillation
AHF	acute heart failure
AIDS	acquired immunodeficiency syndrome
AKI	acute kidney injury
ALF	acute liver failure
ALI	acute liver injury
ALP	alkaline phosphatase
ALT	alanine aminotransaminase
AP	acute pancreatitis
ARDS	acute respiratory distress syndrome
ARS	Agenzia Regionale di Sanita Toscana
AV	atrioventricular
AZ	AstraZeneca
BC	Brighton Collaboration
BCCD	Brighton Collaboration case definition
BNP	brain natriuretic peptide
BP	Bell's palsy
CD	case definition
CDC	Centers for Disease Control and Prevention (United States)

CK	creatine kinase
CMR	cardiac magnetic resonance
CMV	Cytomegalovirus
CNS	central nervous system
COVID-19	coronavirus disease of 2019
CRP	C-reactive protein
CSF	cerebrospinal fluid
CT scan	computed tomography scan
CV	cutaneous vasculitis
CXR	chest X ray
dB	decibel
DILI	drug-induced liver injury
DNA	deoxyribonucleic acid
DPT	diphtheria, pertussis, and tetanus vaccine
DT	diphtheria and tetanus vaccine – childhood
DTaP	diphtheria, tetanus, and acellular pertussis vaccine
DTwP	diphtheria, tetanus, and pertussis vaccine – whole-cell
DVT	deep vein thrombosis
EBV	Epstein-Barr virus
ECG	electrocardiogram or EKG
ECHO	ecocardiogram
EM	erythema multiforme
EMA	European Medicines Agency
ESR	erythrocyte sedimentation rate
FDA	Food and Drug Administration (United States)
FT	typhoid fever vaccine
GBS	Guillain-Barré syndrome

GFR	glomerular filtration rate
HA	hepatitis A vaccine
HB	hepatitis B vaccine
HE	hepatic encephalopathy
HF	heart failure
HFmrEF	heart failure with mid-range ejection fraction
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
Hib	Haemophilus influenzae type b
HIV	human immunodeficiency virus
HPV	human papillomavirus
HSV	herpes simplex virus
HZ	herpes zoster
IgE	immunoglobulin E
IMR	index of coronary muscular resistance
INR	international normalized ratio
IR	incidence rate
IRR	internal rate of return
ITP	idiopathic thrombocytopenia
KD	Kawasaki disease
KDIGO	Kidney Disease: Improving Global Outcomes
LAE	left atrial enlargement
LCR	low complexity region
LOC	level of certainty
LV	left ventricular
LVEF	left ventricular ejection fraction
LVH	left ventricular hypertrophy

MERS	Middle East Respiratory Syndrome
MFS	Miller Fisher syndrome
MI	myocardial infarction
MIS-A	multisystem inflammatory syndrome in adults
MIS-C	multisystem inflammatory syndrome in children
MMR	measles, mumps, and rubella
MMRV	measles, mumps, rubella, and varicella vaccine
MRA	magnetic resonance arteriography
MRI	magnetic resonance imaging
MRV	magnetic resonance venography
MSLT	mean sleep latency
NSAID	non-steroidal anti-inflammatory drug
NT-proBNP	N-terminal proBNP
PAC	premature atrial contraction
PAD	peripheral artery disease
PAHO	Pan American Health Organization
PALICC	Pediatric Acute Lung Injury Consensus Conference
PCR	polymerase chain reaction
PD	Parkinson's disease
PE	pulmonary thromboembolism
PFSAT	painful (De Quervain´s; granulomatous) thyroiditis
PIV3	parainfluenza 3
PT	prothrombin time
PTT	partial thromboplastin time
PVC	premature ventricular complex
PY	population year
RIFLE	risk of renal dysfunction, injury to the kidney, failure or loss of kidney function, and end-stage kidney disease

RNA	ribonucleic acid
RSV	respiratory syncytial virus
SAGE	Strategic Advisory Group of Experts on Immunization
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SAT	subacute thyroiditis
SCr	serum creatinine
SLE	systemic lupus erythematosus
SNHL	sensorineural hearing loss
SOCV	single organ cutaneous vasculitis
SPEAC	Safety Platform for Emergency vACcines
Td	tetanus and diphtheria vaccine – adults
Tdap	tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine
TP	thrombocytopenia
TSS	toxic shock syndrome
TTS	thrombosis with thrombocytopenia syndrome
ULN	upper limit of normal
US	ultrasound
UTI	urinary tract infection
VAED	vaccine-associated enhanced disease
VAERD	vaccine-associated enhanced respiratory disease
VTE	venous thromboembolism
VZV	varicella-zoster virus
WBC	white blood count
WHO	World Health Organization

INTRODUCTION

The pandemic caused by the coronavirus disease of 2019 (COVID-19) pressured the scientific community to innovate, develop, and implement new technologies to meet the challenges needed to prevent and treat the disease. The response was successful; to date, several vaccines have been produced and many others are in the process of being developed. These vaccines are being used in many people in different environments and in different populations.

The development of these vaccines required creativity and flexibility, employing processes that often take several years to complete. However, these vaccines went from design to production and authorization for use in less than a year. Manufacturers took risks by starting vaccine production while carrying out the necessary development and authorization work. The use of vaccines developed and made available to countries for mass vaccination requires close monitoring by various stakeholders, including national regulatory authorities, immunization programs, health professionals, and civil society, in order to ensure that the use of these vaccines will continue to be as good, safe, and effective in the field as demonstrated during clinical trials.

In response to the COVID-19 pandemic, the World Health Organization (WHO) recommends that the introduction of vaccines be contingent on the development and implementation of a national deployment and vaccination plan. Said plan must contemplate the definition of appropriate, agile, and efficient regulatory mechanisms to facilitate timely access to the vaccines, without compromising the evaluation of their quality, safety, and efficacy.

In the framework document for the task and prioritization of vaccines against COVID-19, the Strategic Advisory Group of Experts on Immunization (SAGE) indicates as a general objective the significant contribution to the equitable protection and promotion of human well-being for all the world's population. Among the principles of this objective are human well-being, equal respect, global and national equity, reciprocity, and legitimacy.[1]

Of all the vaccines produced or under development, 21 have been authorized for emergency use (a mechanism to facilitate the availability and use of medical countermeasures, including vaccines, during public health emergencies) issued by countries and/or regions on different platforms, such as inactivated virus, viral vector non-replicating, RNA, and protein subunit-based vaccines (as of September 2021). Among these vaccines, WHO has included eight in the Emergency Use List (a risk-based procedure to evaluate and list unlicensed vaccines, therapeutics, and in vitro diagnostics with the goal of expediting the availability of these products for people affected by a public health emergency).[2]

According to recorded data, the 51 countries in the Americas that have already started vaccination informed that as at September 2021 589.2 million first doses and 429.1 million second doses, and 33.1 million single doses of the vaccine against COVID-19 had been administered, totaling 1,065.9 million doses.[3]

Safety surveillance of the COVID-19 vaccine is a top priority, which has required the collaboration of all interested parties. Sharing data and information is critical and, therefore, criteria and definitions for adverse events and clinical developments need to be standardized as part of vaccine safety surveillance.[4]

WHO alerted that the unprecedented rapid development of the COVID-19 vaccines on novel platforms followed by their rapid deployment on a mass scale poses unique challenges for monitoring vaccine safety. Timely detection and reporting of adverse events following COVID-19 immunization is the first step in the continuous verification of vaccine safety. In the context of COVID-19 vaccination, surveillance systems need to be prepared for identifying and responding to both adverse events following immunization (AEFI) and adverse events of special interest (AESI) as well as other safety events that may cause public concern, including incidents of substandard or counterfeit vaccines. Clearly distinguishing genuine vaccine product-related events from coincidental events or concomitant medication-related adverse events will be a challenge.[5]

Adverse event of special interest (AESI): This is a pre-identified, predefined, prespecified medically significant event that has the potential to be causally associated with a vaccine product, and that needs to be carefully monitored and confirmed by further specific studies.

The list of such events considered potentially applicable to COVID-19 vaccines includes serious events that have occurred with other vaccines (such as Guillain-Barré syndrome [GBS], acute disseminated encephalomyelitis, and anaphylaxis); serious events potentially related to new platforms, to adjuvants, to the failure/immunogenicity (vaccine-associated enhanced disease [VAED]); or events that are potentially specific to special populations.

Such conditions are shortlisted if there is a proven association with immunization that is true for most, if not all, vaccines; proven association with a known vaccine platform or adjuvant that is being used in any COVID-19 vaccine; theoretical concern based on immunopathogenesis of COVID-19 disease; theoretical concern related to viral replication during COVID-19 infection; or theoretical concern because it has been demonstrated in an animal model with one or more candidate vaccine platforms.

The list can potentially include the exacerbation of the disease intensified by the vaccine (if vaccination is related to a more severe subsequent infection with severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]). Other events of special interest may include respiratory, cardiac, acute kidney and liver damage, neurological disorders, sepsis and septic shock, hypercoagulability, rhabdomyolysis, and multisystemic inflammatory syndrome in children (MIS-C). One reason for updating the AESI list is to be prepared to monitor these events pre- and post-introduction and to assess whether case definitions are needed.[6]

Adverse event following immunization (AEFI): This is any untoward medical event that follows immunization and that does not necessarily have a causal relationship with the use of the vaccine. The adverse event may be any unfavorable or unintended sign, abnormal laboratory finding, symptom, or disease. This definition will be used to identify and report all AEFIs following COVID-19 immunization.[6]

Notification of AEFI is an important component of the overall safety assessment of any vaccine. This type of surveillance, commonly referred to as post marketing or post licensing surveillance, allows for monitoring of vaccines throughout implementation in the context of "scale-up" production of the vaccine and expansion of the population that receives the vaccine. Individual case reports of AEFI represent an important source of data as they have the potential to generate signs of adverse events not previously recognized in clinical studies that can be evaluated. This is particularly important for rare adverse events that may not have been evident in clinical trials due to the limited sample size.[7]

AEFI and AESI can be detected through passive and active surveillance, respectively. However, if countries do not implement active surveillance for AESI, all AESI-like adverse events occurring following COVID-19 immunization should be considered as AEFI, and the standard procedure for AEFI response, described below, should be adopted.

This is needed because there are likely to be a lot of unknown associations as COVID-19 is a new infectious disease with many of its manifestations still unknown; a broad target population will be exposed to one of the many new vaccines being evaluated, produced by various manufacturers; and different countries will probably adopt different immunization strategies.[6]

The objective of the present consultation document is to list and provide definitions of AESI and AEFI for COVID-19 vaccines that can be used as a common language for reporting these events. The importance of standardizing definitions of adverse events and their guidelines is that this will allow for data comparability and will lead to a better understanding of the adverse event. Standardized definitions may facilitate the implementation of study protocols as well as contribute to increasing global awareness of harmonized terminologies, educating about their benefits, monitoring their global use, and facilitating access.

METHODS

A pharmacovigilance working group was formed to develop the COVID-19 Pharmacovigilance Table for Vaccines, incorporating available resources related to COVID-19 vaccines. The group was created to support regulatory processes and monitor the safety of these vaccines, considering the safety profiles of the different COVID-19 vaccine platforms. To complement this table, three members of the pharmacovigilance group were responsible for preparing the Consultation Document for Case Definitions, Adverse Events of Special Interest, and Adverse Events After Immunization during COVID-19 Vaccine Introduction. For the document, case definitions and guidelines for AESI and AEFI were included, considering information about other risk factors that contribute to the occurrence of adverse events. For each AESI and AEFI, information on diseases and other risk factors, medications/drugs, and other vaccines that may also be the causes of adverse events was included.

Definitions of AEFI and AESI were collected and pooled from different sources prioritizing publications from the Brighton Collaboration (BC) and, if not available, also including those from WHO, the Safety Platform for Emergency vACcines (SPEAC), and vACcine covid-19 monitoring readinESS (ACCESS).

The document has been supplemented with reviews of the BC adverse event case definitions (CDs) of special interest published as CDs, supplementary guides, related to generalized seizure, anaphylaxis, facial nerve palsy, including Bell's palsy, acute disseminated encephalomyelitis (ADEM), acute encephalitis, thrombocytopenia (TP), aseptic meningitis, GBS, acute respiratory distress syndrome (ARDS), acute myelitis, a multisystem inflammatory syndrome in children and adults (MIS-C/A), VAED, sensorineural hearing loss (SNHL), thrombosis and thromboembolism, myocarditis, and an interim CD related to thrombosis with thrombocytopenia syndrome (TTS).[8]

Data from reviews that provide estimates of background incidence rates (IRs) were used to allow monitoring of AESI during COVID-19 vaccine safety surveillance. Knowledge of these previous IRs is a critical component of vaccine safety monitoring to help assess adverse events temporarily associated with vaccination and to put these events in context with what would be expected due to chance alone.

To guide the search for information on other risk factors for each AESI and AEFI, the group performed a systematic literature search, using the terms adverse reactions associated with diseases, drugs, vaccines, and other factors, for searches in: BC publications; Cochrane Library; Gavi, the Vaccine Alliance; Medline; National Health Service website; PubMed; SAGE; SPEAC; and WHO. The search resulted in the identification of articles (evaluated based on title and abstract), systematic reviews, and textbooks that were summarized to include information that complemented the information on adverse events.

PART A – ADVERSE EVENTS OF SPECIAL INTEREST

An AESI (serious or nonserious) is an event of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate.

Such an event might warrant further investigation to characterize and understand it. Depending on the nature of the event, rapid communication by the trial sponsor to other parties (e.g., regulators) might also be warranted.[9]

Post marketing surveillance has been conducted to monitor the safety of COVID-19 vaccines, after authorization for use and during the implementation of immunization programs.

The notification of AESI for COVID-19 vaccines in the context of general AEFI surveillance allows for enhanced monitoring by pre-specifying events that otherwise could not be captured or readily analyzed from a passive surveillance system.[10]

To harmonize the safety assessment of vaccines, guides to the Brighton AESI CD are now being prepared for each AESI separately. These guides were used to complement the information in this document, providing interested parties with conditions to assess the occurrence of anaphylaxis in various environments, including as an AEFI.[11]

ANAPHYLAXIS

Brighton Collaboration case definition (BCCD) and SPEAC. Relevant for vaccination in general.

Category: Immunologic

Listed: BC/SPEAC

Rationale for inclusion: Proven association with immunization encompassing several different vaccines.[6] For SPEAC, AESIs are prioritized in four tiers. Anaphylaxis is prioritized as Tier 1.[11]

About the AESI: For Rüggeberg et al., "anaphylaxis is an acute hypersensitivity reaction with multiorgan-system involvement that can present as, or rapidly progress to, a severe life-threatening reaction. It may occur following exposure to allergens from a variety of sources including food, aeroallergens, insect venom, drugs, and immunizations. Anaphylaxis is triggered by the binding of allergen to specific immunoglobulin E (IgE)".[12]

Case definition: As the current allergic terminology does not distinguish between "aphylactic" and "anaphylactoid" events, a proposed definition by BC refers only to "anaphylaxis." According to the CD of Rüggeberg et al., for Levels 1, 2, and 3 of diagnostic certainty, anaphylaxis is a clinical syndrome characterized by sudden onset and rapid progression of signs and symptoms and involving multiple (≥ 2) organ systems, as follows.[12]

In the SPEAC review, Law et al. describe the key elements of the CD as predominantly a clinical diagnosis based on the objective assessment of the dermatological, cardiovascular, respiratory, and gastrointestinal presentations that constitute the main and secondary CD criteria. That the three levels of diagnostic certainty have nothing to do with severity, requiring for all three levels an event time course involving "sudden onset" (meaning "the event occurred unexpectedly and without warning leading to a marked change in condition previously stable of a subject") and "rapid progression" (no exact time specified). It reinforces that a response to treatment is not specifically included in the CD, it is important to emphasize the rapid documentation of objective signs as opposed to subjective symptoms – that is, observation of the swollen tongue rather than a patient's history of feeling swollen on the tongue.[13] (Complete_casedefinitionAnaphylaxis)

Background: There are many reference rates based on all types of anaphylaxes. In most countries, rates vary between 1–10/100,000 population year (PY).[14] Other data show pooled historical rates of AESI from electronic health records databases from eight countries (Table 1).[15]

Table 1: Incidence Rate per 100,000 Person-years (95% Prediction Interval), Data from Australia, France, Germany, Japan, the Netherlands, Spain, United Kingdom, and United States[15]

Incidence rate per 100 000 person years (95% prediction interval)									
Country	**Gender**	**1 - 5 years**	**6 - 17 years**	**18 - 34 years**	**34 - 54 years**	**55 - 64 years**	**65 - 74 years**	**75 - 84 years**	**≥ 85 years**
Australia, France, Germany, Japan, the Netherlands, Spain, United Kingdom and United States	Female	16-150	16-154	16-95	13-91	14-85	11-76	7-73	4-36
	Male	26-209	18-75	14-63	11-53	11-53	9-68	7-49	2-50

Anaphylaxis risk factors:

- Diseases and other factors:

  Age: Children (the large majority of anaphylaxis triggered by foods; less than 5% by insect venom), adults (relative to children, medication-triggered anaphylaxis more common – about one-third; food-triggered anaphylaxis less common – about one-third; insect venom more common – close to 20%). Increased severity of anaphylaxis: infants (where recognition can be more difficult) and older persons.

  Gender: Males (more common in those aged < 15 years); females (more common in those aged > 15 years), and increased severity of anaphylaxis (pregnancy, menses).

  Genetics (atopy): Multigenic including genes for cytokines and IgE receptor, idiopathic anaphylaxis – most common in females with known atopy history.

  Geography: More common in northern latitudes.

  Comorbidity: Increased frequency of anaphylaxis: severe asthma, pulmonary disease, mastocytosis, thyroid disease, coronary artery disease, ischemic dilated cardiomyopathy).[13]

  Food-induced anaphylaxis is more common in young people, while drug and hymenopteran-induced anaphylaxis is more common in older patients). Death from anaphylaxis is a rare and extraordinary event (0.12–1.06 deaths per million person-years), and more likely in older individuals in the case of drug anaphylaxis and Hymenoptera. The anaphylaxis can be associated with atopy or Hymenoptera venom in high-exposure areas. Fatal food-induced anaphylaxis usually occurs before 35 years, while drug and Hymenoptera anaphylaxis occur after 40–50 years. Fatal anaphylaxis seems to be more frequent in older people than in younger people.[16] The frequency of anaphylaxis depends on lifestyle; foods such as celery, cow's milk, chicken egg, peach, peanut, seeds (e.g., sesame), seafood, nuts, wheat, and buckwheat; and insect venom (bee and wasp venom, fire ants, horse-flies).[17]

- **Medicines:** Medicines are a major cause of anaphylaxis. The most common agents are analgesics, non-steroidal anti-inflammatory drug (NSAIDs; dipyrone, ketoprofen, diclofenac, ibuprofen, ketorolac), antibiotics (penicillin and those in the beta-lactam class such as ampicillin, amoxicillin, cephalexin, cefuroxime, ceftriaxone), neuromuscular blockers used in surgical and anesthetic procedures,[18] and biologics, chemotherapeutics, contrast media, proton pump inhibitors,[17] and acyclovir.[19] There is increased severity of anaphylaxis: antihypertensive medications (beta-adrenergic blockers, calcium channel blockers, angiotensin-converting-enzyme (ACE) inhibitors, angiotensin-receptor

blockers, direct renin inhibitors), polyethylene glycol (sedatives, hypnotics, and recreational drugs may mask recognition of symptoms).[13]

- **Vaccines in general:** Anaphylaxis following immunization is serious. Evidence convincingly supports an association between measles, mumps, and rubella (MMR), varicella-zoster (VZV) vaccine, influenza, hepatitis B, meningococcal and tetanus toxoid vaccines, and anaphylaxis. There is a causal relationship between human papillomavirus (HPV) vaccine and anaphylaxis. Clinical manifestations of anaphylaxis are produced as occurring in seconds to minutes of exposure to a certain substance. Most cases begin within 1 h of exposure, but in a minority of cases, symptoms may show up to 12 h after exposure. A biphasic presentation up to 72 h was also obtained. Clinical manifestations can also vary depending on the route of exposure to the allergen (intravenous versus oral, intramuscular, subcutaneous, etc.).[13] Hepatitis B vaccine (HB), MMR and influenza vaccines (serious event, which can occur between 0 to 1 h) are mentioned in the Pan American Health Organization (PAHO) Manual.[20] Diphtheria, tetanus, pertussis, Haemophilus influenzae type B (Hib) and HB – pentavalent vaccines, diphtheria, tetanus, and acellular pertussis vaccine (DTaP and Tdap), hepatitis A vaccine (HA), typhoid fever vaccine (FT), meningococcal and pneumococcal vaccines, HPV vaccine, anti-rabies vaccine, and measles, mumps, rubella, and varicella vaccine (MMRV) are mentioned in the Adverse Events Surveillance Manual in Brazil, with risk from minutes up to 12 h).[21]
- **Vaccines against COVID-19 SARS-CoV-2:** COVID-19 vaccines have been introduced globally, and millions of people are being vaccinated with the various types of vaccines, many of which use new vaccine platforms.[22] Anaphylaxis, as an AESI, has been reported in clinical trials, by countries, and other sources for different COVID-19 vaccines among the events considered serious.[23, 24, 25]

THROMBOSIS WITH THROMBOCYTOPENIA SYNDROME

BC proposed a process for developing a standard CD for the study of new clinical as applied to thrombosis with thrombocytopenia syndrome (TTS).

Since at least mid-February 2021, several European countries, Australia, the United States of America, and others have reported cases of TTS in people receiving COVID-19 the AstraZeneca (AZ) and the Janssen vaccine. Others have called this new immunological thrombotic syndrome vaccine-induced by thrombotic TP. Considering that this form would assume a causal mechanism, the BC group chose to use TTS for the purpose of finding the initial case. A BCCD was presented, needed for both clinical (e.g., appropriate diagnosis, and treatment) and public health (e.g., epidemiological studies, and data harmonization). Work is ongoing to understand risk factors for TTS.[26]

Category: Hematologic

Listed: BC/SPEAC, WHO, European Medicines Agency (EMA) / ACCESS, Food and Drug Administration (FDA) / Centers for Disease Control and Prevention (CDC)

Rationale for inclusion: Reported cases of TTS in persons who received the COVID-19 vaccine.[26]

TP associated with an immune response has been associated with occurrences of cerebral venous thrombosis following vaccination with the AZ vaccine, specifically with antibodies to platelet factor 4, which causes blood clotting and consumes platelets. These antibodies have been identified in patients who have experienced blood clots. Thirty percent of cases of cerebral venous thrombosis due to COVID-19 occurred in patients under the age of 30 years.[27]

About the AESI: Rare cases of thrombosis and TP have occurred during post authorization vaccination. Cases that present severe venous thrombosis are included in unusual sites such as cerebral venous sinus

thrombosis and splanchnic vein thrombosis, as well as arterial thrombosis, concomitant with TP. Most of the events occurred within the first 14 days after vaccination and some events were fatal.[28] Thrombosis syndrome with TP is added as an important risk identified in the risk plan for the vaccine.[29]

Case definition: BC developed an interim CD with the aim of identifying individuals who could then be studied using a common study protocol and assessment. Per the BCCD (still in final review), for TP this requires a platelet count of less than 150,000/uL. Either of the two levels of certainty (LOC) of TP, Level 1 or Level 2, is sufficient to satisfy the TP condition for the TTS CD. To meet this CD with certainty Level 1 requires confirmation by imaging, surgical, or pathological findings. Level 2 and 3 criteria are for a probable case and a possible case, respectively. Importantly, CDs for probable and possible cases support the screening, identification, and inclusion of cases from countries that may not have access to more sophisticated diagnostic studies. According to BC, TTS cases will be classified according to the LOC obtained for thrombosis and will also be stratified to determine whether the individual has had recent exposure to heparin.[26] (Complete_casedefinitionTTS)

Thrombosis with thrombocytopenia syndrome risk factors:

- **Diseases and other factors:** As these events are a rare, new, and severe combination of thrombosis and TP, the alert is for people with risk factors for thromboembolism and/or TP.[29] TTS seems to have as a key feature, thrombosis in specific sites such as the brain and abdomen; therefore, physicians should be on the lookout for any new, severe, and persistent headaches or other major symptoms, such as severe abdominal pain and shortness of breath, that begin 4–20 days after COVID-19 vaccines are given, based on adenovirus.[30]
- **Medicines:** Clinicians should be aware that although heparin is used to treat blood clots in general, administration of heparin in TTS may be dangerous, and alternative treatments such as immunoglobulins and nonheparin anticoagulants should be considered.[30, 31]
- **Vaccine against COVID-19 SARS-CoV-2:** COVID-19 vaccines have been introduced globally, and millions of people are being vaccinated with various types of vaccines, many of which use new vaccine platforms.[22] TTS has been reported among the events considered serious.[2, 28] At this stage, a "platform-specific" mechanism related to the adenovirus-vectored vaccines is not certain but cannot be excluded.[32] People with risk factors for thromboembolism and/or TP should consider the potential benefits and risks of vaccination against COVID-19.[28] Most cases occur within 14 days after vaccination and in women under 60 years of age; some cases have had a fatal outcome.[33, 34] The Global Advisory Committee on Vaccine Safety COVID-19 subcommittee acknowledges that TTS has occurred with two adenoviral-vectored vaccines. Ongoing assessment for and review of TTS cases, as well as related research, should include all vaccines using adenoviral vector platforms.[35]

  The observed cases occurred with a lower frequency than that which occurs in the population that has not been vaccinated; as a new rare adverse event (fewer than one in 10,000 people).[29]

THROMBOCYTOPENIA

BCCD and SPEAC. Relevant for vaccination in general.

To harmonize the vaccine safety assessment, BC AESI CD guides are being prepared for each AESI separately. These guides are being used to supplement the information in the AESI document. In the case of coagulation disorders, the document is on the list for Tier1, which will provide interested parties with conditions to assess the occurrence as an AEFI.[36]

Category: Hematologic

Listed: BC/SPEAC, WHO, EMA/ACCESS, FDA/CDC

Rationale for inclusion: Proven association with immunization encompassing several different vaccines.[36]

About the AESI: Robert Wise et al. assessed the need to develop CDs and guidelines for thrombocytopenia (TP) as an AEFI. They consider TP to be an abnormally low platelet count. Pathogenic mechanisms include insufficient production, abnormal distribution, or excessive destruction of platelets. Excessive destruction can be caused by microangiopathy, hereditary platelet abnormalities or immune mechanisms. Immune TP can be caused by autoimmune mechanisms, neonatal isoimmunization or a nonspecific immune response. Idiopathic TP (ITP) refers to TP without an identified etiology, although an autoimmune etiology is often suspected but not always verified by exhaustive exclusion of differential diagnoses.[37]

Case definition: The definition of TP as an AEFI proposed by BC is based on a platelet count below $150 \times 10^9/L^{-1}$ the most-used reference value in the pertinent hematology literature. In vaccine safety studies, threshold criteria for TP ranged from 100 to $150 \times 10^9/L^{-1}$, and the use of this value is supported by studies of platelet count reference intervals in different populations and represents about two standard deviations below the mean in a normal distribution of platelet counts in a general population. The standardized CD and guidelines provided by BC aim to improve the reliability and comparability of data collected from immunized patients and immunized or unvaccinated controls. These data can help to assess whether, or to what extent, each vaccine can contribute to the subsequent development of TP.[37] (Complete_casedefinitionthrombocytopenia)

Background: In the first analysis of an administrative database in a major Italian institution, the incidence of TP reactions is estimated at 14.8/100,000 inhabitants per year.[38] In data from Brazil, the incidence is 1.6–2.7/100,000 inhabitants per year.[39]

Other data show pooled historical rates of AESI from electronic health records databases from eight countries (Australia, France, Germany, Japan, Netherlands, Spain, United Kingdom of Great Britain and Northern Ireland, and United States) (Table 2).[15]

Table 2: Incidence Rate per 100,000 Person-years (95% Prediction Interval), Data from Australia, France, Germany, Japan, the Netherlands, Spain, United Kingdom, and United States[15]

Incidence rate per 100 000 person years (95% prediction interval)									
Country	**Gender**	**1 - 5 years**	**6 - 17 years**	**18 - 34 years**	**34 - 54 years**	**55 - 64 years**	**65 - 74 years**	**75 - 84 years**	**≥ 85 years**
Australia, France, Germany, Japan, the Netherlands, Spain, United Kingdom and United States	Female	8-19	4-21	6-36	5-43	6-53	8-82	8-110	11-118
	Male	12-23	3-19	2-23	3-35	6-57	9-105	10-170	15-210
Brazil		4.1-9.5							

Thrombocytopenia risk factors:

- **Diseases and other factors:** Age, gender (adult females), pregnancy, genetics (primary ITP and nonimmune congenital TP), season (childhood ITP has a higher frequency in autumn and winter, reflecting the association with prior viral infection), geography (limited data but childhood disease pattern similar in high- and low-income countries). Diseases: secondary ITP o autoimmune disease (systemic lupus erythematosus [SLE], Evans / Sjögren's / antiphospholipid syndromes), hematologic malignancy (non-Hodgkin lymphoma, chronic lymphocytic leukemia), primary immune deficiency (common variable immune deficiency, autoimmune lymphoproliferative syndrome); vitamin B9 or B12 deficiency; nonimmune TP or decreased production: bone marrow

replacement (proliferative disorders), bone marrow failure (primary or secondary aplastic anemia); increased consumption: hypersplenism, giant hemangioma (Kasabach-Merritt Syndrome).[40]

Certain cancers, cancer treatments, medications, and autoimmune diseases can cause the condition of TP. Platelet levels often improve when the underlying cause is treated. TP can affect people of all ages, ethnicities, and genders. For unknown reasons, approximately 5% of pregnant women develop mild TP right before childbirth. In rare instances, TP is inherited or passed from parent to child. More commonly, certain disorders, conditions, and medications cause a low platelet count: alcohol use disorder and alcoholism, an autoimmune disease which causes ITP (that sometimes is associated with other autoimmune conditions such as lupus), some marrow diseases (including aplastic anemia, leukemia, certain lymphomas, and myelodysplastic syndromes), cancer treatments like chemotherapy and radiation therapy, enlarged spleen caused by cirrhosis of the liver or Gaucher disease, exposure to toxic chemicals, including arsenic, benzene, and pesticides;[41] infections with protozoa, bacteria, and viruses can cause TP with or without disseminated intravascular coagulation; commonly, dengue, malaria, scrub typhus and other rickettsia infections, meningococci, Leptospira, and certain viral infections present as fever with TP.[42]

» **Medicines:** Commonly used drugs that occasionally induce TP are heparin, quinine, trimethoprim/sulfamethoxazole, glycoprotein IIb/IIIa inhibitors (e.g., abciximab, eptifibatide, tirofiban), hydrochlorothiazide, carbamazepine, chlorpropamide, ranitidine, rifampin, vancomycin;[43] medications to treat bacterial infections (antibiotics), seizures (epilepsy), and heart problems, or the blood thinner heparin and viruses, such as hepatitis C, Cytomegalovirus (CMV), Epstein-Barr virus (EBV), and human immunodeficiency virus (HIV).[41]

Reduced production due to bone marrow myelosuppression: anticancer drugs, valproic acid. Secondary ITP: many drugs may cause TP. Listing them is beyond the scope of this guide; however, when investigating TP that follows immunization, all concomitant medication, especially newly added drugs, should be reviewed for any possible association with TP.[40]

» **Vaccines in general:** Clinically apparent TP after immunization is rare. The incidence of hospitalization for TP after immunization with MMR vaccine has been estimated to be 3–4 per 100,000 children immunized. Despite what is known about TP as an AEFI, there are not widely used standardized criteria defining TP in the context of immunization. There is no difference in the clinical presentation of hospitalized patients with TP after immunization compared with viral illnesses. Median intervals between immunization with MMR vaccine and onset of symptoms are 12–25 days (range 1–83 days), with an increased relative risk for hospitalization due to clinical manifestations between 15 and 28 days after immunization. Most postimmunization episodes of TP resolve within 3 months, although low platelet counts may rarely persist for more than 6 months.[37]

The vaccine-related TP is considered a secondary ITP, and MMRV is the only vaccine for which there is a proven attributable risk of TP. A study of managed care data found a possible association with HA in children aged 7–17 years and with chickenpox and Tdap in children aged 11–17 years but noted that further studies were needed to confirm the association. Although several other vaccines have been reviewed (influenza, HA, HB, meningococcus, HPV), no studies involving TP or ITP have been mentioned.[40]

A transient but sometimes profound fall in platelet counts has been reported after immunization against hepatitis B, hepatitis A, influenza, diphtheria-tetanus-pertussis whole-cell (DTwP), Hib, pneumococcal disease, poliomyelitis, varicella, smallpox, rabies, HIV (gp120 or gp60 derived antigens),[37] MMR,[20] and MMRV;[21] also, DTaP, and Shingrix zoster vaccines.[44] The working group emphasizes that TP, like any adverse event observed after immunization, may be temporarily associated, but not necessarily due to immunization.[37]

» **Vaccines against COVID-19 SARS-CoV-2:** These vaccines have been introduced globally, and millions of people are being vaccinated with various types of vaccines, many of which use new vaccine platforms.[22] Suspected cases of TP have been reported and monitored among events considered serious after vaccination against COVID-19.[23, 24,45]

GENERALIZED CONVULSION

BCCD and SPEAC. Relevant for vaccination in general.

To harmonize the safety assessment of vaccines, guides to the BC AESI CD are now being prepared for each AESI separately. These guides were used to complement the information in this document, providing interested parties with conditions to assess the occurrence of generalized convulsion in various environments, including as an AEFI.[11]

Category: Neurologic

Listed: BC/SPEAC, WHO, EMA/ACCESS, FDA/CDC

Rationale for inclusion: Proven association with immunization encompassing several different vaccines and theoretical concern related to viral replication during wild-type disease.[6] For SPEAC, AESI were prioritized at four tiers. The generalized seizure is prioritized as Tier 1.[11]

About the AESI: Bonhoeffer et al. describe seizures as "episodes of neuronal hyperactivity most commonly resulting in sudden, involuntary muscular contractions. They may also manifest as sensory disturbances, autonomic dysfunction and behavioral abnormalities, and impairment or loss of consciousness. Descriptions and classifications of seizures are complex and subject to change because the etiology and pathogenesis of most seizures remain to be elucidated. Of primary interest in vaccine safety studies is the diagnosis certainty, whether a seizure was truly present or not, and whether fever was present immediately prior to the onset of a seizure. The certainty about the type of seizure is of secondary importance from the vaccine safety point of view."[46]

Case definition: Seizures are episodes of neuronal hyperactivity that most commonly result in sudden involuntary muscle contractions, which can manifest as sensory disturbances, autonomic dysfunction and behavioral abnormalities, and impairment or loss of consciousness. The etiology and pathogenesis of most crises require elucidation, and descriptions and classifications of crises are complex. The definition of generalized seizures represents most childhood seizures, regardless of immunization. The diagnosis of generalized seizures is based on descriptive terms for clinical signs and symptoms and does not require knowledge of the ictal pathophysiology, and nor does it imply its etiology. As postimmunization generalized seizures are usually short-lived, diagnosis is often based on clinical history alone.[46] (Complete_casedefinitiongeneralized_convulsion)

Background: About 3–4% of all children will have at least one "febrile seizure." Other factors include a history of a first unprovoked seizure that is associated with an increased risk of recurrence of 36–37% in 1 year; 43–45% at 2 years.[11] [46] Other data show pooled historical rates of AESI from electronic health records databases from the United States: single unprovoked seizures in 23–61/100,000 persons per year, and acute symptomatic seizures in 29–39/100,000 per year. Spain presents, in the period from 2007 to 2015, seizure IRs after vaccination with the HPV vaccine of 3.2 and other vaccines of 0.4 per 100,000 applied doses.[15]

Generalized convulsion risk factors:

» Diseases and other factors: Any diagnosis of generalized convulsive seizure should be accompanied by information about the following specific predisposing conditions for generalized convulsive seizure: drug withdrawal, hypoxia, head trauma, central nervous system (CNS) infection, neoplasm, or metabolic

causes (e.g., uremia, hypoglycemia, and electrolyte disorders), and psychogenic cause. As elevated body temperature is frequently observed following immunization, and febrile seizures are the most common seizure disorder in infants and children, they are the most common type of nonepileptic seizure observed following immunization. There might be a family history of febrile seizures in siblings and parents. Atypical febrile seizures have been defined as recurrent generalized convulsive seizures or focal seizures of more than 15 min duration or postictal drowsiness or neurologic sequelae.[46] The complements to the risk factors for generalized seizure are age, gender (incidence and prevalence of epilepsy slightly higher in men than in women), genetics, geography (incidence and prevalence of epilepsy is higher in low-middle-income countries than high-income countries). Vascular disease (hypertension, history of stroke, diabetes) and autoimmune diseases in children are associated with a fivefold higher risk of epilepsy. The first onset of seizures in an adult is usually due to an identifiable cause, including trauma, CNS infection, CNS space-occupying lesion, cerebrovascular accident, metabolic disorder, or drugs.[11]

- Medicines: Concurrently administered medication including prescription and nonprescription medication (e.g., herbal or homeopathic medication) as well as medication with long half-life such as immunoglobulins, blood transfusion, etc.[46]
- Vaccines in general: The seizure working group recognizes that generalized convulsive seizure (or any other adverse event) that follows the administration of an inactivated component or live vaccine may be temporally associated with, but is not necessarily the result of, administration of a vaccine. It stresses that generalized seizures after immunization are usually short-lived; the diagnosis is often based only on clinical history. It is particularly relevant for the surveillance of generalized seizures as an adverse event after new vaccines against chronic diseases (e.g., diabetes mellitus and rheumatoid arthritis), therapeutic vaccines (e.g., tumor vaccines), as well as genetically modified vaccines, mucosa, or vaccines with slow-release delivery systems, which may require different standards.[46] PAHO/WHO indicates vaccines such as HB (severe), with a risk of causing this event in the period of 1 month, and diphtheria, pertussis, and tetanus (DPT) severe with a risk for a period of 3 days,[20] and in the Manual of the Ministry of Health of Brazil, the vaccines identified with the risk for this event are pentavalent, diphtheria, tetanus, and acellular pertussis (DTaP), diphtheria and tetanus (Td) (up to 72 h, but usually in the first 12 h), meningococcal (first 3 days), pneumococcal (up to 72 h), and MMRV (5–10 days).[21]

  No evidence that vaccines cause epilepsy has been documented. However, some vaccines can very rarely cause febrile seizures (MMR and MMRV [7–10 days after vaccination], influenza, pneumococcal conjugate vaccines). The risk window for seizures, as a reaction related to the vaccine product, is linked to the reactogenicity period, when fever may occur; inactivated or subunit vaccines (usually in the first days after vaccination), and live attenuated vaccines during the incubation period. As noted above, the evidence strongly supports an association with MMR and the most typical time to onset is 7–10 days after vaccination.[11]
- **Vaccines against COVID-19 SARS-CoV-2:** COVID-19 vaccines have been introduced globally, and millions of people are being vaccinated with various types of vaccines, many of which use new vaccine platforms.[22] Suspected cases of generalized convulsion have been reported and monitored among events considered serious after vaccination against COVID-19.[23, 24,45]

GUILLAIN-BARRÉ SYNDROME

BCCD and SPEAC. Relevant for vaccination in general.

To harmonize the safety assessment of vaccines, guides to the BC AESI CD are now being prepared for each AESI separately. These guides were used to complement the information in this document, providing interested parties with conditions to assess the occurrence of GBS in various environments, including as an AEFI.[11]

Category: Neurologic

Listed: BC/SPEAC, WHO, EMA/ACCESS, FDA/CDC

Rationale for inclusion: Proven association with immunization encompassing several different vaccines and theoretical concern related to viral replication during wild-type disease.[6] For SPEAC, AESI were prioritized at four tiers. GBS is prioritized as Tier 1.[47]

About the AESI: GBS is described, "among the various events reported as adverse outcomes following immunizations, neurologic adverse events following immunization (AEFI) are among the most severe and the most difficult to assess. The multifaceted presentation of neurologic illness, the relative lack of familiarity of many clinicians with the approach to and diagnosis of neurologic disease, and the relative scarcity of trained neurologists in many parts of the world make neurologic AEFI some of the most challenging issues in clinical vaccinology."

GBS constitutes an important proportion of acute flaccid paralysis cases worldwide. It is a condition characterized by various degrees of weakness, sensory abnormalities, and autonomic dysfunction due to damage to peripheral nerves and nerve roots. Although the underlying etiology and pathophysiology of GBS are not completely understood, it is believed that immune stimulation plays a central role in its pathogenesis. It is an immune-mediated disorder resulting from the generation of autoimmune antibodies and/or inflammatory cells that cross-react with epitopes on peripheral nerves and roots, leading to demyelination or axonal damage, or both.[48]

Case definition: Key elements of CD for GBS and Miller Fisher syndrome (MFS) have three levels of diagnostic certainty, with Level 3 limited to clinical findings. Critical for GBS to reach CD level 3 is the demonstration of absent or diminished deep tendon reflexes in the same limbs that are weak. Without that, you cannot reach any level of certainty.

MFS is a rare subtype of GBS that includes bilateral ophthalmoparesis and ataxia, usually without limb weakness. GBS/MFS overlap syndromes can occur, where there are weaknesses and features of MFS. In these cases, the LOC should be based on the GBS criteria, but it can also be described as a GBS/MFS overlap syndrome. For GBS and MFS, there should be sufficient follow-up to demonstrate a monophasic disease pattern and no alternative diagnosis for weakness, not affecting the ability to meet the CD.[48] (Complete_casedefinitionGBS)

Background: The annual incidence of GBS has been estimated at between 0.4 and 4.0 cases per 100,000 population per year, depending upon study methodology and case ascertainment; most well-designed prospective studies in developed countries have suggested an incidence of 1–2 per 100,000 population per year.[47]

Many articles have been published on GBS. Among the most recent, overall incidence rates of GBS were estimated at 1.38/100,000 person-years in Italy and 2.07/100,000 person-years in Spain.[14]

Other data show pooled historical rates of AESI from electronic health records databases from eight countries (Australia, France, Germany, Japan, Netherlands, Spain, United Kingdom and United States) and one territory (Taiwan Province of China) (Table 3).[15]

Table 3: Incidence Rate per 100,000 Person-years (95% Prediction Interval), Data from Australia, France, Germany, Japan, the Netherlands, Spain, United Kingdom, and United States, and Taiwan Province of China[15]

Incidence rate per 100 000 person years (95% prediction interval)									
Country	**Gender**	**1 - 5 years**	**6 - 17 years**	**18 - 34 years**	**34 - 54 years**	**55 - 64 years**	**65 - 74 years**	**75 - 84 years**	**≥ 85 years**
Australia, France, Germany, Japan, the Netherlands, Spain, United Kingdom and United States	Female	16-150	16-154	16-95	13-91	14-85	11-76	7-73	4-36
	Male	26-209	18-75	14-63	11-53	11-53	9-68	7-49	2-50
Taiwan Province of China		**0 - 9 years**	**10 - 19 years**	**20 - 39 years**	**40 -5 9 years**				
		0.76	0.56	0.92 - 1.04	1-36 - 2.12				
United States		**≥ 17 years**		**18 - 19 years**	**40 - 59 years**				
		0.81		1.34	2.84				

GBS risk factors:

- **Diseases and other factors:** GBS are described that "as an immune-mediated disorder, autoantibodies may form in response to a variety of antigenic stimuli, such as bacterial or viral infection; approximately two-thirds of persons with GBS report an antecedent infectious illness, most commonly a diarrhea or respiratory illness, in the days or weeks preceding neurologic signs. One of the strongest associations between an antecedent infectious pathogen and subsequent GBS has been that of infection with the gastrointestinal bacterium Campylobacter jejuni. While immunologic evidence is strongest for antecedent C. jejuni infection, other infectious agents have been temporally associated with subsequent GBS and have included influenza viruses, Mycoplasma pneumoniae, HIV, EBV, cytomegalovirus, and possibly others. In rare cases, other stimuli have been associated with GBS, and include surgical procedures and some malignancies, particularly Hodgkin's disease and other lymphomas.";[52] age (incidence increases with age), gender (in general, males have a higher incidence than females although this varies by age), geography (prevalence of GBS type varies geographically), comorbidity (malignancy, especially Hodgkin's and other lymphomas), infection (influenza, HIV, EBV, CMV, enterovirus D68, Mycoplasma pneumoniae, hepatitis E, Zika; and chikungunya infection); prior surgical procedure – reported following surgery for obesity.[47]

  For Thy et al., case reports detail many other possible etiologies linked to GBS including medications and surgeries (Evidence Level III). Although rare, with an incidence of 0.4–2 per 100,000, GBS has major effects on the healthcare system. Males are affected at a slightly higher incidence than females. Each year, it is estimated 100,000 patients worldwide would contract GBS (Evidence Level III).[49]

  The CDC continues to investigate the link between GBS and Zika to learn more. However, it indicates that several countries that have experienced Zika outbreaks recently reported increases in people with GBS. Current CDC research suggests that GBS is strongly associated with Zika, although only a small proportion of people with recent Zika virus infection develop GBS.[50]

- **Medicines:** In a case-controlled study, GBS patients reported the most frequent use of penicillin and antimotility drugs and a less frequent use of oral contraceptives. However, there are no definite cause-effect relationships. There are case reports in the context of tumor necrosis factor antagonists used in arthritis. There are also case reports related to streptokinase, isotretinoin, danazol, captopril, gold,

and heroin, among others. One study indicated that fluoroquinolone antibiotic therapy is also associated with GBS development. Of the cases reported between 1997 and 2012 to the FDA, it was determined that 539 reports of peripheral neuropathy were associated with fluoroquinolone treatment, 9% were for patients with GBS.[51] Cyclosporin A has also been associated with GBS.[52] More recently, rivaroxaban has been associated as a cause of GBS,[53] as has bortezomib.[54]

» **Vaccines:** According to the review of the Institute of Medicine 2011, based on the evidence for the link between MMR, VZV, influenza, HA/HB, HPV, DTaP, meningococcal vaccines and GBS, it was concluded that the evidence was inadequate to accept or reject a causal relationship. A global collaborative study found a relative GBS incidence of 2.42 (95% CI [1.58, 3.72]) in the 42 days after exposure to the pandemic virus vaccine, with no increased risk after adjuvant vaccines.[47]

Thy et al. describe how in 1976, flu vaccination against the influenza A/H1N1 antigen led to a well-documented, increased incidence of cases of GBS; however, further surveillance data of flu vaccinations in subsequent years have described only one additional case of GBS for every 1 million vaccines. Subsequent studies estimate that developing GBS after a flu infection is up to seven times more likely than developing GBS after a vaccination (Evidence Level IV).[49]

For Sejvar et al., "antigenic challenge by an antecedent infection or immunization leads to antigen-specific humoral and/or cellular immunity, and as such, this immune stimulation could theoretically result in GBS through a number of possible mechanisms." GBS has been temporarily associated with numerous vaccines; however, this temporal association must be differentiated from causality. In general, specific biological markers indicative of a cause-and-effect association with a particular pathogen or vaccine are absent in GBS. Historically, "neuroparalytic accidents" consistent with GBS have been observed after the administration of old rabies vaccines, but subsequent formulations of rabies vaccines generated in embryonic chicken cells have rarely been associated with GBS. Studies that assess the risk of GBS after other influenza vaccine formulations have failed to consistently demonstrate a more than marginal increase in the risk of GBS. The GBS Working Group stresses, that with these notable exceptions, the majority of vaccine associations with subsequent GBS are only of a "temporal nature."[48]

The Manual of the Ministry of Health of Brazil indicates risk of adverse events for GBS with vaccines: Td, dTpA, childhood diphtheria and tetanus vaccine (DT), influenza (from 1 day to 6 weeks), MMR, and MMRV in variable time.[21]

» **Vaccines against COVID-19 SARS-CoV-2:** COVID-19 vaccines have been introduced globally, and millions of people are being vaccinated with various types of vaccines, many of which use new vaccine platforms.[22] Suspected cases of GBS have been reported and monitored among events considered serious after vaccination against COVID-19.[23, 24, 33]

ACUTE DISSEMINATED ENCEPHALOMYELITIS

BCCD and SPEAC. Relevant for vaccination in general.

To harmonize the safety assessment of vaccines, guides to the BC AESI CD are now being prepared for each AESI separately. These guides were used to complement the information in this document, providing interested parties with conditions to assess the occurrence of ADEM in various environments, including as an AEFI.[55, 56]

Category: Neurologic

Listed: BC/SPEAC, WHO, EMA/ACCESS, FDA/CDC

Rationale for inclusion: Theoretical concern based on immunopathogenesis. Occurs rarely and has not been proven to be caused by immunization. Known/possible association with live viral vaccines including measles.[48] For SPEAC, AESIs were prioritized at four tiers. ADEM is prioritized as Tier 1.[12] Despite this, a single ADEM case could completely disrupt an immunization program, which is why it has been identified as an AESI.[57]

About the AESI: "ADEM is classically described as a uniphasic syndrome of brain inflammation and demyelination, occurring in temporal association with an antecedent immunologic challenge, such as infection or immunization. In general, ADEM is distinguished from acute encephalitis by (a) a predominance of demyelinating, rather than cytotoxic injury, and (b) a temporal association with a specific inciting immunogenic challenge."[58]

Case definition: For the key elements of the ADEM CD, there are three LOC based on clinical signs, MRI brain imaging, and duration of follow-up for recurrence or relapse. ADEM is a diagnosis of exclusion, and the CD identifies four separate exclusion criteria based on alternative diagnoses, acute infectious etiologies for the disease (as opposed to an infectious disease several weeks before ADEM onset, which is consistent with the diagnosis), histopathological or neuroradiological imaging findings that are considered incompatible with ADEM, and/or a temporal course that presents relapse or recurrence of the disease 3 months or more after the acute presentation. ADEM can be accompanied by evidence of myelitis, and there is also a large overlap between ADEM and encephalitis, and all cases with encephalopathy should be evaluated against both CDs.

A 3A LOC can be used to specify cases where there are not enough data to distinguish between Level 3 encephalitis and Level 3 ADEM. However, if one of the two entities achieves a higher LOC, this should be the basis for categorization; for example, ADEM Level 2 and encephalitis Level 3 should be reported as ADEM Level 2.

Differential diagnoses of ADEM (all considered to exclude ADEM as one case; not an exhaustive list): infection; other demyelinating disorders of the CNS; autoimmune encephalitis, CNS vasculitis disorders, CNS malignancy, toxic disorders, nutritional or metabolic and others (posterior reversible leukoencephalopathy).[59] (Complete_casedefinitionADEM)

Background: IRs from the literature in the United States showed an incidence rate of 0.4 per 100,000 PY for persons below age 20, very similar to that observed by Willame at al.[14] Estimates of the frequency in the general population of viral encephalitis rates have ranged from 0.08/100,000 population in national passive surveillance studies to 1–6 cases per 100,000 in hospital-based studies, and to 7.4 cases per 100,000 in one population-based study.[58]

ADEM risk factors:

- **Diseases and other factor:** Law reviewed ADEM risk factors: age (historically, the highest incidence has been in children, with onset typically in the first decade of life), gender (some evidence for a slightly higher incidence in boys than girls, but not a uniform finding), geography (incidence noted to increase as distance from equator increases). Infection: 55–86% of pediatric ADEM cases have preceding symptoms of systemic viral illness, known association following vaccine-preventable infections: about 1/1,000 wild-type measles or varicella; 1/5,000 rubella. Also noted to follow EBV, CMV, herpes simplex virus (HSV), hepatitis A, enterovirus, human herpesvirus 6, HIV, influenza, dengue, West Nile virus. Has also been noted to follow bacterial (Mycoplasma pneumoniae, Campylobacter jejuni, Chlamydia pneumoniae, Borrelia burgdorferi, Legionella pneumophila, Leptospira spp., beta-hemolytic group A Streptococcus) and parasitic (malaria, toxoplasmosis) infections.[55]

  Sejvar et al. report that "several different antecedent viral infections or vaccinations have been suggested as presenting an antigenic challenge leading to the immunologic response in the form of ADEM. A number of different viral infections, including measles, mumps, rubella, varicella-zoster, EBV, cytomegalovirus, herpes simplex virus, hepatitis A virus, and coxsackievirus have been associated with ADEM".[59] For Kamel et al., "a case report and meta-analysis concluded that the prevalence of ADEM

among dengue and other dengue-related neurological disorders is not too rare: The high fever of ADEM cases at admission and earlier onset day of neurological manifestations are associated with the bad outcomes".[57]

- **Medicines:** Only one case in the literature refers to synthetic cannabinoids. Lethal high: ADEM triggered by toxic effect of synthetic cannabinoid black mamba.[55]
- **Vaccines in general:** Various immunizations have been temporally associated with subsequent ADEM, including Japanese encephalitis, yellow fever, measles, influenza, smallpox, anthrax, and others. However, the only epidemiologically and pathologically proven association of an antecedent event is with anti-rabies vaccination using the Semple rabies vaccine (a vaccine derived from sheep/mouse brains); such association has not been observed with modern formulations of rabies vaccine. The infection/immunization can result in the disturbance of the immunoregulatory mechanisms, interfering with the self-tolerance of the host's myelin proteins.[58, 55, 60] Revised evidence for a link between MMR, VZV, influenza, HA, HB, HPV, DTaP, meningococcal vaccines and ADEM and the completed evidence was inadequate to accept or reject a causal relationship. It was observed that the immunomediated mechanisms included autoantibodies, T cells and molecular mimicry.[59] The influenza vaccine shows a risk for the adverse event, between 1 day and 6 weeks.[44]
- Vaccines against COVID-19 SARS-CoV-2: COVID-19 vaccines have been introduced globally, and millions of people are being vaccinated with various types of vaccines, many of which use new vaccine platforms.[22] ADEM has been monitored among events considered serious after vaccination against COVID-19.[24, 34]

ACUTE ENCEPHALITIS

BCCD and SPEAC. Relevant for vaccination in general.

To harmonize the safety assessment of vaccines, guides to the BC AESI CD are now being prepared for each AESI separately. These guides were used to complement the information in this document, providing interested parties with conditions to assess the occurrence of acute encephalitis in various environments, including as an AEFI.[61]

Category: Neurologic

Listed: BC/SPEAC, WHO, EMA/ACCESS, FDA/CDC

Rationale for inclusion: Proven association with immunization encompassing several different vaccines.[6] For SPEAC, AESIs were prioritized at four tiers. Acute encephalitis is prioritized as Tier 1.[61]

About the AESI: Among the various events reported as adverse outcomes following immunizations, neurologic AEFI are perhaps the most severe, and perhaps the most difficult to address. The multifaceted presentation of neurologic illness, and relative lack of familiarity with the approach to and diagnosis of neurologic disease by many clinicians, makes neurologic AEFI some of the most challenging issues in clinical vaccinology. Moreover, the severity of central and peripheral nervous system events in individual patients often heightens the concern when such illnesses are associated with antecedent immunizations. The estimated incidence of encephalitis, in general, has varied widely, and is dependent upon age, demographics, season, causative agent, and presence of epidemic illness. Almost all previous studies on encephalitis have been hospital-based.[59]

Case definition: Encephalitis may have features that indicate spinal cord involvement (myelitis) and may be difficult to distinguish from acute disseminated encephalomyelitis.

As key diagnostic caveats, consideration should be given to data analysis and presentation as the characteristic findings of encephalitis brain biopsy are all that are needed to reach Level 1, but it is recognized that this will rarely be achieved. Of critical importance to achieving Level 2 or 3 is documentation of encephalopathy or focal/multifocal neurological signs, along with evidence of brain inflammation (fever, cerebrospinal fluid [CSF] pleocytosis, characteristic computed tomography (CT) / magnetic resonance imaging [MRI] / electroencephalogram findings in encephalitis) and no diagnosis alternatives (meningitis, parameningeal processes such as brain abscess, traumatic brain injury, encephalopathy associated with: sepsis, toxin, metabolic abnormality, neurodegenerative disease, endocrine disorder, and neoplastic disease).

These tests can be useful in assessing the causality of cases following vaccination. Encephalitis may be accompanied by evidence of myelitis, and there is a large overlap between encephalitis and ADEM. If there is evidence of myelopathy that accompanies encephalitis, if both reach the same LOC, then the case is encephalomyelitis. If both reach different LOC, Level 1 encephalitis (if there was a brain biopsy) and Level 2 myelitis (no spinal cord biopsy but meets Level 2 of the CD) must be specified separately for each. If there is evidence of demyelination in the brain or spinal cord, a Level 3A of certainty can be used to specify cases where there are insufficient data to distinguish between Level 3 encephalitis and Level 3 ADEM. However, if one of the two entities achieves a higher LOC, this should be the basis for categorization; for example, Level 2 encephalitis and Level 3 ADEM should be reported as Level 2 encephalitis; ADEM Level 1 and encephalitis Level 2 should be reported as ADEM Level 1.[59] (Complete_casedefinition_acute_encephalitis)

Background: Estimates of viral encephalitis rates have ranged from 0.08/100,000 population in national passive surveillance studies to 1–6 cases per 100,000 in hospital-based studies, and to 7.4 cases per 100,000 in one population-based study.[62] Acute encephalitis referral rates are generally below 10/100,000 PY, according to a study by the ACCESS group.[14]

Acute encephalitis risk factors:

- **Diseases and other factors:** The underlying causes of acute encephalitis are many, and include infectious, toxic, neoplastic, autoimmune, and metabolic etiologies. Most cases of encephalitis are thought to be infectious in nature and may be attributed to several different viral, bacterial, fungal, and parasitic agents. Toxic and metabolic agents may lead to a chemical encephalitis, while neoplasm may lead to either neoplastic or paraneoplastic encephalitis. Finally, various autoimmune conditions may lead to acute encephalitis.[59] HIV-infected individuals can have a variety of neurologic presentations. In addition, they and other immunocompromised individuals can be at risk of specific etiologies: human herpesvirus 6, CMV, EBV, measles, VZV, lymphocytic choriomeningitis virus, Toxoplasma sp., Cryptococcus sp., human polyomaviruses, Bartonella sp.[62]

  Other factors: Age (increased incidence in children, especially < 1 year; and older persons), gender (increased risk of specific etiologies: female: anti-NMDAR encephalitis), genetics (human leukocyte antigen polymorphisms may be associated with increased risk of infection by herpesviruses and arboviruses), geography (increased risk of specific etiologies – inhabitant / travel history), seasonal (warmer months for insect spread encephalitis); animal exposure with increased risk of specific etiologies: monkeys/bats/dogs (endemic areas); rabies, cats (Bartonella henselae [cat scratch disease]; horse: Hendra virus, Kunjin virus; rodents: lymphocytic choriomeningitis virus, Leptospira sp.; snails/ other mollusks; swine: Nipah virus; occupational: increased risk of specific etiologies; recreational: increased risk of specific etiologies as sexually transmitted (HIV); freshwater (Naegleria fowleri, Leptospirosis); and soil/mud (Balamuthia mandrillaris).[62]

- **Medicines:** In the literature, there is only a reference to a case with nivolumab, for a demyelinating encephalitis.[63]

- **Vaccines in general:** Immunizations may very rarely lead to acute encephalitis, particularly in the setting of live-attenuated viral vaccines. However, the introduction of immunizations has served to reduce the incidence of encephalitic complications in several viral and bacterial infections.[59] Concluded evidence was strong for an association between live-attenuated measles vaccine and measles inclusion body encephalitis in individuals with proven immunodeficiency. Strong evidence for encephalitis due to reactivation of Oka strain vaccine virus based on a single case in a 3-year-old female who had facial herpes zoster (HZ) and mild encephalitis, with onset 20 months after vaccination. Inadequate evidence to accept or reject a causal relationship between MMR, influenza (inactivated), HB, diphtheria and tetanus toxoid, acellular pertussis and meningococcal vaccines and encephalitis/encephalopathy. Immune-mediated mechanisms include autoantibodies, T cells and molecular mimicry. Strong evidence for disseminated VZV vaccine strain Oka infection with other organ involvement in individuals with demonstrated immunodeficiencies. Other organ involvement included pneumonia, hepatitis, and meningitis but not encephalitis. Risk window for encephalitis as a vaccine product related reaction. Postvaccinal encephalitis – likely immune-mediated with onset most commonly 7–14 days post vaccine. Measles inclusion body encephalitis in immunocompromised host: 4–9 months, suggesting persistent infection following immunization with live-attenuated measles virus – which is contraindicated in such individuals. Disseminated VZV vaccine strain Oka infection with other organ involvement: the time frame of observed cases was from 10 days to 2 months following immunization, suggesting active infection. VZV reactivation associated with encephalitis (one case) or meningitis (seven cases): interval from immunization to reactivation and associated CNS involvement ranged from 19 months to 8 years.[62]
- **Vaccines against COVID-19 SARS-CoV-2:** COVID-19 vaccines have been introduced globally, and millions of people are being vaccinated with various types of vaccines, many of which use new vaccine platforms.[22]

ACUTE MYELITIS

BCCD and SPEAC. Relevant for vaccination in general.

To harmonize the safety assessment of vaccines, guides to the BC AESI CD are now being prepared for each AESI separately. These guides were used to complement the information in this document, providing interested parties with conditions to assess the occurrence of myelitis in various environments, including as an AEFI.[11]

Category: Neurologic

Listed: BC/SPEAC, WHO, EMA/ACCESS, FDA/CDC

Rationale for inclusion: Proven association with immunization encompassing several different vaccines.[6] For SPEAC, AESIs were prioritized at four tiers. Acute myelitis is prioritized as Tier 1.[11]

About the AESI: The underlying causes of acute myelitis are many and include infectious, toxic, neoplastic, autoimmune, and metabolic etiologies.[11]

Case definition: As key elements of the acute myelitis CD, three LOC are relevant based on clinical and laboratory characteristics. The characteristic findings of myelitis spinal cord biopsy are all that are needed to reach Level 1, but it is recognized that this will rarely be achieved. Critically important to achieving Level 2 or 3 is documentation of at least one feature of myelopathy plus evidence of spinal cord inflammation (fever, CSF pleocytosis, characteristic CT/MRI findings in myelitis), and absence of alternative diagnoses. If there are features of encephalitis or ADEM in addition to myelitis, the LOC for myelitis should be determined, also evaluating the encephalitis/ADEM tools for the case. Myelitis can present in combination with encephalitis. In this event and if both reach the same LOC, the case is encephalomyelitis. In this event but where both reach

different LOC, it is necessary to specify separately for each. Myelitis can also manifest as part of ADEM. A Level 3A certainty can be used to specify cases where there are not enough data to distinguish between Level 3 myelitis and Level 3 ADEM. However, if one of the two entities reaches a higher LOC, this should be the basis for categorization; for example, Level 2 myelitis and Level 3 ADEM should be reported as Level 2 myelitis.

Recommendations for real-time assessment: Neurological consultation should be obtained, where possible, as early as possible in the course of the disease; fever is a criterion for inflammation and should be documented in accordance with the BCCD of temperature ≥ 38.0 °C by any measurement; other criteria for inflammation require CSF examination for pleocytosis and spinal cord imaging with CT and/or MRI; the recommended frequency of neurological assessment is at the initial presentation for medical care, at the clinical nadir (defined as when the clinical status is at its worst), at all subsequent points of significant change in neurological status until the end of the clinical course (recovery, death, or end of follow-up).[64] (Complete_casedefinition_acute_myelitis)

Background: Incidence rate all ages per 100,000 person-years [95% confidence interval] (total cases):[64]

- In the United States (North California), period 1998–2004, 3.1 (95% CI [2.6, 3.6]);
- In the United States, 12 (Minnesota, Olmsted County), period 2003–2016, 0.95 (95% CI [0.06, 1.48]) and 0.86 (95% CI [0.39, 1.66]);
- In the United States, 13 (California), period 2011–2016, [1–18 1.46];
- Canada, 14 (nationwide), period 2004–2007 is ≤ 18 0.2 [0.15, 0.3].

For transverse myelitis, the incidence does not vary much with age, with a conservatively estimated incidence of 1–8 new cases per million per year.[14]

Acute myelitis risk factors:

- Diseases and other factors: May be part of the presentation of other diseases that would be important for causality assessment:
  - Connective tissue / autoimmune diseases: sarcoidosis, Behçet's disease, Sjögren's syndrome, SLE, antiphospholipid antibody syndrome, mixed connective tissue disease, systemic sclerosis, urticarial vasculitis, perinuclear antineutrophil cytoplasmic antibody systemic vasculitis;
  - Neoplastic disease as a paraneoplastic syndrome;
  - Thyroid disease;
  - Nutritional deficiency: vitamin B12, vitamin E; copper;
  - Conditions that cause spinal cord compression: atrioventricular (AV) malformation, spinal cord tumors, abscess, or posttransplant graft versus host disease;
  - Common variable immunodeficiency;
  - Conditions that resulted in spinal cord radiation.

  Infection (12% of cases) are relevant for causality assessment when acute myelitis is an AEFI. These are all known etiologies and would exclude the vaccine unless a vaccine strain was found:

  - Viral: VZV, enterovirus, HSV 2, most common CMV; but many others have been reported, including: EBV; West Nile virus; ecoviruses; coxsackie viruses A and B; poliovirus 1, 2 and 3; enteroviruses D68, 70 and 71; influenza A and B; hepatitis A, B, C and E; HIV; human T-lymphotrophic virus, human herpesvirus 6; measles; mumps; rubella; HZ; Zika virus; dengue; parvovirus B19; human coronavirus, hantavirus; chikungunya; Japanese, St. Louis, Murray Valley, tick-borne encephalitis virus; Vaccinia virus;
  - Bacterial: *Mycobacterium tuberculosis*; *Borrelia burgdorferi* (Lyme disease); *Treponema pallidum* (neurosyphilis); *Mycoplasma pneumoniae, Campylobacter jejuni,*

Chlamydia species, Legionella pneumophila, brucellosis, group A and B beta-hemolytic *streptococci*, *Salmonella* Paratyphi B, *Acinetobacter baumannii, Orientia tsutsugamushi* (scrub typhus);

- Parasite: *Toxocara species*; *Schistosoma species*, *Gnathostoma spinigerum*, *Echinococcus granulosus*, *Toxoplasma gondii*, *Acanthamoeba* species, *Trypanosoma brucei, Taenia solium, Paragonimus westermani*, neurocysticercosis;
- Fungal: *Actinomyces* species, *Blastomyces* species, *Coccidioides immitis*, *Aspergillus* species, *Cryptococcus* species, *Cladophialophora bantiana*.

Other disorders that may cause acute myelopathy (exclude acute myelitis):

- Neoplasm;
- Toxic/metabolic encephalopathy;
- Vascular disorder;
- Trauma.

Age (children have a lower incidence than adults; bimodal peaks between ages 10–19 and 30–39 years), gender (may be higher in females due to it being seen commonly in multiple sclerosis but no known gender predisposition for acute transverse myelitis), genetics (no evidence for familial or ethnic predisposition), geography (no evidence for geographical variation in incidence other than a higher reported incidence in children in Finland).[64]

- Medicines: Tumor necrosis factor alpha inhibitors, sulfasalazine, epidural anesthesia, chemotherapeutic agents, heroin, benzene, toxin from brown recluse spider.[64]
- Vaccines in general: The revised evidence for the link between MMR, VZV, influenza, HA, HB, HPV, DTaP, meningococcal vaccines and ADEM and the completed evidence was inadequate to accept or reject a causal relationship. It is observed that the immune-mediated mechanisms include autoantibodies, T cells and molecular mimicry.

  Risk window for myelitis as a vaccine product related reaction:

  - Inactivated or subunit vaccines – immune-mediated mechanism for myelitis likely as for ADEM, where recommended risk window for individuals is 2–42 days, and for epidemiologic studies 5–28 days for primary analysis, and 2–42 days for secondary analysis,
  - Live attenuated vaccines – this should be based on the incubation period for the vaccine strain, adding as above, 5–28 days for primary analysis and 2–42 days for secondary analysis following the end of the incubation period.[64]
- Vaccines against COVID-19 SARS-CoV-2: COVID-19 vaccines have been introduced globally, and millions of people are being vaccinated with various types of vaccines, many of which use new vaccine platforms.[22] Suspected cases of acute myelitis and transverse myelitis have been reported and monitored among events considered serious after vaccination against COVID-19.[23, 24]

ASEPTIC MENINGITIS

BCCD and SPEAC. Relevant for vaccination in general.

To harmonize the safety assessment of vaccines, guides to the BC AESI CD are now being prepared for each AESI separately. These guides were used to complement the information in this document, providing interested

parties with conditions to assess the occurrence of aseptic meningitis in various environments, including as an AEFI.[65]

Category: Neurologic

Listed: BC/SPEAC, FDA/CDC

Rationale for inclusion: Allow standardized assessment and improve comparability of cases of aseptic meningitis.[11]

About the AESI: "Aseptic meningitis is commonly defined as a syndrome characterized by acute onset of signs and symptoms of meningeal inflammation, cerebrospinal fluid (CSF) pleocytosis and the absence of microorganisms on Gram stain and/or on routine culture. Aseptic meningitis is frequently caused by viral agents, particularly by enteroviruses. Aseptic meningitis following immunization usually is benign and resolves without sequelae."[66]

Case definition: In the review by Law, only two levels of diagnostic certainty. Lumbar puncture for CSF examination is critical to meeting the CD, with leukocyte pleocytosis and Gram stain results more important than culture results. No other measurable CSF parameters were incorporated into the CD for reasons observed such as glucose / low complexity region (LCR) protein, which has low diagnostic accuracy to distinguish bacterial from nonbacterial meningitis in cases of Gram-negative staining. For LCR/LCR, it is not available in all configurations. Differential polymorphonuclear cell counts may be present early in viral meningitis and is therefore not useful as a criterion for ruling out aseptic meningitis. Latex agglutination results are not included due to poor diagnostic accuracy, and polymerase chain reaction (PCR) was also not included owing to false positive results that may arise due to contamination, and false negative results due to amplification reaction inhibitors that may be present in the sample.

The CSF criteria are part of the CD for encephalitis; however, for cases with other diagnostic features of encephalitis (altered level of consciousness, focal neurological abnormalities), the recommendation is that the case be evaluated as encephalitis, not aseptic meningitis. In addition, if a case reaches an LOC for encephalitis and aseptic meningitis, it should be reported as encephalitis. All reports of aseptic meningitis must be collected regardless of the time elapsed between vaccination and the adverse event, ensuring that the safety data collected are clearly defined.[65] (Complete_casedefinition_asepticmeningitis)

Background: Aseptic meningitis background rates, all ages (adjusted rate), incidence rate per 100,000 person-years [95% confidence interval] (total cases), period:[65]

The United States (Minnesota):

- 1950–1959 – 11.4 (95% CI [8.6, 14.3]);
- 1960–1967 – 8.5 (95% CI [6.4, 10.6]);
- 1970–1975 – 9.5 (95% CI [6.9, 12.0]);
- 1976–1981 – 17.8 (95% CI [14.3, 21.3]).

Europe – England, nationwide and northwest (confirmed viral meningitis), period 1999–2003, age ≥ 16, 2.73 (95% CI [2.13, 3.44] 1.389) and 1.27 (95% CI [0.99, 1.60] 71), respectively. Finland, period 1999–2003, 16–84 7.6 [144] and, 1980 all ages, 26.7 [128].

Aseptic meningitis risk factors:

» **Diseases and other factors:** Frequently caused by viral agents, particularly enteroviruses and also by other known etiologies: bacteria not cultivable in routine culture (Mycobacterium tuberculosis, Treponema pallidum, Borrelia species, etc.); Chlamydia, Mycoplasma, and Rickettsia species; fungi; protozoa (toxoplasmosis, malaria, etc.); other parasites; parameningeal infections; malignancies; sarcoidosis; immunological diseases, drugs; foreign bodies and cysts in the CNS or adjacent to it;

measles and mumps viruses – important causative agents of aseptic meningitis before measles and mumps vaccines;[66] persistent enteroviral viral infection in patients with congenital hypo- or agammaglobulinemia; age (premature babies, adults ≥ 60), season (infectious causes: enteroviruses cause 85–95% of cases and are prevalent from May to October in temperate climates but occur throughout the year in tropical climates); arboviruses spread by mosquitoes are more common in the rainy season in tropical climates or in spring – summer – early autumn in temperate climates; differential diagnosis of aseptic meningitis: meningeal infection (viral, bacterial, parasitic, fungal), parameningeal infection, malignancy, autoimmune or immune-mediated vasculitis, drugs.[65]

The etiology of aseptic meningitis can be categorized into infectious causes and noninfectious causes. Infectious causes include viruses, bacteria, fungi, and parasites. Noninfectious causes include postinfection/vaccination inflammation, drugs, systemic diseases, and neoplastic disorders, to name a few. The cause, ultimately, can only be identified in 30–65% of cases. The most common cause is viral, most often enteroviruses, followed by HSV type 2, and chickenpox. Other associated viruses include respiratory viruses (adenovirus, influenza virus, rhinovirus), mumps virus, arbovirus, HIV, and lymphocytic choriomeningitis. Bacterial causes may include partially treated meningitis, parameningeal infection, Mycoplasma pneumoniae, endocarditis, Mycobacterium tuberculosis, Borrelia burgdorferi, ehrlichiosis, Brucella, Treponema pallidum, Bartonella henselae, and leptospirosis. Rocky Mountain spotted fever and typhus are common rickettsiae in the differential. Fungal causes may include Candida, Cryptococcus neoformans, Histoplasma capsulatum, Coccidioides immitis, and Blastomyces dermatitidis. Parasites that cause aseptic meningitis include Toxoplasma gondii, naegleria, neurocysticercosis, trichinosis, and Hartmannella. Systemic diseases that can cause aseptic meningitis include Behçet's disease, Vogt-Koyanagi-Harada´s syndrome, sarcoidosis, leptomeningeal cancer, collagen vascular disorders, and posttransplant lymphoproliferative disorder.[67]

» **Medicines:** NSAIDs and intravenous immunoglobulins;[65] other drugs including isoniazid, azathioprine, intrathecal medications (methotrexate, cytosine arabinoside), antibiotics (trimethoprim-sulfamethoxazole, amoxicillin), allopurinol, carbamazepine, and sulfasalazine have all been associated with aseptic meningitis.[67]

» **Vaccines in general:** The review assessed the risk of aseptic meningitis following mumps containing vaccines: adjusted overall relative incidence 10.8 (95% CI [4.0, 29.2]). The risk following Leningrad-Zagreb mumps strains was significantly increased: 10.8 (95% CI [1.3, 87.4]). Estimates for other mumps virus strains (S79, Urabe Am9, RIT 4385/Jeryl-Lynn) could not be assessed. The highest internal rate of return (IRR) was in Iran (Islamic Republic of): 20.3 (95% CI [4.8, 85.2]) and applied to Hoshino/Leningrad-Zagreb/UrabeAm9 with inability to distinguish between the strains. Risk interval of 8–35 days for aseptic meningitis following mumps containing vaccines.[65]

Cases of aseptic meningitis have been reported after immunization with several live-attenuated viral vaccines, including oral polio, combined MMR, varicella, yellow fever, and smallpox vaccines. Aseptic meningitis accompanying radiculitis and myelitis has also occurred following administration of Semple-type inactivated rabies vaccine. The increased risk of aseptic meningitis after MMR immunization has been well documented. Immunization with MMR containing the Urabe, Leningrad-Zagreb, and Hoshino mumps strains results in a 5.5–38-fold increased risk of aseptic meningitis approximately 2–7 weeks following immunization. Outbreaks of aseptic meningitis have been documented following mass vaccination campaigns using MMR with the Leningrad-Zagreb or Urabe mumps strains. The Jeryl-Lynn mumps strain has not been shown to increase the risk of aseptic meningitis. There is a paucity of data on the Leningrad-3 mumps strain, a predecessor of the Leningrad-Zagreb strain. Aseptic meningitis following immunization is usually benign and resolves without sequelae.[66] Another author cites yellow fever vaccine, pertussis vaccine, and the influenza vaccine.[67]

» **Vaccines against COVID-19 SARS-CoV-2:** COVID-19 vaccines have been introduced globally, and millions of people are being vaccinated with various types of vaccines, many of which use new vaccine platforms. [22]

PERIPHERAL FACIAL NERVE PALSY

BCCD and SPEAC. Relevant for vaccination in general.

To harmonize the safety assessment of vaccines, guides to the BC AESI CD are now being prepared for each AESI separately. These guides were used to complement the information in this document, providing interested parties with conditions to assess the occurrence of facial nerve palsy in various environments, including as an AEFI.[68]

Category: Neurologic

Listed: BC/SPEAC

Rationale for inclusion: Recognizing the many variables and uncertainties that affect the definition and diagnosis of peripheral facial nerve palsy, including Bell's palsy (BP), it was important to establish useful and practical guidelines to standardize the collection, analysis, and presentation of data on facial nerve palsy, or BP, in the context of pre- and post-licensing clinical trials, surveillance, and epidemiological studies of vaccine safety. [69] For SPEAC, AESIs were prioritized at four tiers. Facial nerve palsy is prioritized as Tier 1.[68]

About the AESI: "Facial nerve palsy is classified based on the location of its lesion. Peripheral facial nerve palsy is the partial (i.e., paresis) or complete (i.e., paralysis) loss of function of some or all the structures innervated by the facial nerve (i.e., cranial nerve VII). Facial nerve palsy is also classified by the time course of its development depending on whether acute (minutes to days), subacute (days to weeks), or chronic (longer than weeks)." [69]

Case definition: Idiopathic facial nerve palsy is a peripheral neuropathy (lower motor neuron) and is a diagnosis of exclusion. CD requires impairment of the ability to wrinkle the forehead OR raise the eyebrow on the affected side – both are spared in the "central" lesions of the upper motor neuron. Ideally, information about both should be collected, but the CD allows one or the other abnormality to be documented, increasing the sensitivity of the CD. There are three LOC, with Level 3 being based on clinical history/physical examination only; however, if alternative diagnoses are found based on clinical findings, the diagnosis will be discarded, but it is not mandatory to look for alternative causes. On the other hand, to achieve a higher LOC, some tests must be done to rule out alternative causes: laboratory tests for Level 2, and laboratory and radiology tests for Level 1.

The CD requires the onset to be sudden (unexpectedly and without warning, leading to a marked change in the subject's previously stable condition), with rapid progression (worsening in a short period of time) and partial/complete resolution (with or without treatment). There is usually a rapid evolution with maximum weakness within 24–72 h but it can last for up to 10 days. Any evolution longer than two weeks should suggest a tumor or cholesteatoma. Most cases of idiopathic peripheral facial nerve palsy are unilateral; bilateral cases are rare and should be reported by a healthcare provider.[68] (Complete_casedefinitionfacialnervepalsy)

Background: BP is a subset of peripheral facial nerve palsy of unknown cause (idiopathic peripheral facial nerve palsy), described in all age groups and in many different parts of the world. More than half of all cases of acute-onset peripheral facial nerve palsy are considered BP, and the annual incidence rate is estimated to be between 13 and 53 cases per 100,000 population.[69]

Other data show pooled historical rates of AESI from electronic health records databases from eight countries (Australia, France, Germany, Japan, the Netherlands, Spain, United Kingdom, and United States) (Table 4).[15]

Table 4: Incidence Rate per 100,000 Person-years (95% Prediction Interval), Data from Australia, France, Germany, Israel, Japan, the Netherlands, Spain, United Kingdom, and United States[15]

Incidence rate per 100 000 person years (95% prediction interval)														
Country	**Gender**	**1-4 years**	**1 - 5 years**	**5-14 years**	**6 - 17 years**	**15 - 24 years**	**18 - 34 years**	**25 - 34 years**	**35 - 44 years**	**35 - 54 years**	**55 - 64 years**	**64 - 74 years**	**75 - 84 years**	**≥ 85 years**
Australia, France, Germany, Japan, the Netherlands, Spain, United Kingdom and United States	Female		9-27		12-51		23-84			26-140	21-184	29-256	31-330	31-274
	Male		10-24		13-34		29-64			37-125	43-172	35-252	29-291	34-292
Israel		18.9		30.9		47.7		72.3	91.11		154.4	190.9	190.74	125 overall

Facial nerve palsy risk factors:

» **Diseases and other factors:** Facial nerve palsy is classified based on the location of its lesion, and most commonly presents on one side of the face, leading to facial asymmetry, or "facial droop." Simultaneous bilateral acute-onset cases have also been described and are now recognized as an uncommon clinical feature. It can be observed in the context of many conditions, including infections such as otitis media with or without cholesteatoma, rubella, Lyme borreliosis, herpesvirus reactivation, influenza, and HIV infection. It may also be associated with traumatic injury, malignancy, and autoimmune disorders, as well as in the context of hormonal changes during pregnancy. It has been described in all age groups and in many different parts of the world. Most cases resolve completely and spontaneously, and re-occurrence of BP in the same individual appears to be rare.[69]

Details of the underlying conditions and diseases associated with facial nerve palsy: a) infectious diseases (echovirus infection, ehrlichiosis, enterovirus infection, HSV infection, human herpesvirus infections, HIV infection, similar disease influenza, leprosy, Lyme disease, meningitis, mumps virus infection, Mycobacterium tuberculosis infection, Mycoplasma infection, otitis media and mastoiditis, chronic or acute, poliomyelitis, rubella virus infection, syphilis, tetanus, cephalic diseases, tick-borne VZV / Ramsay Hunt syndrome, tumors, benign tumors, other, glomus tumor, malignancies, head and neck melanoma, metastatic tumor, neuroma / schwannoma, parotid tumor, primary, rhombencephalitis, paraneoplastic); b) neurological and autoimmune diseases (ADEM, GBS, Kawasaki disease [KD], cranial polyneuritis, Sjögren's syndrome and other autoimmune diseases, small pontine infarctions, SLE, trigeminal neuropathy, dental trauma/surgery, petroleum bone fractures, pontine injuries); and c) other conditions (cholesteatoma, diabetes mellitus, exposure to cold temperature, hemophilia, hereditary neuropathy, histiocytosis, hypertension, toxicity of isoniazid treatment, leukemia, Melkersson-Rosenthal syndrome, Möbius syndrome, Paget's disease of bone, perineural edema, posttraumatic stress, pregnancy, serotherapy for tetanus, sarcoidosis).[69]

In Law's review, about half of all cases of acute peripheral facial nerve palsy are idiopathic, with no specific cause found. In the other half of cases, a specific cause may be found including infection (viral, bacterial, MYCOPLASMA, mycobacteria, spirochetal, tick-borne zoonoses), cancer, neurologic / neuromuscular junction / autoimmune / endocrine disorders, trauma, drug toxicity, inherited disorders; diabetes, pre-diabetes; hypertension; migraine; psychological factors.[68]

Age: The incidence is higher among adults than children. There is some evidence for peak prevalence at age 15–45 years, but some population-based incidence studies suggest a steadily increasing incidence from young to older age (Israel and Laredo studies). Pregnancy: increased incidence among pregnant

women especially 3rd trimester and 1st 2 weeks postpartum but this is controversial. Geography: cold weather season – extremes in wind chill positively correlated with case frequency.[68]

A study defines that, in the five main theories on the causes of BP, it includes anatomical (facial nerve more susceptible to paralysis than other nerves in the body), viral infection (reactivated viruses, such as VZV, HSV type 1, human herpesvirus 6, and Usutu virus), ischemia (acute idiopathic lower motor neuron paralysis is commonly a unilateral and self-limiting inflammatory condition), inflammation (results from acute demyelination caused by inflammation), and cold stimulation. There are several possible risk factors for BP, including severe pre-eclampsia, psychological factors, abnormalities of glucose metabolism, radiation exposure, hypertension, and migraine. Recently, epidemiological studies have revealed that the incidence of BP is also related to exposure to extreme temperatures.[70]

- **Medicines:** No medicines associated with peripheral facial nerve palsy.
- **Vaccines in general:** The proven association between an intranasally administered influenza vaccine adjuvanted with E. coli heat-labile toxin (Nasalflu®, Berna Biotech) and BP is the only one demonstrated to date. Risk window for BP as a vaccine product related reaction or intranasal adjuvanted vaccine: elevated risk from 1 to 91 days, with the highest risk in the 31–60 days period following immunization; inactivated or subunit vaccines: theoretically the same risk period as used for ADEM26 might apply, i.e., 2–42 days for individual risk and for epidemiologic studies 5–28 days for primary analysis, and 2–42 days for secondary analysis; live attenuated vaccines: similar to inactivated vaccines but adjusted for the known incubation period for the vaccine strain, adding as above, 5–28 days for primary analysis and 2–42 days for secondary analysis following the end of the incubation period.([68], [69]) MMR vaccine has been temporally association related to the occurrence of facial paralysis.[21]
- **Vaccines against COVID-19 SARS-CoV-2:** COVID-19 vaccines have been introduced globally, and millions of people are being vaccinated with various types of vaccines, many of which use new vaccine platforms.[22] Suspected cases of facial nerve palsy have been reported and monitored among events considered serious after vaccination against COVID-19.[24]

VACCINE-ASSOCIATED ENHANCED DISEASE

BCCD and SPEAC. Case Definition and Guidelines for Data Collection, Analysis, and Presentation of Immunization Safety Data. Relevant for vaccination in general.

This is a BCCD of the term “vaccine-associated enhanced disease” (VAED) to be utilized in the evaluation of AEFI.[71]

Category: Immunologic

Listed: BC/SPEAC, FDA/CDC

Rationale for inclusion: In the Priority List of Adverse Events of Special Interest: COVID-19, it justifies the inclusion of this event due to the documented serious disease, after the use of inactivated viral vaccines for measles and respiratory syncytial virus (RSV), because of infection in individuals treated with nonprotective antibodies. The increase in the disease was also observed with dengue and pandemic influenza.[6]

The CD was developed in the context of active development of vaccines for SARS-CoV-2 vaccines and other emerging pathogens.[72]

About the AESI: VAEDs are modified presentations of clinical infections affecting individuals exposed to a wild-type pathogen after having received a prior vaccination for the same pathogen. Vaccine-associated enhanced respiratory disease (VAERD) refers to disease with predominant involvement of the lower respiratory tract.

Classic examples of VAED are atypical measles and enhanced RSV occurring after administration of inactivated vaccine for these pathogens.[72]

Case definition: Munoz et al. developed a consensus CD and defined levels of diagnostic certainty, after an exhaustive review of the literature and expert consultation:

a. It is an illness that occurs in persons who receive a vaccine and who are subsequently infected with the pathogen that the vaccine is meant to protect against. This definition assumes previously antigen-naïve vaccine recipients, which can be assessed by determining seronegative status prior to vaccination, when feasible. The need for documentation of seronegativity prior to vaccination, which can be done retrospectively, is particularly relevant in Phase II–III clinical trials. In the context of such trials, the working group acknowledged the difficulty in distinguishing between vaccine failure and VAED. Thus, all cases of vaccine failure should be evaluated for VAED.

b. VAED may present as severe disease or modified/unusual clinical manifestations of a known disease presentation. The illness presumably is more severe or has characteristics that distinguish it from illness that might occur in unvaccinated individuals.

c. VAED may involve one or multiple organ systems.

d. VAED may also present as an increased incidence of disease in vaccinees compared with controls or known background rates.

Vaccines vary based on the antigen utilized and the addition of adjuvants. At this time, there is insufficient data to determine a priori if any of these platforms is less or more likely to be associated with VAED/VAERD. The working group agrees that it is not possible to know the potential risk for VAED/VAERD of an individual vaccine given various mechanisms leading to disease enhancement, and the different affinity for specific receptors. The use of convalescent sera or monoclonal antibodies might inform potential antibody mediated effect vs. cell mediated mechanisms. Vaccine enhancement vs. vaccine failure: In the event of low/poor vaccine efficacy, infection will occur in vaccinated subjects, with breakthrough disease associated with viral replication. When assessing the safety of a vaccine, there is a need to distinguish between a case where an immune response is not induced from a case where an aberrant non-protective immune response is induced. A thorough assessment of immune responses along with protection from serious disease outcomes is necessary to distinguish enhancement from break-through infection.[72] (Complete_casedefinitionVAED)

Background: In the first large placebo-controlled clinical trial (STEP trial) of an Ad5-HIV, later with an expanded analysis of data, the annual incidence was 4.6% (95% CI [3.4, 6.1]) to vaccine recipients, and for placebo recipients, the annual incidence was 3.1% (95% CI [2.1, 4.3]). Possible explanations for this increased susceptibility to HIV infection in vaccinees included the lack of an HIV-Env antigen in the vaccine, with the possibility that the vaccine-induced HIV immune response potentially induced HIV binding to the cell surface, but without killing or neutralizing the virus, thus allowing the virus to enter the cell.

In two of the RSV vaccines trials, attack rates, particularly in infants under 12 months of age, were higher than in the control group for the vaccine candidate parainfluenza 3 (PIV3). In one study, 23 out of 31 (74%) RSV vaccinated infants later developed RSV infection compared with 21 out of 40 (53%) RSV infections in infants who received PIV3 (chi-square unadjusted 5.1505; p-value 0.023). In a second study, 13 out of 43 (30%) infants vaccinated with RSV later developed RSV infection compared with 5 of 46 (11%) RSV infections in infants who received PIV3 (chi-unadjusted square 5.1645; p-value 0.023).[72]

VAED risk factors:

- **Diseases and other factors:** Severe disease has been documented resulting from infection in individuals primed with nonprotective immune responses against the respective wild-type viruses. Given that these enhanced responses are triggered by failed attempts to control the infecting virus, VAED typically presents with symptoms related to the target organ of the infection pathogen. In order to recognize VAED,

it is therefore necessary to have a clear understanding of the clinical presentation and usual course of the natural disease.[72]

- **Vaccines in general:** VAED or VAERD may occur at any time after vaccination. The timing of occurrence of clinical manifestations of VAED or VAERD after vaccination will be dependent on the mechanism or pathophysiological pathway leading to disease enhancement after natural infection. VAED or VAERD may present within 2–4 weeks of natural infection, if the expected initial antibody responses are inadequate; or may present later (> 1 month or longer) after natural infection if antibody waning is noted or if the mechanism is not exclusively antibody mediated.
- Classic examples of VAED are cases of atypical measles and increased RSV disease that occurred after administration of the initial inactivated measles and respiratory syncytial virus (RSV) vaccines. No single or combination of specific confirmatory tests is available to diagnose VAED. As the clinical manifestations of VAED lies within the spectrum of natural disease – occurring more frequently and/or severely in vaccinated individuals – it is also difficult to separate vaccine failure (also called breakthrough disease) from VAED in vaccinated individuals. All cases of vaccine failure should be investigated for VAED. Vaccine failure is defined as the occurrence of the specific vaccine-preventable disease in a person who is appropriately and fully vaccinated, taking into consideration the incubation period and the normal delay for the protection to be acquired as a result of immunization.[72]
- **Vaccines against COVID-19 SARS-CoV-2:** COVID-19 vaccines have been introduced globally, and millions of people are being vaccinated with various types of vaccines, many of which use new vaccine platforms.[22]

MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN AND ADULTS

BCCD and SPEAC. Case Definition and Guidelines for Data Collection, Analysis, and Presentation of Immunization Safety Data. Relevant for vaccination in general.

This is a BCCD of the terms “multisystem inflammatory syndrome in children (MIS-C)” and “multisystem inflammatory syndrome in adults (MIS-A)” to be utilized in the evaluation of AEFI.[73]

Category: Immunologic

Listed: BC/SPEAC, EMA/ACCESS, FDA/CDC

Rationale for inclusion: Theoretical concern based on immunopathogenesis and related to viral replication during wild-type disease.[6]

About the AESI: Children and adolescents are as susceptible to infection with SARS-CoV-2 as adults but develop symptomatic COVID-19 primary infection at significantly lesser rates and rarely develop severe disease. However, it has become clear that a fraction of children develops a life-threatening hyperinflammatory state 4–6 weeks after infection with primary COVID-19 termed MIS-C. MIS-C was first recognized in the United Kingdom in April 2020, prompting an alert issued by the Paediatric Intensive Care Society describing a recognized increase in critically ill children presenting with hyperinflammatory shock and evidence of SARS-CoV2 infection.

A similar condition (since June 2020) has also been reported as a rare complication of COVID-19 in adults (MIS-A), and the syndrome that appears in adults can be more complicated than that in children. It is currently unknown whether MIS-C/A might follow immunization against SARS-CoV-2, but a need exists to define this potential entity for monitoring as an adverse event following immunization (AEFI). Patients with MIS-A have been reported up to the age of 50 years and, compared with MIS-C, are more likely to have underlying health problems and have an identifiable antecedent respiratory disease.[74]

Case definition: Children and adults infected with the virus that causes COVID-19 can develop a severe hyperinflammatory response during primary infection (MIS) days or weeks after becoming ill with SARS-CoV-2.

MIS-C is a rare but serious complication in children and adolescents infected with SARS-CoV-2, being possible that the child has been infected by asymptomatic contact and, in some cases, it is possible that the child and their caregivers may not even know that they have been infected. Patients with MIS-C experienced persistent fever, fatigue, and a variety of signs and symptoms, including multiple organ involvement (e.g., cardiac, gastrointestinal, renal, hematologic, dermatologic, neurologic) and elevated inflammatory markers.

MIS-A is recognized as a serious illness requiring hospitalization in a person ≥ 21 years of age, with laboratory evidence of current or previous SARS-CoV-2 infection (within 12 weeks), severe extrapulmonary organ dysfunction (including thrombosis), laboratory evidence of severe inflammation and absence of severe respiratory disease. Adults with MIS-A may experience fever, low blood pressure, abdominal (intestinal) pain, vomiting, diarrhea, neck pain, rash, chest tightness/pain, feeling very tired. MIS-A can be very serious, so it is important to seek medical attention as soon as possible. Patients with MIS-A have clinical features that markedly overlap with MIS-C, although the severity of cardiac dysfunction, incidence of thrombosis, and mortality from MIS-A may be higher.

The clinical presentations of these and other patients reported shortly thereafter invoked similarities to known pathological entities such as KD, toxic shock syndrome (TSS), and macrophage activation syndrome / secondary hemophagocytic lymphohistiocytosis.[74, 75] (Complete_casedefinitionMIS_C_A)

Background: KD incidences of 7.3 per 100,000 person-years after DTaP and 21.9 per 100,000 person-years after DTaP-IPV / PRP-T;[74] MIS events using narrow definition were observed by the ACCESS study group across all databases and across all years of study. Overall, the incidence rates (IRs) found were low, ranging between two databases 0.30/100,000 person-years in 2018 to 6.94/100,000 person-years (data for pediatric population only).[14]

The diagnoses for MIS-C/A: These include KD, Kawasaki shock, hemophagocytic lymphohistiocytosis, TSS, macrophage activation syndrome, and a variety of other entities, particularly ones that cause myocarditis or hyperinflammation. Some individuals may meet full or partial criteria for KD, but it must be reported whether they meet the CD for MIS-C. It is recommended that MIS-C be considered in any pediatric death with evidence of SARS-CoV-2 infection.[75]

Multisystem inflammatory syndrome risk factors

- **Diseases and other factors:** According to the CDC, learning about MIS-C and MIS-A and how it affects children and adults is still ongoing. It is not known why some children and adults became sick with MIS-C or MIS-A and others did not, and it is not known whether these groups with certain health conditions are more likely to develop MIS-C.[75]
- **Medicines:** No medicines associated with MIS-C/A.
- **Vaccines in general:** Currently, there is an incidence after vaccination with DTaP and DTaP-IPV / PRP-T for KD; however, it is unknown whether MIS-C/A could follow routine immunization.[74]
- **Vaccines against COVID-19 SARS-CoV-2:** It is currently unknown whether MIS-C/A could follow immunization against SARS-CoV-2, but there is a need to define this potential entity for follow-up as an AEFI. MIS-C is a new syndrome in children that presents in temporal association with SARS-CoV-2 infection and had not been previously described in association with any vaccine. To date, MIS-A has not been reported in adult participants of SARS-CoV-2 vaccine trials and few children have been included in these trials so far. MIS-C overlaps with KD and TSS, which have been reported as AEFI.[74] MIS-C/A is being monitored among events considered serious.[24]

ACUTE RESPIRATORY DISTRESS SYNDROME

BCCD and SPEAC. Case Definition and Guidelines for Data Collection, Analysis, and Presentation of Immunization Safety Data. Relevant for vaccination in general.

This is a BCCD of the term "acute respiratory distress syndrome (ARDS)" to be utilized in the evaluation of AEFI.[76]

Category: Respiratory

Listed: BC/SPEAC, FDA/CDC

Rationale for inclusion: Theoretical concern based on immunopathogenesis and related to viral replication during wild-type disease.[6] The CD for the assessment of ARDS as a potential adverse event following any immunization was developed by a group of experts in the context of active development of vaccines for SARS-CoV-2 vaccines and other emerging pathogens to a consensus and defined LOC.[77]

About the AESI: ARDS is a life-threatening condition resulting from acute inflammatory lung injury. It is characterized by diffuse alveolar damage with hypoxemia and poor lung compliance. While multiple insults can result in ARDS, the final common pathway ends in direct epithelial pulmonary injury with or without injury to the endothelium. A temporal association consistent with the expected clinical course of ARDS would be suggested by a typical interval of one to two weeks between the insult and ARDS. Therefore, when considering the possibility of ARDS as an AEFI, it is unlikely that ARDS would occur months after the exposure.[77]

Case definition: ARDS is an acute inflammatory lung process that leads to protein-rich nonhydrostatic pulmonary edema, causes refractory hypoxemia, increases lung "stiffness", and impairs the ability of the lung to eliminate carbon dioxide.[14]

Existing definitions of ARDS were evaluated for the development of a CD for the evaluation of ARDS as a possible adverse event after any vaccine. According to the BC working group, in this definition, a level of diagnostic certainty is attributed based on the quality of the evidence to support the criteria used to make the diagnosis. The Tier 1 definition is very specific to ARDS. Considering that maximum specificity normally implies a loss of sensitivity, two additional diagnostic levels were included in the definition, which offer a gradual increase in sensitivity from Level 1 to Level 3, while maintaining an acceptable specificity in all levels, allowing the characterization of severity as mild, moderate, or severe according to the degree of hypoxemia.[77] (Complete_casedefinitionARDS)

Background: ARDS is responsible for significant morbidity and mortality worldwide, and quantifying this burden depends on the morbidity measure used. Regardless, a population-based estimate of the incidence of ARDS is not available, and the available burden of disease estimates are likely to be underestimated. However, ARDS is the most common complication of COVID-19, and its incidence has ranged between 14 and 52%.[77]

Data from Iceland show that the age-standardized incidence of ARDS was 7.2 cases per 100,000 person-years and was increased by 0.2 cases per year ($P < 0.001$). The most common causes of ARDS were pneumonia (29%) and sepsis (29%). An overview paper reports rates between 10 and 79 per 100,000 PY.[14]

Other data show pooled historical rates of AESI from electronic health records databases from Europa and United States are 1.5–79 per 100,000 persons/year. In Brazil, the rates are 1.8–31 per 100,000 persons /year.[15, 21]

ARDS risk factors:

- Diseases and other factors: ARDS are a life-threatening condition resulting from acute inflammatory lung injury. It is characterized by diffuse alveolar damage with hypoxemia and poor lung compliance. While multiple insults can result in ARDS, the final common pathway ends in direct epithelial pulmonary injury with or without injury to the endothelium. This process increases permeability of the lung epithelial barrier, filling of the alveolar spaces with inflammatory fibrinous exudates, and collagen deposition with minimal interstitial edema. ARDS can result from a number of different clinical insults.

These are typically categorized as either resulting from direct lung injury (such as pneumonia) or indirect lung injury (such as sepsis).

Examples of clinical insults associated with ARDS:

- Direct lung injury – more common: pneumonia (bacterial): Streptococcus pneumoniae (A and B), S. aureus, H. influenzae, Chlamydia pneumoniae, mycobacteria (M. tuberculosis, M. avium), Neisseria sp., Enterococcus sp.; viral: influenza A and B, parainfluenza 1–3, RSV, coronavirus, SARS-CoV-1, SARS-CoV-2 and Middle East Respiratory Syndrome (MERS), adenovirus, Human metapneumovirus, measles, varicella; fungal (Aspergillus, Blastomyces, Cryptococcus, Pneumocystis jirovecii) and parasites (malaria); less common: pulmonary contusion, pneumonia, viral (SARS-CoV-1, MERS, measles), fungal (Aspergillus), mycobacteria (M. avium), near-drowning, fat emboli, aspiration of gastric contents, inhalational injury, burn injury, reperfusion pulmonary edema after procedure.
- Indirect lung injury – more common: sepsis, severe trauma with shock and multiple transfusions.
- Less common: cardiopulmonary bypass, drug overdose, acute pancreatitis (AP), transfusion of blood products.[77]

- **Medicines:** Overdose of certain drugs or medications, such as heroin, methadone, propoxyphene, or aspirin.[78]
- **Vaccines in general:** Although several infectious diseases are associated with the development of ARDS, there are no reports suggesting a temporal association of ARDS after vaccination with currently licensed vaccines. In fact, a reduction in ARDS has been reported in people vaccinated against certain respiratory pathogens, such as influenza. The occurrence of possible intensified VAED, a phenomenon that may present clinically as ARDS, but which is distinct in its pathogenesis, was described after the administration of vaccines inactivated by formalin against RSV in the 1960s, and some measles, influenza pandemic, and other respiratory virus vaccines.[77]
- **Vaccines against COVID-19 SARS-CoV-2:** COVID-19 vaccines have been introduced globally, and millions of people are being vaccinated with various types of vaccines, many of which use new vaccine platforms.[22] However, for people exposed to SARS-CoV-2 vaccines, additional long-term monitoring is required in the pre- and post-licensing stages to determine the risk of increased vaccine-associated disease, particularly when neutralizing antibody titers begin to decrease.[82] Suspected cases of ARDS have been reported and monitored among events considered serious after vaccination against COVID-19.[24]

SENSORINEURAL HEARING LOSS

BCCD and SPEAC. Case Definition and Guidelines for Data Collection, Analysis, and Presentation of Immunization Safety Data. Relevant for vaccination in general.

The CD format of the BC was followed to develop a consensus CD and defined levels of diagnostic certainty, after an exhaustive review of the literature and expert consultation.[79]

Category: Sensorineural

Listed: BC/SPEAC

Rationale for inclusion: Need for developing case definitions and guidelines for data collection, analysis, and presentation for SNHL as an AEFI.[80]

About the AESI: SNHL is a specific type of hearing deficit, first described by De Kleyn in 1944 and distinct from conductive hearing loss. SNHL results from damage to the inner ear, the vestibulocochlear nerve, or the central

processing centers of the brain. SNHL can be unilateral or bilateral, and the degree of the hearing loss is graded as mild to profound.[80]

Case definition: SNHL is a hearing loss of at least 30 dB at three sequential frequencies in the standard pure-tone audiogram. SNHL is the result of dysfunction of the inner ear, vestibulocochlear nerve, or central processing centers of the brain. Definitive diagnosis of SNHL requires a physical examination to exclude conductive hearing loss AND an audiometric evaluation consistent with SNHL. A key element in the definition of SNHL is the differentiation between conductive hearing loss and SNHL. A careful physical examination and a properly performed audiometry test are considered essential to establish a definitive diagnosis of SNHL (definitive case). The BC working group recommends using the standard definition of SNHL endorsed by the American Academy of Otolaryngology-Head and Neck Surgery, the National Institute on Deafness and Other Communication Disorders, and the American Association of the Speech, Language and Hearing (ASHA).[80] (Complete_casedefinitionSNHL)

Background: WHO estimates that 6.1% of the world's population (466 million persons) have disabling hearing loss (7% [34 million] are children, 93% [432 million] are adults). The prevalence is higher in males as compared to females across all age groups. According to WHO criteria, an overall prevalence of mild hearing loss (> 25 dB) of 16.2% has been reported in adults. Mild hearing loss is diagnosed in 6.6% of patients 50–59 years of age, 20.3% of patients 60–69 years of age, 42.3% of patients 70–79 years of age, and 71.5% of patients over 80 years of age.[80]

SNHL risk factors:

- **Diseases and other factors:** Common specific causes include infections, vascular lesions, hematologic, neoplastic, autoimmune, trauma, ototoxic drugs, CNS disorders, and idiopathic. The etiology of SNHL may be difficult to ascertain. In relation to congenital causes, half are of genetic etiology and the other half are related to environmental exposures. The genetic causes are either part of a syndrome (Pendred syndrome followed by Usher syndrome, STAR syndrome, Alport syndrome, JS-X syndrome, and X-linked hypophosphatemia). Environmental causes include prenatal infections, prematurity, prenatal ototoxic medications exposure, neonatal jaundice, birth asphyxia and other environmental exposures.
  The acquired causes of SNHL are largely due to infections and predominantly occur in resource-limited settings. However, the overall prevalence has decreased due to vaccination. Infections that result in SNHL may be part of systemic infections, CNS infections, or specific infections that result in SNHL as sequelae. Several viruses can cause SNHL, including HIV, HSV, measles, mumps, VZV, EBV, enteroviruses, Lassa fever and other hemorrhagic fever viruses, influenza, and other viral upper respiratory tract infections. Other infections known to result in SNHL include syphilis, Lyme disease, toxoplasmosis, bacterial meningitis, and cryptococcal meningitis, among others. SNHL is an important sequelae of Lassa fever. The risk factors for SNHL depend on the age of the patient and exposure to a plausible etiology. They include CMV, toxoplasmosis, syphilis, or rubella infection, syndromes associated with progressive hearing loss, neurodegenerative disorders, trauma, culture positive postnatal infections, hyperbilirubinemia, meningitis, low APGAR scores, low birth weight, extracorporeal membrane oxygenation, and chemotherapy. The major risk factor in the adult population is cardiovascular disease, including hypertension, hypotension, stroke, myocardial infection, and ischemic cardiomyopathy.[80]
- **Medicines:** Aminoglycoside antibiotics are proposed to cause hearing loss by several mechanisms, and ototoxic drugs. They generate reactive oxygen species that cause destruction of cochlear hair cells by apoptosis. The drugs disrupt mitochondrial protein synthesis in hair cells, and some mitochondrial polymorphisms have been associated with aminoglycoside-induced hearing loss.[80]
- **Vaccines in general:** Specific time frames for onset of SNHL following immunization should be considered. Cases of SNHL have been reported in the literature after receipt of certain immunizations, such influenza, mumps and/or measles, HB, tetanus, diphtheria, meningococcal polysaccharide, and rabies vaccines; however a causal association has not been established. A report regarding SNHL

after MMR vaccination conducted by the Institute of Medicine indicated that there was no sufficient evidence to accept or reject a causal relationship between vaccine and hearing loss.[80]

- Vaccines against COVID-19 SARS-CoV-2: COVID-19 vaccines have been introduced globally, and millions of people are being vaccinated with various types of vaccines, many of which use new vaccine platforms.[22] SNHL is an event of special interest that is being monitored in mass vaccination against COVID-19.

SINGLE ORGAN CUTANEOUS VASCULITIS

BCCD and SPEAC. Relevant to COVID-19. The CD format of the BC was followed to develop a consensus CD and defined levels of diagnostic certainty.[6]

Category: Dermatologic

Listed: BC/SPEAC, WHO, EMA/ACCESS

Rationale for inclusion: Theoretical concern based on immunopathogenesis and related to viral replication during wild-type disease.[6]

About the AESI: Vasculitides are a group of heterogeneous conditions characterized by inflammation of the blood vessel wall, which can occur in any organ system. Cutaneous involvement occurs almost exclusively with vasculitis of small and medium-sized vessels. Cutaneous vasculitis (CV) may be a single organ disease limited to the skin, primary CV with secondary systemic involvement, or a cutaneous manifestation of systemic vasculitis. A proposed CD of single organ cutaneous vasculitis (SOCV) aims to capture the cutaneous manifestations of vasculitis with lesions typical for any of the phenotypes (leukocytoclastic vasculitis, cutaneous small-vessel vasculitis, urticarial vasculitis, acute hemorrhagic edema of infancy), possibly accompanied by mild symptoms.[81]

Case definition: The definition levels are entirely about diagnostic certainty, not clinical severity of the event, which has been formulated such that the Level 1 definition is highly specific for the condition. As maximum specificity normally implies a loss of sensitivity, two additional diagnostic levels have been included in the definition, offering a stepwise increase of sensitivity from Level 1 (clinical and histological criteria are present and consistent with SOCV), to Level 2 (clinical features are consistent with vasculitis and skin biopsy has been performed, but the results are not fully conclusive), and down to Level 3 (clinical features are consistent with CV but skin biopsy has not been performed), while retaining an acceptable level of specificity at all levels.[81] (Complete_casedefinitionSOCV)

Background: CV occurs in all age groups (mean age in adults, 47 years; mean age in children, 7 years), has a slight female predominance, and is much more common in adults than in children (about 90% of cases in adults and 10% in children). The incidence of CV of all biopsy-proven types is 15–60 patients per million per year.[81] In 2017, the IRs ranged among data sources from 7.42/100,000 person-years (95% CI [6.52, 8.45]) in a data source that did not include outpatient diagnoses, to 32.88/100,000 person-years per year (95% CI [31.37, 34.46]).[14]

SOCV risk factors:

- **Diseases and other factors:** Disease-inducing or promoting factors are not known for more than half of cases of cutaneous small-vessel vasculitis and these are currently classified as “idiopathic.” The remainder is most often either postinfectious or drug induced. Small-vessel vasculitis can also be associated with connective tissue diseases, and it may be a heralding sign of such diseases, particularly SLE. Vasculitis due to underlying connective tissue disease may be associated with more significant involvement of other organ systems. Furthermore, a series of various other conditions can be associated with the CV disease. They includes chronic infections, hematologic diseases, malignancies, physical exercise, or exposure to physical stimuli. In acute hemorrhagic edema of infancy, there is almost

always a preceding trigger, more frequently an upper viral or bacterial respiratory tract infection, and less commonly medications or immunizations.[81]

Possible precipitating agents of cutaneous small vasculitis that are related bacterial infections (group A beta-hemolytic Streptococcus, Staphylococcus aureus, Mycobacterium leprae), viral infections (hepatitis A, B, C, herpes simplex, influenza virus), protozoa (Plasmodium malaria), helminths (Schistosoma mansoni, Schistosoma haematobium, Onchocerca volvulus). It can also occur associated with other diseases: chronic (rheumatoid arthritis, Behçet's disease, SLE, Sjögren's syndrome, intestinal bypass syndrome, cystic fibrosis, primary biliary cirrhosis, ulcerative colitis, cryoglobulinemia, hypercoagulable states, HIV infection), malignant neoplasms (lymphoproliferative diseases, leukemias, and lymphomas; solid tumors such as carcinoma of the lung, breast, prostate, colon; neoplasms of the head and neck, and kidney).[82]

- **Medicines:** Possible precipitating agents of cutaneous small vasculitis that are related to drugs (hormonal contraceptives, derived from serum, vitamins, sulfonamides, phenolphthalein, amino-salicylic acid, streptomycin, hydantoin, insulin, thiazide diuretics, phenothiazine, streptokinase, tamoxifen), chemical products (insecticides and petroleum products), food allergens (milk proteins, gluten).[82]
- **Vaccines in general:** Specific time frames for onset of symptoms following immunization was not included in the CD for the etiological spectrum of SOCV and remains to be elucidated. It is unclear whether SOCV may be induced or promoted by specific single or cumulative exposures. Defining a time to onset of disease is not possible based on the current pathophysiological understanding of the disease. The potential role of immunization in this process also remains to be elucidated. However, CV as an AEFI has been identified in publications with the hypothesis of a potential association between induction of immunization or promotion of CV. The articles refer that to vaccination against influenza, HA, HB, Bacillus Calmette–Guerin, anthrax, vaccine against HPV, MMR and pneumococcal vaccination, H1N1, there is possible or probable association.[81]
- **Vaccines against COVID-19 SARS-CoV-2:** COVID-19 vaccines have been introduced globally, and millions of people are being vaccinated with various types of vaccines, many of which use new vaccine platforms.[22]

ACUTE ASEPTIC ARTHRITIS

BCCD and SPEAC. Relevant to COVID-19.

The CD format of the BC was followed to develop a consensus CD and defined levels of diagnostic certainty.[6]

Category: Immunologic

Listed: BC/SPEAC, WHO, EMA/ACCESS

Rationale for inclusion: It has been recognized to be potentially associated with the recombinant vesicular stomatitis virus platform.[6]

About the AESI: The terms acute aseptic arthritis (AAA) was introduced to capture the entity of acute arthritis without an identifiable organism. This comprises acute inflammation of the joint with identifiable noninfectious immunological etiology, as well as para- and post-infectious inflammatory responses, which may theoretically be induced or promoted by wild-type infections or immunization. Delineation between these different acute clinical entities and differentiation from posttraumatic, septic, and chronic arthritis is paramount both for causality assessment as well as for clinical management of AEFI. A common finding of chronic inflammatory diseases and AAA is the absence of any microbial agents associated with the occurrence of arthritis.[83]

Considering this definition of AAA by BC, types of diseases that fit this definition are gout and gout flare, inflammatory arthritis other that septic (bacterial), psoriatic arthritis, viral arthritis.[84]

AAA is one presentation of arthritis commonly defined by acute onset of joint inflammation, increased white blood cell count in the synovial fluid, and the absence of an identifiable causative organism.[7]

These conditions are chronic and are diagnosed after 6 weeks.[14]

Case definition: AAA is commonly defined as a clinical syndrome characterized by acute onset of signs and symptoms of joint inflammation, increased white blood count (WBC) in synovial fluid, and the absence of an identifiable causative organism. It is a clinical manifestation of various inflammatory conditions directly affecting the synovium of a joint space. The differential diagnosis of joint inflammation is broad, and a clear delineation of peri-, post-infectious and noninfectious joint inflammation is challenging, considering that arthritis can be difficult to differentiate from a periarticular process based on clinical signs and symptoms, and additional investigations (e.g., imaging studies or synovial aspirates) may be required to identify the synovial space as the site of inflammation.

The diagnostic use of PCR has become more common in addition to standard and specialized culture techniques to exclude infectious agents in synovial fluid. To corroborate or exclude an existing or previous joint infection, they include synovial membrane biopsy, synovial immunofluorescence microscopy, or synovial fluid leukocyte investigations.[83] (Complete_casedefinitionAAA)

Background: In the study of the ACCESS group, no narrow codes for AAA were identified in any of the vocabularies. They concluded that only a broad definition that includes many other arthritic diseases could be used to generate IRs. Among six data sources, rates ranged from 8.17/100,000 PY in the year 2018 to 1,110.53/100,000 PY in 2014.[14]

AAA risk factors:

- **Diseases and other factors:** AAA is commonly defined as a clinical syndrome characterized by acute onset of signs and symptoms of joint inflammation, increased WBC in synovial fluid, and the absence of an identifiable causative organism. It is a clinical manifestation of various inflammatory conditions directly affecting the synovium of a joint space, and must be distinguished from reactive arthritis (usually defined by aseptic peripheral arthritis that occurs within four weeks of a primary gastrointestinal or genitourinary infection, mainly associated with Yersinia, Campylobacter, Salmonella, Shigella and Chlamydia trachomatis), and septic arthritis (the concept based on the presence and replication of bacteria in the synovial fluid with subsequent inflammation and destruction of the joints, which can lead to sepsis and death if left untreated). Systemic signs of illness (e.g., fever, malaise, vomiting) commonly accompany septic arthritis and risk factors include, older persons and children, preexisting joint diseases, patients with compromised immune status, patients on hemodialysis or who use intravenous drugs, diabetes, skin infections, orthopedic procedures such as arthroscopy or intra-articular injections.[83] Lay terms and synonyms for the AAA event: arthralgia, viral arthropathy, arthropathy, arthritis, gout, acute gout, joint inflammation, joint pain, articular pain, inflammatory arthritis.[84]
- **Medicines:** No drug identified for AAA.
- **Vaccines in general:** A systematic review of the literature focused on arthritis as an AEFI, with an incidence of arthritis and arthralgia with influenza vaccines (often evaluated), MMR for the rubella component, HB, vaccines containing tetanus and HPV.[85]
- **Vaccines against COVID-19 SARS-CoV-2:** COVID-19 vaccines have been introduced globally, and millions of people are being vaccinated with various types of vaccines, many of which use new vaccine platforms.[22, 86]

NARCOLEPSY

BCCD

Category: Autoimmune

Listed: WHO, EMA/ACCESS, FDA/CDC

Rationale for inclusion: "The history of a possible relationship between narcolepsy and the H1N1 vaccine and can be used to monitor the risk-benefit profile of upcoming COVID-19 vaccines."[87]

About the AESI: Narcolepsy is a sleep disorder primarily characterized by excessive daytime sleepiness and cataplexy – episodes of muscle weakness brought on by emotions.[87]

Case definition: The levels of diagnostic certainty are intended to reflect the likelihood that a patient with sporadic narcolepsy will be hypocretin-1 deficient: the pathophysiological hallmark of the disease. The highest level of diagnostic certainty requires a CSF hypocretin-1 measurement. In the absence of hypocretin-1 measurement, the second level of the definition strongly relies on the presence of unambiguous cataplexy, evaluated on the basis of unequivocal clinical features, to minimize the likelihood of misclassification. The presence of unambiguous cataplexy strongly suggests narcolepsy with cataplexy even when hypocretin-1 measurement is lacking (Level 2), while the presence of doubtful cataplexy would reflect a lower level of diagnostic certainty (Level 3). Level 3 then includes cases of narcolepsy without cataplexy, at least until unambiguous cataplexy may appear. When the hypocretin-1 level is unknown, and there is no history of unambiguous cataplexy, the third level of diagnostic classification relies on the mean sleep latency (MSLT). The physiopathology of narcolepsy without cataplexy is probably different from that of narcolepsy with cataplexy. In rare cases, a suspected narcolepsy case may not be classifiable according to the levels above (e.g., when there is cataplexy, no objective sleepiness, and CSF hypocretin-1 level is unavailable). In these instances, the case will be classified at the fourth level.[87] (Complete_casedefinitionNarcolepsy)

Background: Narcolepsy with cataplexy has an estimated prevalence of 2–5/10,000 and an average incidence of 7.4 per million person-years. More than 50% of cases appear to have disease onset before 18 years of age. Onset as late as 70 years of age is rare but has been described. Bimodal peaks have been reported, with one around 15 years of age (range 10–19 years) and the other around 35 years.[87]

In a study in Germany of children and adolescents, the age-adjusted adjusted incidence rate increased significantly from 0.14/100,000 person-years in the pre-pandemic period to 0.50/100,000 person-years in the postpandemic period (incidence density ratio 3.57 (95% CI [1.94, 7.00]).[14]

Narcolepsy risk factors:

- **Diseases and other factors:** In a review, narcolepsy is described as the most common neurological cause of chronic drowsiness, caused by the selective loss of orexin-producing neurons (also known as hypocretins). There is also developing evidence that narcolepsy is an autoimmune disorder that can be caused by a T-cell-mediated attack on orexin neurons.[88] It is important to note that the greatest environmental risk is seen with influenza A (H1N1) infection and immunization,[89] and it is also likely that genetics play a role in the development of narcolepsy. However, the risk of a parent passing this disorder to a child is exceptionally low — only about 1%.[90] A number of factors may increase a person´s risk of narcolepsy or cause an autoimmune problem, and they include: an inherited genetic fault, hormonal changes (including those that take place during puberty or the menopause), major psychological stress, a sudden change in sleep patterns, an infection, such as swine flu or a streptococcal infection.[91] Important differential diagnoses such as schizophrenia, epilepsy, Kleine-Levin syndrome, idiopathic hypersomnia, and increased airway resistance should be remembered.[92]
- **Medicines:** No drugs identified that are related to the cause of narcolepsy.

- **Vaccines in general:** There are reports of narcolepsy after vaccination against H1N1, having as an adjuvant squalene and alpha-tocopherol, and this was observed only in certain populations.[21]
- **Vaccines against COVID-19 SARS-CoV-2:** COVID-19 vaccines have been introduced globally, and millions of people are being vaccinated with various types of vaccines, many of which use new vaccine platforms. Narcolepsy has been monitored among the events considered serious.([22], [23], [24])

COAGULATION DISORDER

SPEAC listed the event as prioritized on 25 May 2020. Relevant for COVID-19.

To harmonize the vaccine safety assessment, BC AESI CD guides are being prepared for each AESI separately. These guides are being used to supplement the information in the AESI document. In the case of coagulation disorders, the document is on the list for Tier2, which will provide interested parties with conditions to assess the occurrence as an AEFI.[11]

Category: Hematologic

Listed: BC/SPEAC, WHO, EMA/ACCESS, FDA/CDC

Rationale for inclusion: Theoretical concern based on immunopathogenesis and related to viral replication during wild-type disease. Should be of higher priority in settings where there are other infections that could present with bleeding, such as dengue. It will be important to have testing in place to establish whether any observed coagulation disorders are coincidental to immunization or are caused by immunization. For SPEAC, AESI were prioritized at four tiers. Tier 1 prioritizes the generalized seizure.[11]

About the AESIs: For the contributing authors of ACCESS, this event definition is about several groups of diseases under the broad name of coagulation disorder (deep vein thrombosis, pulmonary embolism, stroke, limb ischemia, hemorrhagic disease). A clotting disorder is a blood clotting problem. This can be too much clotting leading to thrombosis, emboli, or stroke, or too little clotting leading to bleeding and, again, stroke.[93]

Case definition: The event definition form lists as events deep vein thrombosis (DVT), pulmonary embolism along with DVT called venous thromboembolism, cerebrovascular stroke, limb ischemia (occlusion of an artery that supplies blood to limbs), and hemorrhagic disease (bleeding disorders). In the event definition form, the congenital causes of a coagulation disorder in the perioperative period were excluded.[93]

- **Venous or arterial thrombosis/thromboembolism:** The BC group developed a proposed CD for thrombosis/thromboembolism, which should be applied when there is no clear alternative diagnosis for the reported disease event to explain the combination of symptoms.[94] (Complete_casedefinition_thrombosis_thromboembolism)
- **Pulmonary thromboembolism (PE):** When a thrombus, origination most often in the lower limb, breaks loose from the vessel wall, it travels freely through the blood vessel on its way to the heart and lungs until it hits a point where it can no longer pass. In PE, the thrombus becomes trapped in the lung artery and closes off the blood supply to the part of the lung after the occlusion. This causes a drop in lung perfusion, a declining blood oxygen saturation, and sharp chest pain.[93] (Complete_casedefinition_PE)
- **Stroke:** Acute stroke is defined as the acute onset of focal neurological findings in a vascular territory because of underlying cerebrovascular disease.[93] (Complete_casedefinition_stroke)
- **Limb ischemia:** Acute limb ischemia is defined as a quickly developing or sudden decrease in limb perfusion.[93] (Complete_casedefinition_ischemia)
- **Hemorrhagic disease:** This part of coagulation disorders focuses on a lack of blood clotting. The blood is hypocoagulable resulting in bleeding.[93] (Complete_casedefinition_hemorrhagic)

Background: The observed cases of venous or arterial thrombosis/thromboembolism were presented at a lower frequency than that which occurs in the population that has not been vaccinated; as a rare, new, adverse event (fewer than 1 in 10,000 people).[29]

The incidence of acute peripheral arterial occlusion causing acute lower extremity ischemia is approximately 1.5 cases per 10,000 persons per year.[93]

Published IRs show a strong age-dependent pattern, with incidence increasing with age. DVT rates ranged from 117/100,000 person-years for all types of venous thromboembolism (VTE). Small differences are reported according to DVT only (48/100,000 person-years) or pulmonary embolism (PE) with and without DVT (69/100,000 person-years). Recent data suggest an increase in incidence over time, with estimates increasing from 95 to 133/100,000 people/year from 1999 to 2009. In the general population of the United States, VTE rates range from 108 to 167/100,000 person-years.[14]

The incidence of ischemic stroke was estimated to be 134/100,000 person-years in the general population from a study carried out in the Danish registries between 1997 and 2017. A clear pattern of increasing age was observed. Another study reported rates of 103 and 75 per 100,000 in Denmark and Norway, consistent with data from the previous study.[14]

Hemorrhagic stroke accounts for about 20% of all strokes In calculating this incidence, subarachnoid hemorrhagic was not included due to different etiology. Intracerebral hemorrhage has an overall incidence of 24.6/100,000 person-years. A study conducted in the Netherlands showed stable IRs over time with a strong age pattern. In the year 2020, the rates were 5.9/100,000 person-years, 37.2/100,000 person-years and 176.3/100,000 person-years between the age groups of 35–54, 55–74 and 75–94, respectively. Rates for intracerebral hemorrhage are 20 and 14 per 100,000 PY in Denmark and Norway. Another study reports combined rates of hemorrhagic stroke ranging from 7 to 500/100,000 with increasing age, higher than previously observed. [14]

Other data show pooled historical rates of AESI from electronic health records databases from eight countries (Australia, France, Germany, Japan, the Netherlands, Spain, United Kingdom, and United States) (Table 5).[15]

Table 5: Incidence Rate per 100,000 Person-years (95% Prediction Interval), Data from Australia, France, Germany, Japan, the Netherlands, Spain, United Kingdom, and United States [15]

Event	Gender	1 - 5 years	6 - 17 years	18 - 34 years	35 - 54 years	55 - 64 years	65 - 74 years	75 - 84 years	≥ 85 years
Deep vein thrombosis	Female	3 - 50	8 - 40	66 - 298	117 - 797	150 - 1,224	257 - 1,820	360 - 2,642	407 - 3,572
	Male	4 - 55	6 - 32	28 - 228	88 - 836	184 - 1,289	250 - 1,931	254 - 2,720	278 - 3,616
Pulmonary embolism	Female	<1 - 36	1 - 13	11 - 124	21 - 309	33 - 470	77 - 611	135 - 951	154 - 1,184
	Male	<1 - 24	<1 - 12	5 - 80	20 - 318	59 - 497	96 - 683	119 - 1030	124 - 1,277
Non-hemorrhagic stroke	Female	2 - 9	1 - 12	4 - 86	11 - 617	25 - 1,882	77 - 2,198	197 - 3,884	320 - 7,239
	Male	2 - 20	2 - 10	4 - 75	21 - 664	67 - 2,046	145 - 2,578	242 - 4,662	260 - 8,607

Coagulation disorder risk factors:

» **Diseases and other factors:** Abnormal bleeding can result from disorders of the clotting system, platelets, or blood vessels, such as bleeding (little clotting which causes an increased risk of bleeding) or thrombosis (too much clotting that causes blood clots to obstruct blood flow). Coagulation disorders can be acquired or hereditary. The most common hereditary disorder of hemostasis is von Willebrand disease, and the most common inherited clotting disorder is hemophilia. The main causes of acquired coagulation disorders are vitamin K deficiency, liver disease, disseminated intravascular coagulation, development of circulating anticoagulants and severe liver disease (e.g., cirrhosis, fulminant hepatitis, and acute liver steatosis of pregnancy, which can disturb pregnancy hemostasis by impairing the synthesis of the clotting factor). As all coagulation factors are produced in the liver (by hepatocytes and endothelial cells), both prothrombin time (PT) and partial thromboplastin time (PTT) are prolonged in severe liver disorders (PT results are usually reported as international normalized ratio (INR). Occasionally, decompensated liver disease also causes excessive fibrinolysis and bleeding due to decreased hepatic synthesis of alpha 2-antiplasmin.[95]

The causes that result in too much clotting: factor V Leiden (genetic disorder), deficiency of antithrombin III, deficiency of protein C or protein S, mutation of the prothrombin gene (PT), antiphospholipid antibody syndrome.

Symptoms of clotting disorders with difficulty in clotting: blood in the urine or feces, bruising easily and excessively, extreme fatigue, a bleeding injury, joint pain caused by internal bleeding, nosebleeds that seem to have no cause, a painful headache that does not go away, prolonged bleeding from common cuts or from surgery or dental work, sudden pain, swelling and heat in the joints or muscles, vision problems such as double vision, repeated vomiting.

Symptoms of clotting disorders with too much clotting: a blood clot in one of the deep veins of the body (also called DVT) that shows symptoms of pain in a specific area of the body, swelling of an arm or leg, redness or color change, skin heat, a blood clot that has traveled to the lung (called pulmonary embolism [PE]) with symptoms of chest pain, shortness of breath, rapid heartbeat, heart attack or stroke at a young age.[96]

Major risk factors for VTE: Clinical factors (advanced age, hospitalization for acute medical illness, long-haul flights (duration > 4 h), obesity, pregnancy, including the postpartum period); surgical factors (central venous access, major surgery, orthopedic surgery, trauma, or fracture); inherited factors (antithrombin deficiency, dysfibrinogenemia, factor V Leiden mutation, protein C deficiency, protein S deficiency, prothrombin 20210A mutation); medical diseases (antiphospholipid syndrome, congestive heart failure (HF), inflammatory bowel disease, malignancy, myeloproliferative disorders, myocardial infarction, polycythemia vera, previous VTE, sepsis, stroke, and varicose veins).[97]

Pulmonary thromboembolism occasionally presents blockages in blood vessels caused by substances other than blood clots, such as fat from the marrow of a broken long bone, part of a tumor, and air bubbles. The risk factors that can increase the risk of developing blood clots and subsequent PE are medical conditions and related treatments (if a person or any of their family members has had venous blood clots or PE in the past). Cardiovascular diseases, certain types of cancer, surgery, kidney disease, prolonged immobility, smoking, excess weight are risk factors. People with severe symptoms of COVID-19 are at increased risk of PE.

Risk factors for a stroke: older age, a family history of stroke or certain heart conditions, diabetes, kidney disease, or high cholesterol migraine headaches, atrial fibrillation, high blood pressure, or atherosclerosis, smoking cigarettes, drinking too much alcohol, or using drugs such as cocaine, not enough physical activity, or obesity, sleep apnea or other sleep problems that affect breathing.[98]

COVID-19 is caused by the new coronavirus SARS-CoV-2 and is characterized by an exaggerated inflammatory response that can lead to severe manifestations such as adult respiratory syndrome,

sepsis, coagulopathy, and death in a proportion of patients. Among other factors and direct viral effects, the increase in the vasoconstrictor angiotensin II, the decrease in the vasodilator angiotensin, and the sepsis-induced release of cytokines can trigger a coagulopathy in COVID-19. A coagulopathy has been reported in up to 50% of patients with severe COVID-19 manifestations. An increase in D-dimer is the most significant change in coagulation parameters in severe COVID-19 patients, and progressively increasing values can be used as a prognostic parameter indicating a worse outcome.[99]

- **Medicines:** Drugs may play an important role in the development of thrombosis, and in recent years, there has been increased attention to the importance of this issue. Although drug-induced thrombosis usually causes venous thrombotic events, arterial events are also noted due to drug administration. Some drugs, such as oral contraceptive pills, may promote thrombosis by altering the balance between the different coagulation factors, and many drugs can lead to decreased blood flow by increasing blood viscosity, as seen for example after intravenous immunoglobulin administration.[100]

  People with bleeding disorders should avoid the following because they can cause bleeding: products that contain aspirin, multi-ingredient medicines that contain aspirin, herbal medicines (phytomedicines: ginkgo biloba, garlic in large quantities, ginger that is not dry, ginseng, tansy, and Serenoa repens). In addition, other drugs can cause bleeding (aceclofenac, acenocumarol, citalopram, clopidogrel, dexibuprofen, diclofenac, dicumarol, escitalopram, phenprocumon, fluoxetine, fluvoxamine, ibuprofen, indomethacin, ketoprofen, ketorolac, lornoxicam, pyroxamine, sulindac, tenoxicam, ticlopidine, and warfarin).[101]

  There is an association between use of antipsychotic drugs and risk of venous thromboembolism in a large primary care population. The increased risk was more marked among new users and those prescribed atypical antipsychotic drugs.[102]

- Drug-related factors in VTE: Antiestrogens, chemotherapy, and heparin-induced TP, high-dose therapy with progestogens, hormone replacement therapy, oral contraceptives, and vaginal ring for contraception, strontium ranelate, thalidomide and lenalidomide).[97]
- Pulmonary thromboembolism – Drug-related risk factor is supplemental estrogen. Estrogen in birth control pills and hormone replacement therapy can increase blood clotting factors, especially if the person smokes or is overweight. Pregnancy: the weight of the baby pressing on the veins in the pelvis can slow the return of blood through the legs. Clots are more likely to form when blood thinning or pooling. Risk factors for a stroke: in women, hormone replacement therapy or oral birth control pills.[98]
- **Vaccines in general:** No vaccines identified.
- **Vaccines against COVID-19 SARS-CoV-2:** COVID-19 vaccines have been introduced globally, and millions of people are being vaccinated with various types of vaccines, many of which use new vaccine platforms. ([22], [6]) Coagulation disorders has been reported among the events considered serious and suspected cases of coagulation disorders have been monitored among events considered serious after vaccination against COVID-19.[23]

ACUTE CARDIAC INJURY

BCCD and SPEAC. Relevant to COVID-19. The CD format of the BC was followed to develop a consensus CD and defined levels of diagnostic certainty. Acute cardiac injury includes: microangiopathy, HF and cardiogenic shock, stress cardiomyopathy, coronary artery disease, arrhythmia, myocarditis, pericarditis.[6]

Category: Cardiac

Listed: BC/SPEAC, WHO, EMA/ACCESS

Rationale for inclusion: Theoretical concern based on immunopathogenesis and related to viral replication during wild-type disease. It is known that there is an association with Modified Vaccinia Virus Ankara platform).[6] Would be of higher priority in settings and populations where there is a known high frequency of comorbid conditions (hypertension, chronic hepatitis, and chronic renal failure).[5]

Myocarditis and Pericarditis

BC myocarditis and pericarditis CD (Pandemic Emergency Response Process Draft Release). Version Myocarditis_ Version_1.5.0_16. July.2021, and Version Pericarditis_1.0.0_15. July.2021.[103]

About the AESI: Myocarditis and pericarditis is a relevant event on the Priority List of Adverse Events of Special Interest COVID-19, and often results from common viral infections and postviral immune-mediated responses. Early draft release under BC's Pandemic Emergency Response Process.[103]

Myocarditis is inflammation of the myocardium with necrosis of cardiac myocytes. Symptoms may vary and may include fatigue, dyspnea, edema, palpitations, and sudden death.[104]

Pericarditis usually leads to pericardial effusion, or constrictive pericarditis,[105] and is the inflammation of the pericardium from various origins, such as infection, neoplasm, autoimmune process, injuries, or drug induced. Pericarditis usually leads to pericardial effusion or constrictive pericarditis.[14]

Case definition: Myocarditis is an inflammatory disease of the myocardium caused by different infectious (viral and nonviral) and noninfectious triggers (autoimmune diseases, hypersensitivity reactions to drugs, toxic reactions to drugs, toxics, etc.).[14] Diagnosis is based on clinical symptoms and findings of abnormal electrocardiogram (ECG), cardiac biomarkers, and cardiac imaging in the absence of cardiovascular risk factors. Endomyocardial biopsy confirms the clinical diagnosis of myocarditis.[103] (Complete_casedefinitionMyocarditis)

Pericarditis is the inflammation of the pericardium from various origins, such as infection, neoplasm, autoimmune process, injuries, or drug induced. The diagnosis of acute pericarditis is a clinical diagnosis based on proper history and the presence of typical symptoms of chest pain, pericardial rub (it is pathognomonic for pericarditis, but is frequently not present) and characteristic electrocardiographic changes. Pericarditis usually leads to pericardial effusion, or constrictive pericarditis. Terms or synonyms are inflammation of pericardium, pericardial inflammation, inflammation of heart sac (ICD-9), and inflamed covering of heart (ICD-9).[103],[105] (Complete_casedefintion_pericarditis)

Background: According to database studies from five countries (Denmark, Germany, Italy, Spain, and United Kingdom), the IRs of AESI were quite stable over time in each of the data sources. Rates in reported by Agenzia Regionale di Sanita Toscana (ARS) were high, the highest being 63.64/100,000 person-years, with rates increasing with age.[14]

Other data show pooled historical rates of AESI from electronic health records databases from eight countries (Australia, France, Germany, Japan, Netherlands, Spain, United Kingdom, and United States) (Table 6).[15]

Table 6: Incidence Rate per 100,000 Person-years (95% Prediction Interval), Data from Australia, France, Germany, Japan, the Netherlands, Spain, United Kingdom, and United States[15]

Myocarditis or pericarditis																	
Country	Incidence rate per 100 000 person years (95% prediction interval)																
	Gender	1 - 5 years		6 - 17 years		18 - 34 years		35 - 54 years		55 - 64 years		65 - 74 years		75 - 84 years		≥ 85 years	
		n	IR	n	IR	n	IR	n	IR	n	IR	n	IR	n	IR	n	IR
Australia, France, Germany, Japan, the Netherlands, Spain, United Kingdom and United States	Female	6	1 - 25	7	2 - 21	16	8 - 32	22	9 - 53	31	13 - 72	35	12 - 97	39	11 - 138	34	8 - 143
	Male	7	1 - 32	11	5 - 24	37	16 - 88	37	16 - 87	45	20 - 102	49	17 - 139	54	15 - 193	41	9 - 193

Myocarditis and pericarditis risk factors:

- **Diseases and other factors:**

  Myocarditis is an inflammatory disease of the myocardium caused by different infectious (viral and nonviral) and noninfectious triggers (autoimmune diseases, hypersensitivity reactions to drugs, toxic reactions to drugs, toxics, etc.). It may be caused by many disorders, and systemic disorders such as sarcoidosis, but often the cause is unknown. Myocarditis may result from infectious or noninfectious causes. Many cases are unable to be identified (idiopathic). Viral causes are parvovirus B19 and human herpesvirus 6, influenza virus, coxsackie B virus. The SARS-CoV-2 virus sometimes causes myocarditis. In developing nations, infectious myocarditis is most often caused by rheumatic fever, Chagas disease, or acquired immunodeficiency syndrome (AIDS). Noninfectious causes include substances that are toxic to the heart (such as alcohol and cocaine), certain drugs, and some autoimmune and inflammatory disorders.[104]

  Pericarditis: Causes of acute pericarditis include: infection (viral, bacterial, parasitic, or fungal and, in people with AIDS, tuberculosis, or aspergillosis), heart attack, heart surgery (postpericardiotomy syndrome), SLE (lupus), rheumatoid arthritis, kidney failure, chest injury, cancer (such as leukemia, breast cancer, or lung cancer, or, in people with AIDS or Kaposi's sarcoma), rheumatic fever, radiation therapy, unknown (idiopathic or nonspecific pericarditis). In people who have AIDS, a number of infections, including tuberculosis and aspergillosis, may result in pericarditis. Pericarditis due to tuberculosis (tuberculous pericarditis) accounts for less than 5% of cases of acute pericarditis in the United States but accounts for most cases in some areas of India and Africa. After a heart attack, acute pericarditis develops during the first day or two in 10–15% of people and after about from 10 days to 2 months in 1–3% (subacute pericarditis). Subacute pericarditis is caused by the same disorders that cause acute pericarditis.[104]

- **Medicines:** Myocarditis caused by drugs is called hypersensitivity myocarditis and cites some drugs as clozapine, penicillin, some diuretics. Pericarditis: drugs, including warfarin and heparin (anticoagulants), penicillin, procainamide (a drug used to treat abnormal heart rhythms), and phenytoin (an antiseizure drug).[104]
- **Vaccines in general:** No reference of association of the event to the vaccine was found. Possible risk for COVID-19 vaccine.

- **Vaccines against COVID-19 SARS-CoV-2:** Reports of myocarditis and pericarditis as an adverse event occurring after COVID-19 vaccinations with mRNA vaccines intensified the need to further understand a possible association of observed cases with myocarditis and/or pericarditis after administration of COVID-19 vaccines.[103] A study in Israel to evaluate the safety profile of the BNT162b2 vaccine compared the incidence of a broad set of potential short- and medium-term adverse events among vaccinated persons with the incidence among matched unvaccinated persons. It found an elevated risk of myocarditis (hazard ratio, 3.24, 95% CI [1.55, 12.44], risk difference, 2.7 events per 100,000 people, 95% CI [1.0, 4.6]); an excessive risk of myocarditis (1–5 events per 100,000 people).[105]

MICROANGIOPATHY

About the AESI: According to the landscape analysis of SPEAC COVID-19, May 2020, microangiopathy is an AESI relevant to COVID-19.

Case definition: Cerebral microangiopathy, also cerebral small vessel disease, is diagnosed with increasing frequency. Improved neuroimaging techniques, aging, as well as dietary and life-style changes leading to a higher incidence of vascular risk factors may play an important role. The exact reasons however remain unclear. Cerebral microangiopathy refers to pathological changes in small brain vessels, including small arteries, arterioles, capillaries and small veins. It is associated with white matter lesions, lacunar infarcts, and, more recently, microbleeds. Manifestation occurs in various clinical symptoms, including gait disturbances, urinary disturbances, depression and cognitive decline.[106] (Complete_casedefinition_microangiopathy)

Background: The rapid worldwide spread of COVID-19 has made it necessary to generate IRs of antecedents of AESI that can be used to monitor the benefit-risk profile of COVID-19 vaccines. The comparison of IRs by database (2017–2020) carried out by the ACCESS group points to a variation of ranges between 11 data sources for microangiopathy.[15]

Microangiopathy risk factors:

- **Diseases and other factors:** Experts suspect that the causes of small-vessel disease are the same as the causes for disease of the larger vessels of the heart, such as high blood pressure, high cholesterol, obesity, and diabetes. Small-vessel disease is more common in women. Risk factors include tobacco use, unhealthy cholesterol levels, high blood pressure, obesity (body mass index of 30 or higher), unhealthy diet, inactive lifestyle, insulin resistance, estrogen deficiency, in women, polycystic ovarian syndrome, increasing age, older than 45 in men and older than 55 in women, chronic inflammation. It is not clear why the same risk factors, such as obesity or an inactive lifestyle, cause some people to develop small-vessel disease instead of large-vessel coronary artery disease.[107]

  Microvascular angiopathy is a pathological sequela of a multitude of conditions that results from overactivation of host immune defense mechanisms. Patients impacted by sepsis or septic shock from a bacterial or viral infection, or autoimmune process, may fall victim to hyperimmune responses that can lead to significant host consequences, for example, dengue viral infections. The body of evidence demonstrating the role of microvascular angiopathy in COVID-19 is evolving rapidly. It is evident from the current body of knowledge that COVID-19-induced microvascular angiopathy can lead to a wide range of tissue pathology and clinical complications. Additional research is necessary to help further understanding of microvascular angiopathic complications related to COVID-19.[108]
- **Medicines:** No drugs identified that are related to the cause of microangiopathy.

- **Vaccines in general:** No reference of association of the event to the vaccine was found. Possible risk for COVID-19 vaccine.
- **Vaccines against COVID-19 SARS-CoV-2:** COVID-19 vaccines have been introduced globally, and millions of people are being vaccinated with various types of vaccines, many of which use new vaccine platforms. [22]

HEART FAILURE

According to the landscape analysis of SPEAC COVID-19, May 2020, HF is the AESI relevant to COVID-19.

About the AESI: Heart failure is a major public health problem worldwide. New data actually suggest that the incidence of heart failure among young adults has increased in recent year.[109]

Case definition: The common symptoms of heart failure include shortness of breath during daily activities, having trouble breathing when lying down, weight gain with swelling in the feet, legs, ankles, or stomach, generally feeling tired or weak. [110] (Complete_casedefinition_heartfaillure)

Background: HF showed an increasing pattern in the databases of all databases participating in the study, with a clear increase in rates with age. IRs in European countries and in the United States ranges widely from 1 to 9 cases per 1,000 person-years and depend heavily on the population studied and the diagnostic criteria used. In developed countries, IRs stabilized between 1970 and 1990 and are now declining. In Canada, the rate presented was 306/100,000 person-years. A recent study conducted in the claims database in Germany found an HF IR of 655/100,000 person-years. A study carried out in the United States showed an increased incidence in older persons.[14]

HF risk factors:

- **Diseases and other factors:** Cardiac and systemic factors can compromise cardiac performance and cause or worsen HF. The mechanisms of heart failure are myocardial disease (pathological change in the myocardium; structural heart disease (valvular disease, congenital heart disease); arrhythmias; conduction disturbances and hemodynamic conditions. The underlying cause determines whether heart failure is transient or chronic. For example, heart failure due to myocardial infarction is chronic, whereas heart failure due to tachycardia (e.g., atrial fibrillation) can be cured with restoration of sinus rhythm.[109] Other causes include diseases that affect the heart valves (degenerative or inflammatory, such as rheumatic disease), congenital diseases, alcoholism, genetic diseases, autoimmune, inflammatory (peripartum), by toxicity (cancer treatment, anorectic and sympathomimetic), and infectious (most commonly viral or mediated by parasites, such as Trypanosoma cruzi, responsible for the development of Chagas disease).([111], [112])
- **Medicines:** No drugs identified that are related to the cause of HF.
- **Vaccines in general:** No reference of association of the event to the vaccine was found. Possible risk for COVID-19 vaccine.
- **Vaccines against COVID-19 SARS-CoV-2:** COVID-19 vaccines have been introduced globally, and millions of people are being vaccinated with various types of vaccines, many of which use new vaccine platforms. [22]

STRESS CARDIOMYOPATHY

According to the landscape analysis of SPEAC COVID-19, May 2020, stress cardiomyopathy is an AESI relevant to COVID-19.

About the AESI: Stress cardiomyopathy is a condition caused by intense emotional or physical stress that leads to rapid and severe reversible cardiac dysfunction. It mimics myocardial infarction with changes in the electrocardiogram and echocardiogram, but without any obstructive coronary artery disease.[113]

Case definition: The diagnosis of stress cardiomyopathy is difficult because of its clinical phenotype may closely resemble acute myocardial infarction regarding ECG and abnormalities and biomarkers.[114] (Complete_casedefinition_stress_cardiomyopathy)

Background: Few published incidence data (recently recognized disease). There are reports of a significant increase in the incidence of Takotsubo syndrome or Takotsubo cardiomyopathy from 2006 to 2012, which in the study, points to an increased incidence of almost 20 times over the period. Another study shows that hospitalization rates for stress cardiomyopathy are increasing, with an incidence of primary Takotsubo syndrome increasing from 2.3 hospitalizations per 100,000 person-years in 2007 to 7.1 in 2012. There are also reports of an increase in cardiomyopathy of stress during the COVID-19 pandemic.[14]

Stress cardiomyopathy risk factors:

- **Diseases and other factors:** Stress cardiomyopathy is a condition in which intense physical or emotional stress can cause rapid and severe weakness of the heart muscle. The pattern of left ventricular (LV) dysfunction was first described in Japan and referred to as "Takotsubo cardiomyopathy," in honor of the narrow-necked, wide-base fishing pot used to catch octopuses. Takotsubo cardiomyopathy, also known as apical ballooning syndrome, ampoule cardiomyopathy, stress cardiomyopathy, or broken heart syndrome, is now increasingly recognized in other countries. "Transitional left ventricular apical ballooning" has also been used to describe similar cardiac contractile function in patients after physical or emotional stress. Stress cardiomyopathy can occur after a variety of emotional stressors, such as sadness, fear, extreme anger, and surprise. On the other hand, several physical stressors, such as stroke, seizure, or acute asthma, can also trigger the disease. Common signs of this syndrome are chest pain, the elevation of the ST segment in the precordial leads, mild elevation of cardiac enzyme levels and biomarkers, and transient apical systolic LV dysfunction in the absence of obstructive epicardial coronary disease. According to the medical literature available to date, women – especially middle-aged or older women – are the most affected. Although it can also occur in women and young men, most patients are postmenopausal women.[113]
- **Medicines:** No drugs identified that are related to the cause of stress cardiopathy.
- **Vaccines in general:** In relation to vaccination, a related anxiety reaction or response triggered by stress due to vaccination may occur. This may include vasovagal syncope, hyperventilation reactions, or reactions resulting from psychiatric disorders, and the stress responses triggered by vaccination can occur pre-vaccination, in anticipation of the procedure and are usually immediate with transient and spontaneous resolution. After immunization, preceded or not by stress peri vaccination, with signs and symptoms that can take from a few hours to days to develop.[21]
- **Vaccines against COVID-19 SARS-CoV-2:** COVID-19 vaccines have been introduced globally, and millions of people are being vaccinated with various types of vaccines, many of which use new vaccine platforms.[22]

CORONARY ARTERY DISEASE

According to the landscape analysis of SPEAC COVID-19, May 2020, coronary artery disease is an AESI relevant to COVID-19.

About the AESI: Coronary artery disease is caused by plaque buildup in the walls of the arteries that supply blood to the heart (called coronary arteries) and other parts of the body. Plaque is formed by deposits of cholesterol and other substances in the artery. The build-up of plaque causes the inside of the arteries to narrow over time, which can partially or completely block blood flow, a process called atherosclerosis.[115]

Case definition: Angina, or chest pain and discomfort, is the most common symptom of CAD, which can occur when too much plaque builds up inside the arteries, causing them to narrow. Narrow arteries can cause chest pain because they can block blood flow to the heart muscle and the rest of the body. The first clue to a CAD is a heart attack with symptoms of pain or discomfort in the chest (angina) or arms or shoulders, weakness, dizziness, nausea (feeling sick) or cold sweat, shortness of breath. Over time, CAD can weaken the heart muscle, which can lead to heart failure, a serious condition in which the heart cannot pump blood as it should.[115] (Complete_casedefinition_coronaryarterydisease)

Background: Database studies showed IRs that differed based on the provenance of the diagnosis, from 95.33/100,000 person-years (primary care records) to 322.04/100,000 person-years (discharge diagnoses). A clear pattern of increasing rates with age was observed in all databases. The recently published European Society of Cardiology article found coronary artery disease IRs of 176.3/100,000 person-years (95% CI [150, 238]).[14]

Coronary artery disease risk factors:

- **Diseases and other factors:** Usually, coronary artery disease is due to coronary artery atherosclerosis:
  - Subintimal deposition of atheroma in large and medium-sized coronary arteries, and, less often, coronary artery disease is due to coronary artery spasm.
  - Vascular endothelial dysfunction can promote atherosclerosis and contribute to coronary artery spasm. Of increasing importance, endothelial dysfunction is now also recognized as a cause of angina in the absence of epicardial coronary artery stenosis or spasm.

  Rare causes include coronary artery embolism, dissection, aneurysm (e.g., in KD), and vasculitis (e.g., in SLE, syphilis). Risk factors for coronary artery disease are the same as risk factors for atherosclerosis: high blood levels of low-density lipoprotein cholesterol (see dyslipidemia), high blood levels of lipoprotein(a), low blood levels of high-density lipoprotein cholesterol, diabetes mellitus (particularly type 2), smoking, obesity, physical inactivity, high level of apoprotein B, and high blood levels of C-reactive protein (CRP).[116]
- **Medicines:** No drugs identified that are related to the cause of coronary artery disease.
- **Vaccines in general:** No reference of association of the event to the vaccine was found. Possible risk for COVID-19 vaccine.
- **Vaccines against COVID-19 SARS-CoV-2:** COVID-19 vaccines have been introduced globally, and millions of people are being vaccinated with various types of vaccines, many of which use new vaccine platforms.[22] Coronary artery disease has been monitored among the events considered serious.

ARRHYTHMIA

According to the landscape analysis of SPEAC COVID-19, May 2020, arrhythmia is an AESI relevant to COVID-19.

About the AESI: A cardiac arrhythmia is an abnormality or perturbation in the normal activation or beating of the heart myocardium.[117]

Case definition: When diagnosing cardiac arrhythmia, a physical exam will usually be performed with questions about the patient's medical history and symptoms. Tests can be done to confirm an irregular heartbeat and look for conditions that can cause arrhythmias, such as heart disease or thyroid disease, including electrocardiogram (ECG or EKG); echocardiogram. For very rare symptoms, an event recorder can be implanted under the skin in the chest area to continuously record the electrical activity of the heart and detect irregular heart rhythms. If you do not find an arrhythmia during these tests, you may be trying to trigger the arrhythmia with other tests, which may include stress testing, tilt table test, electrophysiological tests, and mapping. The electrodes can sometimes be used to stimulate the heart to beat at rates that can trigger - or stop - and arrhythmia, helping to determine the location of the arrhythmia, its possible causes, and the best treatment options. This test can also be done to determine whether a person with certain health conditions is at risk for developing cardiac arrhythmias.[117] (Complete_casedefinition_arrhythmia)

Background: From published articles, arrhythmia IRs range from 208/100,000 in Denmark to 780/100,000 person-years in the United Kingdom. Overall rates in men were 242/100,000 in men < 55 years of age, 739/100,000 for 55–64 years of age, and 1370/100,000 for > 65 years of age. The corresponding rates for women in these age categories were 117, 342, and 729, respectively.[14]

Arrhythmia disease risk factors:

- **Diseases and other factors:** The normal heart beats in a regular, coordinated way because electrical impulses generated and spread by myocytes with unique electrical properties trigger a sequence of organized myocardial contractions. Arrhythmias and conduction disorders are caused by abnormalities in the generation or conduction of these electrical impulses or both. Any heart disorder, including congenital abnormalities of structure (e.g., accessory AV connection) or function (e.g., hereditary ion channelopathies), can disturb rhythm. Systemic factors that can cause or contribute to a rhythm disturbance include electrolyte abnormalities (particularly low potassium or magnesium), hypoxia, hormonal imbalances (e.g., hypothyroidism, hyperthyroidism), and drugs and toxins (e.g., alcohol, caffeine).[118]
- Medicines: There are several remedies such as tricyclic antidepressants; anti-inflammatories; contraceptives, antipsychotics, antineoplastics, and levodopa that, although not used to treat heart problems, influence the heart and may, over time, cause changes that lead to the emergence of heart diseases such as arrhythmia.[118]
- Vaccines in general: No reference of association of the event to the vaccine was found. Possible risk for COVID-19 vaccine.
- Vaccines against COVID-19 SARS-CoV-2: COVID-19 vaccines have been introduced globally, and millions of people are being vaccinated with various types of vaccines, many of which use new vaccine platforms.[22]

ACUTE KIDNEY INJURY

SPEAC listed the event as prioritized on 25 May 2020. Relevant for COVID-19.

Category: Renal

Listed: BC/SPEAC, WHO, EMA/ACCESS

Rationale for inclusion: Theoretical concern based on immunopathogenesis and related to viral replication during wild-type disease.[6] Would be of higher priority in settings and populations where there is a known high frequency of comorbid conditions (hypertension, chronic hepatitis, chronic renal failure).[5]

About the AESI: "AKI [acute kidney injury] is not a single disease entity. It is a heterogeneous group of conditions characterized by sudden decrease in glomerular filtration rate (GFR) followed by an increase in serum creatinine concentration or oliguria. It occurs in the setting of acute or chronic illness."[119]

Case definition: For the prior listed AESI AKI the use of the international criteria defined by the Kidney Disease: Improving Global Outcomes (KDIGO) expert consensus group in 2012 is recommended, rather than developing a new BCCD.[120]

"AKI is defined by contributing authors ACCESS as an abrupt (within hours) decrease in kidney function, which encompasses both injury (structural damage) and impairment (loss of function). It is a syndrome that rarely has a sole and distinct pathophysiology." Other symptoms can occur after major complications of AKI: volume depletion/overload (swelling or retaining fluid [in lungs, ankles, stomach]), shortness of breath, high blood pressure; dehydration leading to dizzy or lightheaded, hemorrhagic shock, weight loss, orthostatic hypotension, postural tachycardia; electrolyte disorders, e.g., hyperkaliemia, metabolic acidosis, hyponatremia, and hypernatremia, hypo/hypercalcemia, hyperphosphatemia, hypermagnesemia (cardiac arrythmias, fatigue, lethargy, convulsions, seizures, nausea, vomiting, diarrhea or constipation, abdominal cramping, confusion, headaches, muscle cramping, muscle weakness, numbness, and tingling); uremic complications: encephalopathy, pericarditis, pleuritis, bleeding due to platelet dysfunction.[119] (Complete_casedefinition_AKI)

Background: The referral rate in hospitalized patients is 4.8% and can be obtained from the worldwide meta-analysis of AKI.[14]

AKI risk factors:

- **Diseases and other factors:** The major cause of acute AKI is prerenal (extracellular fluid volume depletion, low CO, low systemic vascular resistance, vasoconstriction of afferent and glomerular arterioles, decreased efferent arteriolar tone), renal (acute tubular injury, acute glomerulonephritis, acute tubulointerstitial nephritis, acute vascular nephropathy, infiltrative diseases), and postrenal (tubular precipitation, ureteral obstruction, bladder obstruction).[121]

  AKI normally happens as a complication of another serious illness and is usually seen in older people who are unwell with other conditions, and the kidneys are also affected. Most cases of AKI are caused by reduced blood flow to the kidneys, usually, in someone who is already unwell with another health condition that could be caused by: low blood volume after bleeding, excessive vomiting or diarrhea, or severe dehydration, heart pumping out less blood than normal as a result of HF, liver failure or sepsis, problems with the blood vessels – such as inflammation and blockage in the blood vessels within the kidneys (a rare condition called vasculitis), glomerulonephritis (this may be caused by a reaction to some drugs, infections or the liquid dye used in some types of X-rays), or it may also be the result of a blockage affecting the drainage of the kidneys (an enlarged prostate, tumors in the pelvis, such as an ovarian or bladder tumor, kidney stones).[122]

  AKI is prevalent in critically ill COVID-19 patients. Kidney involvement is associated with poor outcomes. Several mechanisms are possibly involved in kidney injury during SARS-CoV-2 infection, including direct invasion of SARS-CoV-2 into the renal parenchyma, an imbalanced renin-angiotensin-aldosterone system and microthrombosis but also kidney injury secondary to hemodynamic instability,

inflammatory cytokines and the consequences of therapeutics that are used in intensive care units (nephrotoxic drugs, mechanical ventilation).[123]

- **Medicines:** The toxins that can cause renal AKI: aminoglycosides, amphotericin B, ethylene glycol, foscarnet, heavy metals, hemoglobin (as in hemoglobinuria), ifosfamide, methotrexate, myoglobin (as in myoglobinuria), radiopaque contrast agents, streptozotocin. For the prerenal causes: acyclovir, calcium oxalate (due to ingestion of ethylene glycol or excessive vitamin C), indinavir, methotrexate, myeloma protein, myoglobin, sulfonamides, triamterene, uric acid (tumor lysis).[120] NSAIDS, such as ibuprofen, or blood pressure drugs, such as ACE inhibitors or diuretics; diuretics are usually beneficial to the kidneys but may become less helpful when a person is dehydrated or suffering from a severe illness and is given aminoglycosides – a type of antibiotic; again, this is only an issue if the person is dehydrated or ill, and these are usually only given in a hospital setting.[122]
- **Vaccines in general:** No reference of association of the event to the vaccine was found. Possible risk for COVID-19 vaccine.
- **Vaccines against COVID-19 SARS-CoV-2:** COVID-19 vaccines have been introduced globally, and millions of people are being vaccinated with various types of vaccines, many of which use new vaccine platforms.[22]

ANOSMIA, AGEUSIA

SPEAC listed the event as prioritized on 25 May 2020. Relevant for COVID-19.

Category: Neurologic

Listed: BC/SPEAC, WHO, EMA/ACCESS

Rationale for inclusion: Theoretical concern based on immunopathogenesis and related to viral replication during wild-type disease.[6] These effects are so common with acute COVID-19 infections that they have been proposed for COVID-19 screening. It is recommended that relatively high priority should be placed on raising awareness about these conditions and determining their background rates, as they are also known to occur with other viral respiratory infections like influenza. This will be especially high priority in settings where there is ongoing community spread of COVID-19 disease.[5]

About the AESI: "Ageusia is the loss of taste functions of the tongue, and Anosmia the loss of the ability to detect one or more smells." [124]

Case definition: Anosmia, ageusia is defined by the contributing authors of ACCESS as:

Anosmia: Absent smell function. Two causes for anosmia: conductive and/or traumatic AND sensorineural.

Ageusia: Absent taste function. Staging system to assess whether the patient has ageusia or dysgeusia. A scale that ranges from 0, which refers to no taste, to 4, which refers to total taste loss, may be useful in evaluation.[124] (Complete_casedefinition_AnosmiaAgeusia)

Background: The IRs found among the databases were between 0.05/100,000 person-years (95% CI [0.01, 0.35]) and higher with 28.82/100,000 person-years (95% CI [27.41, 30.30]) in 2017. Significantly higher rates were observed in 2020 in all databases, which increase with age, but decrease in the older age group.[14]

Anosmia, ageusia risk factors:

- **Diseases and other factors:**

  Ageusia is due to damage to the nerve of taste sensation, dietary deficiencies, systemic conditions such as hypothyroidism, and diabetes mellitus, pernicious anemia, Sjögren's syndrome, Crohn's disease,

cranial nerve lesions (neuritis due to HZ, meningioma, or neurinoma), neoplastic lesions affecting the skull base, iatrogenic lesions, neuralgia, and polyneuropathies; patients with cancer in any head and neck region receiving radiotherapy, zinc deficiency, local injury, and inflammation in the surrounding structure (the result of burns, lacerations, surgery, and local anesthesia). Taste function can also be affected by local antiplaque medicaments that are excreted into saliva, some infections (dentoalveolar, periodontal, and soft-tissue infections), vesiculobullous conditions, complete and partial removable prostheses, metallic dental restorations, and dysfunction of the salivary gland. Moreover, aging or factors associated with aging may also render individuals more vulnerable to dysfunction of the gustatory system.[125]

Anosmia, the loss of sense of smell, is a common nonmotor feature of Parkinson's disease (PD). Ageusia, the loss of sense of taste, is additionally an underappreciated nonmotor feature of PD. The olfactory tract is involved early in PD as indicated by the frequent occurrence of hyposmia or anosmia years or decades before motor symptoms, and by autopsy studies showing early synuclein pathology in the olfactory tract and anterior olfactory nucleus even in the early stages of PD;[125] allergic rhinitis, nasal polyps, atrophic rhinitis, chronic sinusitis, some viral upper respiratory infections, coronavirus disease 2019, toxins, tumors (rare cause), Alzheimer's disease, degenerative neurologic disorders, head trauma, intracranial surgery, infection, or tumor.[126]

- **Medicines:**

  Anosmia: Commonly prescribed medications, such as antihypertensive and antihyperlipidemic drugs, are associated with smell disturbance. ACE inhibitors, diuretics, calcium channel blockers, and statins, amphetamines, enalapril, estrogen, naphazoline, phenothiazines, reserpine; prolonged use of decongestants. Usually, an apparent history of exposure.[127]

  Ageusia: Certain drugs including antibiotics (ampicillin, macrolides, metronidazole, quinolones, tetracycline), antineoplastic agents, neurologic medications (antiparkinsonism, CNS stimulants, migraine medications), cardiovascular drugs (antihypertensives, diuretics, statins, antiarrhythmics), antipsychotics, tranquilizers, tricyclic antidepressants, thyroid medications, antihistamines, bronchodilators, antifungals, and antivirals have also been reported to cause ageusia as a side effect.[125]

- **Vaccines in general:** No reference of association of the event to the vaccine was found. Possible risk for COVID-19 vaccine.
- **Vaccines against COVID-19 SARS-CoV-2:** COVID-19 vaccines have been introduced globally, and millions of people are being vaccinated with various types of vaccines, many of which use new vaccine platforms.[22]

CHILBLAIN-LIKE LESIONS

SPEAC listed the event as prioritized on 25 May 2020. Relevant for COVID-19.

Category: Dermatologic

Listed: BC/SPEAC, WHO, EMA/ACCESS

Rationale for inclusion: Theoretical concern based on immunopathogenesis and related to viral replication during wild-type disease.[6]

About the AESI: "Chilblains (CHILL-blayns) are the painful inflammation of small blood vessels in your skin that occur in response to repeated exposure to cold but not freezing air. Also known as pernio, chilblains can cause itching, red patches, swelling and blistering on your hands and feet.".[128]

Case definition: The contributing authors of ACCESS highlight that there is not yet an internationally clinical definition of or guidelines for chilblains and chilblain-like lesions. For chilblain-like lesions, the group describes that, during the recent COVID-19 pandemic, patients with few or no symptoms presented themselves with the event located on the toes and fingers. These patients had no underlying autoimmune disease (such as lupus erythematosus), Raynaud's phenomenon, or previous episodes of idiopathic chilblains. It mostly affected children and young adults, and the lesions occurred later during the (suspected) COVID-19 disease.[129] (Complete_casedefinition_chilblainlikelesions)

Background: A range of IRs was observed for chilblain-like injuries. Annual rates showed significant differences in each year for the FISABIO data source, ranging from 37.05/100,000 person-years (95% CI [35.42, 38.75]) in 2020 to 64.05/100,000 person-years (95% CI [62.93, 66.24]) in 2017. Rates were very low only in hospital data sources.[14]

Chilblain-like lesions risk factors:

- **Diseases and other factors:** Chilblains is described as painful inflammation of small blood vessels in the skin that occur in response to repeated exposure to cold but not freezing air. Also known as pernio, chilblains can cause itching, red patches, swelling, and blistering on hands and feet. They usually clear up within 1–3 weeks, especially if the weather becomes warmer. Affected persons may have recurrences seasonally for years. Factors that may increase the risk of chilblains include clothing that is tight or exposes skin to the cold, sex (women are more likely to have chilblains than are men), underweight, environment, and season. People with poor circulation tend to be more sensitive to changes in temperature, making them more susceptible to chilblains; Raynaud's disease.[128]

  Some people are more at risk of chilblains than others. They are people with poor circulation, with a family history of chilblains, regular exposure to cold, people who live in damp or draughty conditions, with a poor diet or low body weight, with lupus – a long-term condition that causes swelling in the body's tissues; also, people with Raynaud's phenomenon – a common condition that affects the blood supply to certain parts of the body, usually the fingers and toes. People who smoke are more at risk of chilblains (as nicotine constricts blood vessels), and chilblains can also occur on areas of the feet exposed to pressure, such as a bunion or a toe that is squeezed by tight shoes.[130]

  COVID-19 chilblains is a well-reported cutaneous pattern of SARS-CoV-2. In the absence of exposure to cold or humidity, COVID-19 should be considered a cause of the acute cold. The timing of the beginning of COVID-19 chilblains in relation to the active SARS-CoV-2 viremia remains unclear. Patients with suspected COVID-19 chilblains should therefore follow public health guidelines for COVID-19 testing and self-isolation.[131]

  Chilblain-like lesions are a recognized sequela of COVID-19 found to affect younger (mean age 32.5 years in published cases) and often otherwise asymptomatic patients. Chilblains normally occur as a reaction to cold wet weather, whereas chilblain-like lesions are attributed to inflammatory or embolic microvascular occlusion. The presence of such lesions should prompt testing for COVID-19.[132]

  Some researchers have noted that a change in habits during the pandemic and lockdown could be tied to chilblains. This may be due to walking barefoot at home, lack of physical activity, and stress.[133]

- **Medicines:** No drugs identified that are related to the cause of chilblains.
- **Vaccines in general:** No reference of association of the event to the vaccine was found. Possible risk for COVID-19 vaccine.
- **Vaccines against COVID-19 SARS-CoV-2:** COVID-19 vaccines have been introduced globally, and millions of people are being vaccinated with various types of vaccines, many of which use new vaccine platforms.[22] Chilblain-like lesions have been monitored among the events considered serious.

ERYTHEMA MULTIFORME

SPEAC listed the event as prioritized on 25 May 2020. Relevant for COVID-19.

Category: Dermatologic

Listed: BC/SPEAC, WHO, EMA/ACCESS

Rationale for inclusion: Theoretical concern based on immunopathogenesis and related to viral replication during wild-type disease.[6]

About the AESI: Erythema multiforme (EM) is an inflammatory reaction, characterized by target or iris skin lesions. Oral mucosa may be involved. Usually occurs as a reaction to an infectious agent such as herpes simplex virus or mycoplasma but may be a reaction to a drug.[134]

Case definition: For the definition of the event revised by the contributing authors of ACCESS, EM is an acute self-limited disease, usually associated with hypersensitivity reactions to viruses, as well as to medications. It is characterized by target erythematous lesions with a predominant acral location and can be subdivided into isolated cutaneous and combined mucocutaneous forms. It is defined by the morphology of individual lesions and by the distribution pattern, and was included only in its main form called erythema multiforme major.[135] (Complete_casedefinition_erythemamultiforme)

Background: In the PHARMO, FISABIO, ARS, and BIFAP data sources, the IRs were distributed between 0.25/100,000 person-years (95% CI [0.16, 0.38]) and 15.09/100,000 person-years (95% CI [14.08, 16.17]). For 2020, the IRs were found to be significantly lower at 3.99/100,000 person-years versus 8.85/100,000 person-years in 2019, 3.87/100,000 person-years versus 6.25 in 2019, and 6.38/100,000 person-years against 12.58/100,000 person-years in 2019 among three data sources. Rates were higher in children.[14]

EM risk factors:

- Diseases and other factors: EM is an acute, self-limited skin eruption, mainly caused by infections and drug allergy. Viral (most commonly HSV), bacterial (Mycoplasma pneumoniae), and fungal infections (histoplasmosis) are precipitating factors of EM. It is rarely related to HIV and is not a common manifestation of drug allergy to antiretrovirals. Setting the diagnosis of EM in an HIV+ patient can be challenging and anamnesis is its cornerstone.[136]

  It is also a rare skin disorder that mainly affects children. When seen in adults, it usually occurs between the ages of 20 and 40, although it can happen to people of any age. Men tend to experience EM more frequently than do women. EM is a rash that is usually caused by an infection or medication. It is typically mild and resolves after a few weeks. This is called EM minor. There is also a much more severe and life-threatening form of EM that may affect the mouth, eyes, and even genitals. This type is called EM major and makes up about 20% of cases. EM is associated with the virus that causes cold sores (HSV). Doctors also believe that many cases of EM occur when other infections stimulate the body's immune system to attack skin cells.[137]

  Most cases are caused by HSV infection. HSV-1 is more often a cause than HSV-2, although it is unclear whether EM lesions represent a specific or nonspecific reaction to the virus. Less commonly, cases are caused by drugs, vaccines, other bacterial or viral diseases (especially hepatitis C), or possibly SLE. EM that occurs in patients with SLE is sometimes referred to as Rowell syndrome.[134]

- **Medicines:** Types of drug reactions and EM typical causative agents: penicillin, barbiturates, sulfonamides (including derivatives used to treat hypertension and diabetes). It expands by focusing on certain drugs that can also cause the development of EM: NSAIDs, antibacterial drugs, and penicillin-based antibiotics, seizure drugs, anesthetic drugs.[134]

- **Vaccines in general:** Becoming immunized against diseases such as Tdap or hepatitis B may also cause a person to develop EM. This is rare and the low risk does not usually warrant remaining unvaccinated.[136] Adverse events, such as EM, are rarely associated temporarily with the varicella vaccine and the MMRV.[21]
- **Vaccines against COVID-19 SARS-CoV-2:** COVID-19 vaccines have been introduced globally, and millions of people are being vaccinated with various types of vaccines, many of which use new vaccine platforms.[22]

ACUTE LIVER INJURY

SPEAC positions in priority list date 25 May 2020. Relevant for COVID-19.

Category: Gastrointestinal

Listed: BC/SPEAC, WHO, EMA/ACCESS.

Rationale for inclusion: AESI that can be used to monitor the risk-benefit profile of upcoming COVID-19 vaccines. Would be of higher priority in settings and populations where there is a known high frequency of comorbid conditions (hypertension, chronic hepatitis, chronic renal failure).[5]

About the AESI: The condition of patients who develop coagulopathy, but do not have any alteration to their level of consciousness is defined as acute liver injury (ALI). For the prior listed AESI ALI, adopt what has been used in many COVID-19 publications reporting elevations above the upper normal limit of more than threefold for aspartate aminotransferase / alanine aminotransaminase (ALT) and more than twofold for total bilirubin, gamma-glutamyl transferase, and alkaline phosphatase (ALP) rather than develop a BCCD.[120]

Case definition: The contributing authors of ACCESS have reviewed the definitions of acute liver failure (ALF) and ALI. They considered approach followed by the European Association for the Study of the Liver, which defines ALF as a highly specific and rare syndrome, characterized by an acute abnormality in liver blood tests in an individual without underlying chronic liver disease. The disease process is associated with the development of a hepatic coagulopathy and alteration of the clinically apparent level of consciousness due to hepatic encephalopathy (HE). The condition of patients who develop coagulopathy is defined, but they do not present any change in their level of consciousness as ALI.[138] (Complete_casedefinition_ALI)

ALI risk factors:

- **Diseases and other factors:** Abnormal liver function tests are common among hospitalized COVID-19 patients. Elevation of liver enzymes has been reported in 20–30% of inpatients. Mild abnormalities of liver function tests are usually transient and thought to be a nonspecific reaction to general inflammation. There is no distinct COVID-19 liver pathology based on limited autopsy studies. Several mechanisms have been proposed for COVID-19-associated ALI, including drug toxicity (documented with the combination of lopinavir-ritonavir), myositis (which could also elevate liver enzymes), aggravation of liver injury among those with preexisting viral hepatitis, viral binding to cholangiocytes leading to liver damage and direct damage to the liver. There is no consensus among the many published reviews and meta-analyses as to cause. Patients with abnormal liver tests were at higher risk of progressing to severe disease. The detrimental effects on liver injury are mainly related to certain medications used during hospitalization, which should be monitored and evaluated frequently.[139]

  ALF occurs when liver cells are damaged significantly and are no longer able to function. Potential causes include autoimmune disease (liver failure can be caused by autoimmune hepatitis – a disease in which the immune system attacks liver cells, causing inflammation and injury), diseases of the veins in the liver (vascular diseases, such as Budd-Chiari syndrome, can cause blockages in the veins of the liver and

lead to ALF), metabolic disease (rare metabolic diseases, such as Wilson's disease and acute fatty liver of pregnancy, infrequently cause ALF); cancer (cancer that either begins in or spreads to the liver can cause it to fail), shock (overwhelming infection [sepsis] can severely impair blood flow to the liver, causing liver failure), heat stroke (extreme physical activity in a hot environment can trigger ALF). Some cases of ALF have no apparent cause.[140]

- **Medicines:** Three types of liver injury are generally noted for potentially hepatotoxic drugs:

  Hepatocellular: Elevated ALT (acarbose, acetaminophen, allopurinol, amiodarone, ART drugs, bupropion, fluoxetine, germander, green tea extract, baclofen, isoniazid, kava, ketoconazole, lisinopril, losartan, methotrexate, NSAIDs, omeprazole, PD-1/PD-L1 inhibitors, paroxetine, pyrazinamide, rifampin, risperidone, sertraline, statins, tetracyclines, trazodone, trovafloxacin, valproate).

  Cholestatic: Elevated ALP and total bilirubin (amoxicillin/clavulanate, anabolic steroids, chlorpromazine, clopidogrel, oral contraceptives, erythromycins, estrogens, irbesartan, mirtazapine, phenothiazines, terbinafine, tricyclic antidepressants).

  Mixed: Elevated ALP and ALT (amitriptyline, azathioprine, captopril, carbamazepine, clindamycin, cyproheptadine, enalapril, nitrofurantoin, phenobarbital, phenytoin, sulfonamides, trazodone, trimethoprim / sulfamethoxazole, verapamil). For acute hepatic failure, the causes include paracetamol overdose (ALF can occur after a large dose of paracetamol or after doses higher than those recommended every day for several days), some prescription drugs (antibiotics, noninflammatory drugs, steroid drugs and anticonvulsants), herbal supplements (kava, ephedra, skullcap, pennyroyal), hepatitis and other viruses. Hepatitis A, hepatitis B and hepatitis E can cause ALF. Other viruses that can cause ALF include EBV, cytomegalovirus, and HSV; toxins (including the poisonous wild mushroom Amanita phalloides, which is sometimes mistaken for one that is safe to eat, carbon tetrachloride).[140]

- **Vaccines in general:** No reference of association of the event to the vaccine was found. Possible risk for COVID-19 vaccine.
- **Vaccines against COVID-19 SARS-CoV-2:** COVID-19 vaccines have been introduced globally, and millions of people are being vaccinated with various types of vaccines, many of which use new vaccine platforms.[22]

SUBACUTE THYROIDITIS

Subacute thyroiditis (SAT) is one of three new events added to the list of AESI for safety monitoring based on COVID-19, generated by SPEAC.[120]

Category: Endocrine

Listed: BC/SPEAC

Rationale for inclusion: Known association with immunization or a specific vaccine platform, theoretical association based on animal models, and occurrence during wild-type disease because of viral replication and/or immunopathogenesis.[120]

About the AESI: SAT occurs predominantly as a postinfectious illness with onset several weeks after acute COVID-19.[120]

Case definition: SAT is a diagnosis made clinically. Anterior neck pain, preceded by an upper respiratory inflammation, alerts the clinician to the classic painful (De Quervain´s; granulomatous) thyroiditis (PFSAT). Differential diagnostic considerations include acute (suppurative, thyroid abscess) thyroiditis, which is usually a painful nodular enlargement of the thyroid or unusual presentations of Graves' or nodular thyroid disease,

with pain generated by capsular stretching. Thyroid function tests during the painful (initial) phase of SAT often reveal a suppressed thyroid-stimulating hormone and elevation of total T4 and T3 levels consistent with the thyrotoxic state. The T3 (ng/dl) to T4 (ug/dl) ratio is less than 20 in all forms of SAT.[141] (Complete_casedefinition_SAT)

SAT risk factors:

- **Diseases and other factors:** Reviews of the literature have shown that evidence for viral infection in SAT is linked to mumps virus, coxsackievirus, adenovirus, EBV, rubella, and cytomegalovirus, although a specific viral cause is not always found. SAT is presumed to be caused by a viral infection or a postviral inflammatory process with clusters of the disease reported during outbreaks of viral infections, drawing many parallels to those of the current COVID-19 pandemic situation. This further highlights the importance for physicians to be vigilant of the diagnosis while treating patients with COVID-19 who may have multiple upper respiratory symptoms. SAT is a rare complication of COVID-19 that should be considered, especially in the setting of persistent tachycardia without any suggestion of progression of COVID-19 and other common cardiorespiratory causes.[142]

  Thyrotoxicosis was observed suggesting SAT was more frequent in patients with severe COVID-19 disease. It is believed that COVID-19 may have induced an atypical form of SAT in some patients. It is atypical, as it does not present with neck pain and does not seem to predominantly affect women, as is the case with the classic form. It is believed that thyroid dysfunction may be one of the symptoms of "long COVID-19." Although thyroid abnormalities appear to be transient, permanent thyroid dysfunction can return in the long run. This is commonly seen in classic subacute viral thyroiditis.[143]

  SAT is an uncommon condition. It is thought to be the result of a viral infection. The condition often occurs a few weeks after a viral infection of the ear, sinus, or throat, such as mumps, influenza, or the common cold.

  SAT occurs most often in middle-aged women with symptoms of a viral upper respiratory tract infection in the previous month.[144] Numerous conditions – especially infections – can cause SAT; however, viral infection (coxsackie, influenza, etc.) is the most common.[145] Unlike other forms of thyroiditis, SAT is thought to be linked to a viral infection. In response to the virus, the thyroid swells and can disrupt hormone production. This causes inflammation and a variety of symptoms. SAT is slightly more common in women aged 40–50 than it is in men of the same age. It generally occurs after an upper respiratory infection, such as influenza or mumps.[146]

- **Medicines:** Causes of drug-associated thyrotoxicosis: amiodarone, lithium, interferon-a, interleukin-2, contrast.[141]

- **Vaccines in general:** Only a few cases of SAT following vaccination have been reported (influenza and HB). However, the development of SAT during the period following vaccination for viruses is a rarely reported clinical entity. Influenza-like symptoms are known to develop after vaccination because of viral antigens. Similarly, vaccination might theoretically trigger subsequent alterations in the thyroid, such as viral agents. The literature review included only five reported cases of SAT following vaccination (influenza: nD 2; HB: nD 1; H1N: n D 1). SAT following viral vaccination causing SAT, similarly to what the virus can do, is a rare example. SAT should be considered in all patients that receive influenza vaccine and subsequently develop flu-like syndrome and thyroid pain. In addition, if patients have a positive history of SAT, close observation for recurrent SAT is warranted.[145]

- **Vaccines against COVID-19 SARS-CoV-2:** COVID-19 vaccines have been introduced globally, and millions of people are being vaccinated with various types of vaccines, many of which use new vaccine platforms.[22]

RHABDOMYOLYSIS

Rhabdomyolysis is one of three new events added to the list of AESI for safety monitoring based on COVID-19, generated by SPEAC.[120]

Category: Musculoskeletal system

Listed: BC/SPEAC

Rationale for inclusion: Known association with immunization or a specific vaccine platform, theoretical association based on animal models, and occurrence during wild-type disease as a result of viral replication and/or immunopathogenesis.[120]

About the AESI: Rhabdomyolysis is part of acute COVID-19 illness (Law, SO2-D2.1.2 Priority List of COVID-19 Adverse events of special interest: Quarterly update. December 2020. Safety Platform for Emergency vACcines [130]). Rhabdomyolysis is a well-known cause of kidney failure and is commonly associated with drugs, toxins, and infections. Muscle syndrome such as rhabdomyolysis is recognized to not infrequently complicate viral infections, the most common associations being with influenza A and B, cytomegalovirus, adenovirus, coxsackievirus, herpesvirus and EBV.[147]

Case definition: Diagnostic for Rhabdomyolysis by Torres et al.: "the classic triad of symptoms of rhabdomyolysis consists of myalgia, weakness, and tea-colored urine. The muscle mass of the patient, the concentration of urine, and glomerular function can affect the color of the urine."[148] (Complete_casedefinition_rhabdomyolysis)

Background: According to Chavez et al., many cases of rhabdomyolysis go undetected, and the incidence of this clinical entity has been reported only in subgroups of populations at risk. Rhabdomyolysis is more frequent among men, African Americans, patients < 10 and > 60 years and in people with a body mass index greater than 40 kg/m2.

The number of cases of rhabdomyolysis associated with surgery seems to have increased in recent years, due to risk factors related to the prolonged extension of surgery and comorbidities.[149]

Rhabdomyolysis risk factors:

- **Diseases and other factors:** In rhabdomyolysis, there is breakdown of skeletal muscle cells, resulting in the release of cellular constituents such as electrolytes, myoglobin, and cellular enzymes, including creatine kinase. The consequences thereof can include life-threatening disseminated intravascular coagulation, electrolyte disturbances, and AKI.[147] Influenza A infection has been described as a major viral cause of infection-induced rhabdomyolysis.[150]

  Rhabdomyolysis is always triggered by muscle injury. This injury can have physical, chemical, or genetic causes. Anything that damages the muscles can cause this condition. Possible causes include trauma, heat, and exertion, genetic and metabolic disorders, infection, and inflammation (viral infections, bacterial infections, polymyositis, dermatomyositis, snakebites).[151] Theoretically, any form of muscle damage and, by extension, any entity that leads to or causes muscle damage, can initiate rhabdomyolysis. In adults, the available data show that the most common causes of rhabdomyolysis are drug or alcohol abuse, medicinal drug use, trauma, neuroleptic malignant syndrome, and immobility. The data in the pediatric population skew toward different leading causes, suggesting that viral myositis, trauma, connective tissue disorders, exercise, and drug overdose are responsible for much of the rhabdomyolysis seen in these patients; viral myositis alone may account for up to one-third of pediatric cases of rhabdomyolysis.

  Physical and nonphysical causes of rhabdomyolysis: Risk factors for the development of statin-induced rhabdomyolysis include high dosages, advanced age, female sex, renal or hepatic insufficiency,

and diabetes mellitus. Clinicians treating rhabdomyolysis concurrent with COVID-19 must assess the many differential diagnoses, including SARS-CoV-2-induced myositis, reactions to medication, cytokine storm, hypoxia, or a thromboembolic event. This differential diagnosis is crucial because each condition has a distinct therapeutic approach.[152]

- **Medicines:** Medications and toxins. One important cause of rhabdomyolysis is statin medications, which are cholesterol-lowering drugs (atorvastatin [Lipitor], rosuvastatin [Crestor], pravastatin [Pravachol]). Although rhabdomyolysis only occurs in a few people who take statins, so many people take these medications that it is important to be aware of the risk. The condition can also occur due to exposure to other drugs, certain toxins, and high levels of alcohol. Other drugs that can cause rhabdomyolysis include cyclosporine, erythromycin, colchicine, cocaine, amphetamines, ecstasy, LSD.[151] Statins, other antilipidic agents, psychiatric agents, abused substances, and antihistamines are drugs and other agents that can cause rhabdomyolysis.[148]

  A retrospective study of 8,610 cases of drug-associated rhabdomyolysis reported to the FDA between 2004 and 2009 revealed that simvastatin, atorvastatin, and rosuvastatin were most frequently suspected and accounted for 3,945 cases (45%).[149]

- **Vaccines in general:** Vaccines are rarely associated with rhabdomyolysis, but there is a reported case described as having been induced by influenza vaccine, and a report on rhabdomyolysis secondary to influenza A H1N1 vaccine resulting in AKI.[153]

- **Vaccines against COVID-19 SARS-CoV-2:** COVID-19 vaccines have been introduced globally, and millions of people are being vaccinated with various types of vaccines, many of which use new vaccine platforms.[22] Rhabdomyolysis has been monitored among the events considered serious.

ACUTE PANCREATITIS

Acute pancreatitis (AP) is one of three new events added to the list of AESI for safety monitoring based on COVID-19, generated by SPEAC.[120]

Category: Endocrine system

Listed: BC/SPEAC

Rationale for inclusion: Known association with immunization or a specific vaccine platform, theoretical association based on animal models, and occurrence during wild-type disease as a result of viral replication and/or immunopathogenesis.[120]

About the AESI: AP is defined as an acute inflammatory disease of the pancreas with variable involvement of peripancreatic tissues and/or remote organ systems.[165] There have been case reports published of pancreatitis associated with COVID-19. Ages ranged from 7 to 76 years, with a median of 38 years.[120]

Case definition: According to Thompson, AP is inflammation of the pancreas with activation of pancreatic enzymes within the organ. This leads to tissue destruction. Patients classically present with pain (94%), vomiting (64%), and fever (33%). This is a relatively uncommon diagnosis in childhood and is often missed.[154] (Complete_casedefinition_AP)

Background: In a study by Roberts et al., the incidence of AP was reported in 17 European countries and ranged from 4.6 to 100 per 100,000 population, being generally highest in eastern or northern Europe (reported rates varied according to case-finding criteria). Of the 20 studies reported, trends in incidence, except for three studies, showed percentage increases over time (overall mean increase = 3.4% per year; range = –0.4% – 73%).[154]

AP risk factors:

- **Diseases and other factors:** Known etiologic causes of pancreatitis (alcohol, gallstones, trauma, recent invasive procedures) (Law. SO2-D2.1.2 Priority List of COVID-19 Adverse events of special interest: Quarterly update. December 2020. Safety Platform for Emergency vACcines).[120]

  AP is usually caused by gallstones or drinking too much alcohol, but sometimes no cause can be identified.

  Gallstones: are small stones that form in the gallbladder. They can sometimes trigger AP if they move out of the gallbladder and block the opening of the pancreas.

  Alcohol consumption: It is not fully understood how alcohol causes the pancreas to become swollen (inflamed). One theory is that it causes enzymes inside the pancreas to start digesting it. Whatever the cause, there is a clear link between alcohol use and AP.

  Binge drinking – drinking a lot of alcohol in a short period of time – is also thought to increase the risk of developing AP.

  Less common causes of AP include accidental damage or injury to the pancreas, a side effect of medicine, viruses such as mumps or measles, the immune system attacking the pancreas (autoimmune pancreatitis).[155]

  Other conditions that can lead to pancreatitis include abdominal surgery, cystic fibrosis, high calcium levels in the blood (hypercalcemia), which may be caused by an overactive parathyroid gland (hyperparathyroidism), high triglyceride levels in the blood (hypertriglyceridemia), infection, injury to the abdomen, obesity, pancreatic cancer. Endoscopic retrograde cholangiopancreatography, a procedure used to treat gallstones, also can lead to pancreatitis. Sometimes, a cause for pancreatitis is never found.[156]

  Some causes of AP are related to: high levels of calcium in the blood (which may be caused by hyperparathyroidism); viruses such as mumps, coxsackie B virus, hepatitis A and hepatitis E, and cytomegalovirus; damage to the pancreas caused by blunt or penetrating injuries, or other blockages of the pancreatic duct; hereditary pancreatitis, including a small percentage of people with cystic fibrosis or cystic fibrosis genes; kidney transplantation, pregnancy (rare), and tropical pancreatitis.[157]

- **Medicines:** Some causes of AP are related to drugs such as ACE inhibitors, azathioprine, furosemide, 6-mercaptopurine, pentamidine, sulfa drugs, and valproate; estrogen use in women with high levels of lipids in the blood.[158]
- **Vaccines in general:** Pancreatitis after HPV vaccination: a matter of molecular mimicry; in conjunction with aluminum adjuvant, the induction of immunity through molecular mimicry may potentially culminate in production of cytotoxic autoantibodies with a particular affinity for pancreatic acinar cells.[159] Another vaccine cited as a possible induction of AP is the viral triple or MMR, being an event associated with the mumps component; suggested 10–21 days after vaccination; however, they are rare.[21]
- **Vaccines against COVID-19 SARS-CoV-2:** COVID-19 vaccines have been introduced globally, and millions of people are being vaccinated with various types of vaccines, many of which use new vaccine platforms.[22]

LYMPHADENOPATHY

Rationale for inclusion: Possible side effects after receiving a COVID-19 vaccine.

About the AESI: Lymphadenopathy, or lymphadenitis, refers to lymph nodes that are abnormal in size, number, or consistency, and is often used synonymously with swollen or enlarged lymph nodes.[160] Lymphadenopathy is palpable enlargement of ≥ 1 lymph nodes. Diagnosis is clinical. Treatment is of the causative disorder. It is categorized as localized (present in only one area of the body) or generalized (present in ≥ 2 areas of the body). Lymphadenitis is lymphadenopathy with pain and/or signs of inflammation (redness, tenderness). Other symptoms may be present depending on the underlying disorder.[161]

Case definition: Collections of superficial lymph nodes are present in the neck, axillae, and inguinal region; a few small (< 1 cm) nodes often are palpable in those areas in healthy people.[161] (Complete_casedefintion_lymphadenopathy)

Lymphadenopathy risk factors:

- **Diseases and other factors:** Many infectious and inflammatory diseases and cancers are potential causes of lymphadenopathy (as lymph nodes participate in the body's immune response). The causes vary depending on the patient's age, associated findings, and risk factors, with the most common causes being idiopathic, self-limiting, such as upper respiratory infection, local soft-tissue infections. The most dangerous causes are cancer, HIV infection, and tuberculosis. It is noteworthy that most cases represent benign disorders or clinically obvious local infections.[161]
- **Medicines:** Drugs such as allopurinol, antibiotics (e.g., cephalosporins, penicillin, sulfonamides), atenolol, captopril, carbamazepine, phenytoin, pyrimethamine, and quinidine can cause lymphadenopathy.[161]
- **Vaccines in general:** Bacillus Calmette–Guerin AND VPM1002 Bacillus Calmette-Guerin recombinant. Incidence 3 (25.0%) and risk hazard 0–6 months.[162] MMR and rabies vaccines are also cited as possible causes of lymphadenopathy.[21]
- **Vaccines against COVID-19 SARS-CoV-2:** COVID-19 vaccines have been introduced globally, and millions of people are being vaccinated with various types of vaccines, many of which use new vaccine platforms.[22] Suspected cases of lymphadenopathy have been reported and monitored among events considered serious after vaccination against COVID-19.[25]

APPENDICITIS

New event added to the list of AESI for safety monitoring based on COVID-19.

Rationale for inclusion: Appendicitis is one of the most common surgical abdominal diseases and is suggested as an adverse event of special post-vaccination interest for COVID-19 vaccines.[163]

About the AESI: While anyone can have appendicitis, it occurs more often in people between 10 and 30 years old. The standard treatment is surgical removal of the appendix. The likely cause of appendicitis is a blockage in the lining of the appendix that results in infection. Bacteria multiply quickly, causing the appendix to become inflamed, swollen, and filled with pus. If not treated immediately, the appendix may rupture.[164]

Case definition: Appendicitis is inflammation of the vermiform appendix. The progression of the inflammatory process can lead to abscess, ileus, peritonitis, or death if left untreated. Complicated appendicitis refers to the presence of gangrene or perforation of the appendix. Free perforation in the peritoneal cavity can cause purulent or starchy peritonitis. A contained perforation can cause an abscess in the appendix or phlegmon (inflammatory mass).[166] (Complete_casedefintion_appendicitis)

Background: In the United States, acute appendicitis is the most common cause of acute abdominal pain that requires surgery. More than 5% of the population develop appendicitis at some point. It most commonly occurs

in adolescence and when people are in their twenties but can occur at any age.[165] Other authors present that appendicitis is the most common abdominal surgical emergency. The reported lifetime risk of appendicitis in the United States is 8.6% in men and 6.7% in women, with an annual incidence of 9.38 per 100,000 people.[166]

Appendicitis risk factors:

- **Diseases and other factors:** The exact cause of appendicitis is unknown in many cases, and there may be blockage of the appendix due to accumulation of hard stools, enlarged lymphoid follicles, intestinal worms, traumatic injury, tumors.[165] Other conditions that affect the appendix include carcinoids, cancer, villous adenoma, and diverticula. The appendix can also be affected by Crohn's disease or ulcerative colitis with pancolitis (inflammatory bowel disease).[164]
- **Medicines:** No drugs identified.
- **Vaccines in general:** No vaccines identified.
- **Vaccines against COVID-19 SARS-CoV-2:** COVID-19 vaccines have been introduced globally, and millions of people are being vaccinated with various types of vaccines, many of which use new vaccine platforms.[22] Suspected cases of appendicitis have been reported and monitored among events considered serious after vaccination against COVID-19.[23]

HERPES

New event added to the list of AESI for safety monitoring based on COVID-19.

Category: Neurologic

Rationale for inclusion: The increased incidence of age-related HZ and its complications is believed to be a result of the decline in cell-mediated immunity (immunosenescence), a higher incidence of age-related comorbidities, and socio-environmental changes. Individuals who are immunocompromised as a result of disease or therapy are also at increased risk, regardless of age.[167]

About the AESI: HSVs (human HSVs types 1 and 2) commonly cause recurrent infection affecting the skin, mouth, lips, eyes, and genitals. Common severe infections include encephalitis, meningitis, neonatal herpes, and, in immunocompromised patients, disseminated infection. Mucocutaneous infections cause clusters of small painful vesicles on an erythematous base.

HZ is infection that results when VZV reactivates from its latent state in a posterior dorsal root ganglion. Symptoms usually begin with pain along the affected dermatome, followed within 2–3 days by a vesicular eruption that is usually diagnostic.[168]

Case definition: HZ is generally diagnosed clinically, once the rash has appeared. However, prior to the rash occurring and for atypical cases, diagnosis can require laboratory confirmation, using PCR analysis, which can detect VZV DNA rapidly and accurately. HZ can sometimes be confused with HSV or several other conditions.[168] (Complete_casedefinition_HerpesZoster)

Background: More than 95% of immunocompetent individuals aged at least 50 years are seropositive for the VZV and, therefore, are at risk of developing HZ.

The lifetime risk of developing HZ is 25–30%, increasing to 50% in people aged at least 80 years. The estimated mean overall incidence of HZ is about 3.4–4.82 per 1,000 person-years, which increases to more than 11 per 1,000 person-years in those aged at least 80 years.

Data from a network of general practitioners in France showed that 1% of patients with HZ were hospitalized, and the mortality rate was 0.2/100,000. HZ-associated mortality is rare, with a reported incidence ranging from 0

to 0.47 per 100,000 person-years, and most deaths occur in people aged at least 60 years. However, many studies use electronic or paper death certificates, which can lead to underestimations or overestimations of the true mortality rate due to infections other than HZ and noninfectious diseases, especially in the older persons.[167]

Herpes risk factors:

- **Diseases and other factors:** HZ is a common disease, with the highest burden in older adults who frequently have at least one chronic disease. The risk of drug–drug interactions is higher in this population when treatment for HZ and postherpetic neuralgia is required, making management challenging, with the risk of unsatisfactory pain relief, adverse events, decompensation of comorbidities, and functional decline.[176] Chickenpox and HZ are caused by VZV (human herpesvirus type 3); chickenpox is the acute, primary infection phase of the virus, and HZ (shingles) represents reactivation of virus from the latent phase.[168]
- **Medicines:** No reference to drug causes.
- **Vaccines in general:** Severe HZ as an adverse event to vaccination was rarely temporally associated with the administration of chickenpox vaccine, MMRV, and chickenpox vaccine.[21]
- **Vaccines against COVID-19 SARS-CoV-2:** COVID-19 vaccines have been introduced globally, and millions of people are being vaccinated with various types of vaccines, many of which use new vaccine platforms.[22] Suspected cases of HZ have been reported and monitored among events considered serious after vaccination against COVID-19.[23]

PART B – ADVERSE EVENTS FOLLOWING IMMUNIZATION

Although all vaccines used in national immunization programs are safe and effective if used correctly, no vaccine is completely risk-free and adverse events will occasionally result after an immunization.

A general definition of an AEFI is any unpleasant medical event that follows immunization and does not necessarily have a causal relationship with the use of the vaccine. The adverse event can be any unfavorable or unintended sign, an abnormal laboratory finding, a symptom, or an illness. Specifically, it is a vaccine product-related reaction (AEFI caused or precipitated by a vaccine due to one or more of the inherent properties of the vaccine product); a reaction related to a vaccine quality defect (AEFI caused or precipitated by a vaccine due to one or more quality defects of the vaccine product, including administration device as provided by the manufacturer); a reaction related to immunization error (AEFI caused by inadequate vaccine manipulation, prescription, or administration and which, therefore, by its nature, is preventable); and a reaction related to immunization anxiety (AEFI arising from anxiety about the immunization); and it can be a coincident event (AEFI caused by something other than the vaccine product, immunization error or immunization anxiety).

The following AEFIs were identified and notified during the clinical trials of the COVID-19 vaccines and were presented to the national regulatory authorities for emergency use authorization.

A vaccination campaign against COVID-19 is a particular challenge for AEFI surveillance as it involves administration of vaccine doses to a large population in a short period. As a result, adverse events may be more noticeable to the staff and the public.[169]

FEVER FOLLOWING IMMUNIZATION

A standardized definition of fever as an AEFI was developed by a working group formed within BC.

Category: Systemic events

Listed: BC/SPEAC

Rationale for inclusion: Fever is a common clinical complaint in adults and children with a variety of infectious diseases, as well as a frequently reported adverse event after immunization.[170]

About the AESI: Fever is defined as an elevation of body temperature above the normal. It is usually caused by infection, but it can also be associated with a few immunologic, neoplastic, hereditary, metabolic, and toxic conditions. Fever is endogenously generated and is distinguished from hyperthermia, which is a warming of the body caused by external environmental factors.[170] Even with many aspects of the societal, medical, economic, and epidemiologic meanings of fever as an AEFI still elusive, it is a generally benign – albeit common – clinical sign. It is important to gain an improved understanding of its importance as an AEFI.[171]

Case definition: The definition of a fever case has been standardized by the BC group to be globally accepted as guidelines for data collection, analysis, and presentation. The CD of fever as an AEFI is presented at three levels of diagnostic certainty. Level 1 of diagnostic certainty: fever is defined as the endogenous elevation of at least one measured body temperature of ≥ 38 °C; Levels 2 and 3 of diagnostic certainty: not applicable.[171] (Complete_casedefinition_fever)

Event rating scale – toxicity grading scale[172]

Event rating scale	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potential life threat (Grade 4)
°C	37.9–38.4	38.5–38.9	39.0–40.0	> 40.0
°F	100.1–101.1	101.2–102.0	102.1–104.0	> 104.0

Fever risk factors:

» **Diseases and other factors:** The presence of fever is only one of many clinical observations that can be used to assess the nature and severity of an illness. It must always be taken in context with a thorough clinical evaluation integrating historical data, physical findings, behavior, age (special caution needs to be given to different approaches for different age groups), and responsiveness. When there is suspicion of significant infection, serial clinical and laboratory examinations, as well as repeated inquiries about medical history, may be necessary to achieve a diagnosis and to determine an appropriate course of management. Despite the recognition that fever is generally a physiological reaction to an underlying disease process and not a disease in itself, the presence of an elevated temperature may cause undue concern.[171]

Infection is not the only cause of fever. Fever may also result from inflammation, a reaction to a drug, an allergic reaction, autoimmune disorders (when the body produces abnormal antibodies that attack its own tissues), and undetected cancer (especially leukemia, lymphoma, or kidney cancer). Disorders as infectious (most common), neoplastic (cancer), and inflammation can cause fever. An infectious cause is highly likely in adults with a fever that lasts 4 days or less.

A noninfectious cause is more likely to cause a fever that lasts a long time or returns. Inflammatory disorders that cause fever include joint, connective tissue, and blood vessel disorders such as rheumatoid arthritis, SLE (lupus), and giant cell arteritis.

Moreover, an isolated, short-lived (acute) fever in people with cancer or a known inflammatory disorder is most likely to have an infectious cause. In healthy people, an acute fever is unlikely to be the first sign of a chronic illness. The most likely infectious causes are upper and lower respiratory tract infections; gastrointestinal infections; urinary tract infections (UTIs); skin infections; and most acute respiratory tract and gastrointestinal infections are viral.[173]

» **Medicines:** Drugs sometimes cause fever. For example, beta-lactam antibiotics (such as penicillin) and sulfa drugs can trigger a fever. Drugs that can cause an extremely high temperature include certain illicit drugs (such as cocaine, amphetamines, and phencyclidine), anesthetics, and antipsychotic drugs.[173] Drug fever is a not infrequent event complicating and confusing patient management. Tissue-toxic drugs such as amphotericin B may cause fever without an immunologic mechanism. Moreover, fever is a component of the Jarisch–Herxheimer reaction, which follows release of endotoxin from organisms (e.g., Treponema pallidum) lysed by the action of the antimicrobial drug (e.g., penicillin). Currently, the penicillins and cephalosporins are the most common cause of drug fever. However, other causative drugs, such as the aminoglycosides, phenytoin, quinidine, procainamide, iodides, and methyldopa, may be encountered in a professional lifetime.[174]

» **Vaccines in general:** It is important that, when fever is being considered as an AEFI, it be evaluated not only in the context of its temporal association with immunization but also in conjunction with other historical and clinical observations that may identify a coincident and unrelated cause. There are difficulties in trying to calculate the risks attributable to a vaccine. For example, clinical trials of routine childhood vaccines have shown that fever typically occurs in 1–10% of vaccinees but can be as frequent as from 30% to > 70% among vaccinees receiving multiple vaccines or DTwP vaccine. Subjects' temperature in these studies was rarely > 39°C (> 102.2°F) and fever was typically self-limiting.

Without the possibility of valid comparison, the calculation of the risk attributable to the vaccine was therefore impossible.[170]

- **Vaccines against COVID-19 SARS-CoV-2:** COVID-19 vaccines have been introduced globally, and millions of people are being vaccinated with various types of vaccines, many of which use new vaccine platforms.[22] Fever following immunization has been reported in clinical trials and by countries for different vaccines among AEFIs.[24]

FATIGUE

A standardized definition of fatigue as an AEFI was developed by a working group formed within BC.

Category: Systemic events

Listed: BC/SPEAC

Rationale for inclusion: Wide range of fatigue states applicable to immunization safety.[175]

About the AESI: Chronic fatigue syndrome was defined by the presence of debilitating fatigue and associated symptoms that must have been coincidentally present for at least 6 months.[175]

Case definition: The CD by the BC Group removes the effort requirement as a central component. However, it includes the consequences of fatigue (functional impairment) as a key descriptor. Fatigue is defined as a perception of lack of energy, or a feeling of tiredness that affects physical and mental activity, which differs from drowsiness or lack of motivation (may be aggravated by, but is not primarily attributed to, exertion or diagnosable illness).[175] (Complete_casedefintion_fatigue)

Event rating scale[172]

Event rating scale	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potential life threat (Grade 4)
	Does not interfere with activity	Some interference with activity	Prevents routine daily activity	Emergency visit or hospitalization for severe fatigue

Fatigue risk factors:

- **Diseases and other factors:** Most serious (and many minor) acute and chronic illnesses produce fatigue. However, many of these have other more prominent manifestations (e.g., pain, cough, fever, jaundice) as the presenting complaint.
  - The most common disorders manifesting predominantly as recent fatigue (lasting < 1 month) are drug adverse effects, anemia, stress, and/or depression.
  - The most common causes manifesting predominantly as prolonged fatigue (lasting 1–6 months) are diabetes, hypothyroidism, sleep disturbances (e.g., sleep apnea), and cancer.
  - The most common causes manifesting predominantly as chronic fatigue (lasting > 6 months) are myalgic encephalomyelitis/systemic exertion intolerance disease/chronic fatigue syndrome, postviral fatigue syndrome, psychological causes (e.g., depression), and drugs.

  Several factors commonly cause or contribute to a chief complaint of fatigue, usually prolonged or chronic fatigue.[176]

- **Medicines:** Antidepressants, antihistamines (first generation), antihypertensives, cocaine cessation (usually recent fatigue), diuretics that cause hypokalemia, muscle relaxants, recreational drugs, sedatives.[176]
- **Vaccines in general:** Vaccines, especially those containing poorly degradable aluminum particulate adjuvants, constitute a major type of adverse effect such as myalgia encephalomyelitis / chronic fatigue syndrome.[177] Cited as one of the main systemic adverse events after vaccination with HA and HB vaccines.[21]
- **Vaccines against COVID-19 SARS-CoV-2:** COVID-19 vaccines have been introduced globally, and millions of people are being vaccinated with various types of vaccines, many of which use new vaccine platforms.[22] Fatigue following immunization has been reported in clinical trials and by countries for different vaccines among AEFIs.[24]

JOINT PAIN

A standardized definition of joint pain (arthralgia and arthritis) as an AEFI was developed by a working group formed within BC.

Category: Systemic events

Listed: BC/SPEAC

Rationale for inclusion: Possible causality of AEFI.[85]

About the AESI: "Arthritis and arthralgia are reported as AEFI with various vaccines. The current evidence linking vaccination to incident arthritis or worsening arthritis is too heterogeneous and incomplete to infer a causal association."[85]

Case definition: Joint pain (arthralgia) or joint inflammation with swelling, redness, and/or warmth (arthritis) that is associated with limitation of regular activities and lasts 24 hours or longer. The temporal criteria for arthritis/arthralgia occur 0–30 days following immunization with an inactivated vaccine or 0–42 days following immunization with a live vaccine.[178] [179] (Complete_casedefinition_jointpain)

Event rating scale[172]

Event rating scale	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potential life threat (Grade 4)
	Does not interfere with activity	Some interference with activity	Prevents routine daily activity	Emergency visit or hospitalization for severe new or worsening joint pain

Joint pain risk factors:

- Diseases and other factors: Joint pain can be the first symptom of a disorder that affects other organs in the body, such as an autoimmune disorder or a whole-body infection. Symptoms of some autoimmune disorders can include fever, mouth sores, and rash. Pain that develops in one joint can also be the first symptom of a disorder that eventually affects many joints.[180] Joint pain refers to discomfort, aches, and soreness in any of the body's joints. Joint pain is a common complaint. Sometimes, joint pain is the result of an illness or injury. The joint pain can be caused by arthritis, bursitis, or inflammation of the cushioning pads around joints, lupus, gout, certain infectious diseases, such as mumps, influenza, and hepatitis, chondromalacia of the patella, or a breakdown of the cartilage in the kneecap, an injury,

tendinitis, or inflammation of the tendon, an infection of the bone or joint overuse of a joint, cancer, fibromyalgia, osteoporosis, sarcoidosis, rickets.[181]

- **Medicines:** Some medicines to treat melanoma (vemurafenib, dabrafenib).[182]
- **Vaccines in general:** The link between vaccination and arthritis or arthralgia may be limited to specific vaccines, evidence by vaccine type (e.g., influenza vaccines, HPV vaccines), with a focus on clinical trials and observational studies providing measures of association with corresponding measures of variance. In the review of studies, vaccines as influenza, rubella, HB, HPV, meningococcal, pneumococcal, rabies, MMR, HA, and DTwP were mentioned as possible to cause joint pain as an adverse event.[85] As general systemic manifestations, joint pain was cited as a possible occurrence in less than 1% of those vaccinated with 23-valent pneumococcal (manifestations are mild and transient, disappearing in approximately 24 hours), and after vaccination with yellow fever.[21] Transient arthritis or arthralgia is not a contraindication to further doses of vaccine.[7]
- **Vaccines against COVID-19 SARS-CoV-2:** COVID-19 vaccines have been introduced globally, and millions of people are being vaccinated with various types of vaccines, many of which use new vaccine platforms.[22] Joint pain was one of the most reported side effects, which typically lasted several days with the Moderna vaccine.[183] One of the common adverse events (may affect more than 1 in 10 people) cited by Serum Institute of India was joint pain.[184]

DIARRHEA

A standardized definition of diarrhea or diarrhea as an AEFI was developed by a working group formed within BC.

Category: Systemic events

Listed: BC/SPEAC

Rationale for inclusion: Diarrhea is also a commonly reported AEFI in both passive surveillance systems and clinical trials, for both oral and nonoral vaccines.[185]

About the AESI: A common medical condition, characterized by increased frequency of bowel movements and increased liquidity of stool. Acute diarrhea is typically self-limiting, but it can be severe and lead to profound dehydration, which can lead to abnormally low blood volume, low blood pressure, and damage to the kidneys, heart, liver, brain, and other organs. Children and older persons are particularly prone to dehydration secondary to diarrhea. In epidemiological studies, diarrhea is usually defined as the passage of three or more loose or watery stools in a 24-h period, a loose stool being one that takes the shape of a stool container.[185]

Case definition: The CD is structured into two levels of diagnostic certainty, with a level of diagnostic certainty that is primarily intended for epidemiological purposes and not as a criterion for treatment, defining a clinical entity without inferring a causal relationship to a given exposure.[185] (Complete_casedefinition_diarrhea)

Event rating scale [172]

Event rating scale	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potential life threat (Grade 4)
	2–3 loose stools in 24 hours	4–5 loose stools in 24 hours	6 or more loose stools in 24 hours	Emergency visit or hospitalization for severe diarrhea

Diarrhea risk factors:

- **Diseases and other factors:** Rotavirus gastroenteritis and several other infectious diarrheal agents: Vibrio cholerae, enterotoxigenic Escherichia coli, rotavirus, and Shigella species. Relevant past medical conditions that may affect the evaluation of diarrhea as an AEFI, including recent hospitalizations, diseases, or travel.[185] Diarrhea is a symptom of infections caused by a few bacterial, viral, and parasitic organisms, most of which are spread through water contaminated with feces. Rotavirus and Escherichia coli are the two most common etiologic agents of moderate to severe diarrhea in low-income countries. Other pathogens, such as Cryptosporidium and Shigella species, may also be important. Site-specific etiological patterns also need to be considered. Other causes such as poor personal hygiene, food when it is prepared or stored in unsanitary conditions, unsafe domestic storage and handling of water, and polluted fish and seafood can also contribute to the disease.[186] In frequent ingestion of dairy products, the development of constant diarrhea is common.[187]
- **Medicines:** Laxatives, antacids containing magnesium, caffeine, anticancer drugs, many antibiotics, colchicine, quinine/quinidine, prostaglandin analogues, and excipients (e.g., lactose) in mouthwashes can also contribute to the disease. In diarrhea caused by antibiotics, antibiotics attack the body's good and bad bacteria, thereby destroying the intestinal microbiota and making digestion difficult. Depending on the type of medication, diarrhea can be constant, especially if the medication needs to be taken every day for a long time.[187]
- **Vaccines in general:** Temporary diarrhea can occur after the rotavirus vaccine.[188] Diphtheria and tetanus vaccine for adults, diphtheria, tetanus and pertussis vaccine, adenovirus vaccine, cholera vaccine, meningococcal B vaccine, and typhoid fever vaccine.[189]
- **Vaccines against COVID-19 SARS-CoV-2:** COVID-19 vaccines have been introduced globally, and millions of people are being vaccinated with various types of vaccines, many of which use new vaccine platforms.[22] Diarrhea is one of the frequent reactions with the COVID-19 vaccine. It could be a sign that the vaccinee's body is making an immune response to the vaccine. It should disappear within 1–2 days.[190] Diarrhea following immunization has been reported in clinical trials and by countries for different vaccines among AEFIs.[24]

CHILLS

A standardized definition of chills as an AEFI was developed by a working group formed within BC.

Category: Systemic events

Rationale for inclusion: Chills are also a commonly reported AEFI in both passive surveillance systems and clinical trials, for both oral and nonoral vaccines.[189]

About the AESI: A feeling of cold without apparent cause, which can occur when muscles expand and contract repeatedly and vessels in the skin contract. Chills can occur with fever and cause chills or shivering. These can be constant, and each episode can last up to an hour. Chills can also occur periodically and last for several minutes.[191] The search for adverse events of rigors and chills has been associated with nausea, neoplasms, headache, infectious disorder, and reaction to medications. Rigors and chills as an adverse event has been linked to fibroblast activation.[192] Chills are the subjective reports of shivering or shaking associated with rapid changes in body temperature. They result from involuntary muscle contractions that occur in response to a sudden lowering of body temperature below the prevailing set point.[193]

Case definition: Cold feeling accompanied by shaking.[192] (Complete_casedefinition_chills)

Event rating scale[172]

Event rating scale	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potential life threat (Grade 4)
	Does not interfere with activity	Some interference with activity	Prevents routine daily activity	Emergency visit or hospitalization for severe chills

Chills risk factors:

- **Diseases and other factors:** Some chills occur after exposure to a cold environment. They can also occur in response to a bacterial or viral infection that causes fever. Chills are commonly associated with bacterial or viral gastroenteritis, influenza, meningitis, sinusitis, pneumonia, streptococcal pharyngitis, UTIs, and malaria.[191]

  Research of rigors and chills as an adverse event has been linked to nausea, neoplasms, headache, infective disorder, medication reaction.[192]

  Health conditions that can cause chills: bacterial infections such as listeria, pneumonia, and UTIs; cancer such as leukemia; hangover; blood sugar (hypoglycemia) in people with diabetes; menopausal night sweats or hot flashes, panic attacks; parasitic infections such as giardiasis; sepsis; viruses including those that cause the flu; general anesthesia for surgery; adrenaline surge after a traumatic event such as an accident or near miss. Psychological trauma, including posttraumatic stress disorder, can also make a person feel shaky.[194] Chills are an important symptom with certain diseases such as malaria.[195]

  "Goose bumps" are not the same as chills. Goose bumps occur due to cold air. They can also be caused by strong emotions such as shock or fear. With goose bumps, the hair on the body sticks up from the skin to form a layer of insulation. When a person has chills, they may or may not have goose bumps.[195]
- **Medicines:** Drug withdrawal (substance abuse).[194]
- **Vaccines in general:** Chills can occur after vaccination against meningitis B and for pneumococcal 13V.[189]
- **Vaccines against COVID-19 SARS-CoV-2:** COVID-19 vaccines have been introduced globally, and millions of people are being vaccinated with various types of vaccines, many of which use new vaccine platforms.[22] Chills are among the most common adverse events reported in adults after vaccination against COVID-19.[196] Chills following immunization have been reported in clinical trials and by countries for different vaccines among AEFIs.[24]

HEADACHE

A standardized definition of headache as an AEFI was developed by a working group formed within BC.

Category: Systemic events

Rationale for inclusion: Possible side effects after receiving the COVID-19 vaccine.

About the AESI: Headache disorders, characterized by recurrent headaches, are among the most common disorders of the nervous system.[197] Headache is a pain in any region of the head. Headaches may occur on one or both sides of the head, be isolated to a certain location, radiate across the head from one point, or have a viselike quality. A headache may appear as a sharp pain, a throbbing sensation, or a dull ache. Headaches can develop gradually or suddenly and may last from less than an hour to several days.[198]

Case definition: Headache is pain in any region of the head. It can occur on one or both sides of the head, be isolated to a particular location, radiate through the head from one point, or have a sensation of screw pressure.[198] (Complete_casedefinition_headache)

Event rating scale[172]

Event rating scale	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potential life threat (Grade 4)
	Does not interfere with activity	Some interference with activity	Prevents routine daily activity	Emergency visit or hospitalization for severe headache

Headache risk factors:

- **Diseases and other factors:** Headache are a painful and disabling feature of a small number of primary headache disorders, namely migraine, tension-type headache, and cluster headache. About 50% has been estimated for the prevalence of headache among adults (symptomatic at least once in the past year). Half to three-quarters of adults ages 18–65 worldwide have had headaches in the past year, and, among these individuals, 30% or more have reported migraine. Headache on 15 or more days each month affects 1.7–4.0% of the world's adult population. Despite regional variations, headache disorders are a worldwide problem, affecting people of all ages, ethnicities, income levels, and geographical areas.[197] The cause of a secondary headache may be pregnancy, systemic conditions, such as an infection, hypothyroidism, giant cell arteritis, stroke, brain tumor.[199] Complaints suggestive of new daily persistent headache following recovery from SARS-CoV2 infection, which is characterized by a clear and distinct onset, persistent headache. It is known that extracranial viral infections are the main triggering factor of new daily persistent headache, in addition to stressful life events and invasive procedures such as intubation. Headache is a frequent symptom associated with ongoing SARS-CoV2 infection (up to 34%); however, headache persistence has been observed even weeks after recovery.[200] Some primary headaches can be triggered by lifestyle factors, including: alcohol, particularly red wine; certain foods, such as processed meats that contain nitrates; changes in sleep or lack of sleep; poor posture; skipped meals; and stress.[198]
- **Medicines:** Headache can also be caused by or occur secondarily to a long list of other conditions, the most common of which is a medication-overuse headache.[197] An adverse drug reaction is a response to a drug that is noxious and unintended and occurs at doses normally used in people for the prophylaxis, diagnosis, or therapy for the disease, or for modification of physiological function. Headache as adverse drug reaction: amoxicillin, carbamazepine, diclofenac, famotidine, ibuprofen, immune globulin, infliximab, ketorolac, leflunomide, levamisole, metronidazole, naproxen, ranitidine, rofecoxib, sulfamethoxazole, sulfasalazine, sulindac, tolmetin, trimethoprim, valacyclovir. others as amiodarone, anabolic steroids, contraceptives combination, ciprofloxacin, danazol, corticosteroids, gentamicin, lithium carbonate, nalidixic acid, nitrofurantoin, ofloxacin, retinoic acid, tetracycline, thyroid hormone replacement, vitamin A. Related to substance withdrawal are caffeine-withdrawal headache, opioid-withdrawal headache, estrogen-withdrawal headache, ergotamine-withdrawal headache, cocaine-withdrawal headache, methysergide-withdrawal headache.[201]
- **Vaccines in general:** Adverse event such as possible headache with HA, HPV, influenza, meningococcal B, pneumococcal 13V, rabies, tetanus, Td, TDaP, yellow fever, zoster vaccine, adenovirus vaccine, against cholera, Japanese encephalitis, and typhoid fever.[189]
- **Vaccines against COVID-19 SARS-CoV-2:** COVID-19 vaccines have been introduced globally, and millions of people are being vaccinated with various types of vaccines, many of which use new vaccine platforms.

[22] Headache following immunization has been reported in clinical trials and by countries for different vaccines among AEFIs.[24]

LOCAL REACTIONS (AT THE INJECTION SITE)

A standardized definition of local reactions as an AEFI was developed by a working group formed within BC, defining specific local reactions as nodule, cellulitis, abscess, induration, swelling, and pain.[202]

Category: Local reactions

Rationale for inclusion: Local reactions are common AEFI, among the most common adverse events reported.[202] Local injection-site reactions such as swelling, redness, and/or pain may occur with up to 80% of vaccine doses, depending on the type of vaccine. Local reactions generally occur within a few hours of the injection, are usually mild, and do not require any specific treatment.[203]

About the AESI: The local reactions can be identified from coding terminologies for injection-site adverse events, abscess, cellulitis, induration, pain/tenderness, rash, swelling.[202]

Case definition:

Local reactions – The general definition: This was developed by the BC group and will allow for an improvement in the comparability of data and better understanding of the injection-site and related local reactions. It serves three different purposes: [1] to determine whether a local reaction can be present, that is, act as a screening tool for the presence of any local reaction; [2] as the decision that a local reaction is present to further guide the decision of which specific local reaction is present; and [3] along with the guidelines to serve as a tool to collect, analyze, and present the information necessary to allow for standardized assessment of a local reaction.[202] (Complete_casedefinition_local_reactions)

Nodule: The discrete (i.e., well-demarcated) clinical feature of a nodule at injection site sufficiently differentiates it from the more common clinical picture of acute induration and swelling, which are more diffuse and of shorter duration. Moreover, no clear cut-off time based on duration and onset of a nodule at injection site versus acute induration and swelling could be identified based on the current understanding of these reactions. A nodule is a solid formation (lump) of more than 2.5 cm in diameter that persists for more than a month, caused by epidermal thickening, inflammatory infiltration of the skin or subcutaneous tissues, or by deposits of substances at the administration site. Nodules are firm and may include increased sensitivity, pain, and itching.[204] (Complete_casedefinition_nodule)

Cellulitis: This is defined as an acute, infectious, and expanding inflammatory condition of the skin that is characterized by the following inclusion and exclusion criteria. Of note, cellulitis may be accompanied by fever and/or regional lymphadenopathy; however, their presence or absence does not influence the level of diagnostic certainty. The clinical manifestations of cellulitis is related to the infecting organism and the vaccination technique, and not the vaccine administered. Because cellulitis as an AEFI is usually a bacterial infection, it is commonly treated empirically with antimicrobial agents. However, identification of the etiologic agent is useful in adapting therapy and avoiding overtreatment with antimicrobial agents of large noninfectious local reactions.[205] (Complete_casedefinition_cellulitis)

Abscess: An abscess at an injection site is a collection of localized soft-tissue materials is defined as an abscess of infectious etiology that may be accompanied by fever and/or regional lymphadenopathy and sterile abscess.[206] (Complete_casedefinition_abscess)

Induration: Induration and swelling at the injection site are commonly reported local reactions following immunization. However, there are no standardized definitions of swelling and induration, and it may be that the term induration is used as synonym for swelling in some reports.[207] (Complete_casedefinition_induration)

Swelling: Swelling at the injection site is the most frequent AEFI reported and in vaccine clinical trials. The swelling at or near the injection site is defined as an increase in size or volume at the injection site that may extend to the entire limb according to severity. It is currently unknown whether localized swelling at or near the injection site and "whole or upper or extensive limb swelling" are pathophysiologically different events.[208] (Complete_casedefinition_swelling)

Immunization site pain: This is an unpleasant sensory and emotional experience associated with actual or potential tissue damage and is the most frequent local AEFI. Pain results from the stimulation of nociceptive sensory neurons at the time of vaccine administration or inflammatory process in the damaged tissue afterwards.[209] (Complete_casedefinition_sitepain)

Redness: This can occur at the injection site. In general, it is a mild and well-tolerated manifestation, lasting 24–48 hours. Local inflammatory signs usually subside within the first 24 hours following vaccine application.[21] Redness at the injection site is common and an expected reaction to vaccine administration. The injection of foreign material into the tissues and irritation of the tissues by the process of injection can produce a localized inflammatory response.[7] (Complete_casedefinition_redness)

Event rating scale[172]

Event rating scale	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potential life threat (Grade 4)
Local reactions	Does not interfere with activity	Some interference with activity	Prevents routine daily activity	Emergency visit or hospitalization for severe pain
Swelling and redness	> 2.0–5.0 cm (5–10 instrument measurement units)	> 5.0–10.0 cm (11–20 instrument measurement units)	> 10 cm (≥ 21 instrument measurement units)	Necrosis or exfoliative dermatitis

Local reactions risk factors:

- **Diseases and other factors:** Extrinsic and intrinsic factors can impact the reactogenicity profile, tolerability, and immunogenicity of vaccines in each individual. They include host characteristics, such as age, gender, ethnicity, body mass, general health and preexisting immunity, and vaccine administration and composition factors, such as route and site of administration, injection technique, type of antigen, vaccine formulation, and type of adjuvant.

  Host characteristics that can influence reactogenicity: Age (functions of the immune and nervous systems evolve throughout life – these changes have implications for defense against infectious diseases at different ages, and can also influence susceptibility to adverse reactions to vaccination); gender (women tend to experience higher incidences a the injection site, but not systemic symptoms after vaccination, and may experience higher rates of immediate hypersensitivity reactions with possible explanations related to genetic or hormonal differences); psychological/physical stressors and circadian cycles (stress in various forms and circadian cycles are known to influence the immune system and in particular the inflammatory response); overweight/obesity (has been demonstrated to be associated with low-level chronic inflammation; however, studies suggest that increases in reactogenicity in the overweight population are most likely due to vaccine administration technique and not to body mass itself); preexisting immunity (preexisting before vaccination and vaccine-induced).[210]
- **Medicines:** An adverse drug reaction is an undesired and unintended response to a drug that occurs with usual therapeutic doses.[211]

- **Vaccines in general:** May cause local reactions after vaccination: DTaP, Hib, HPV, influenza, meningococcal B, pneumococcal 13V, polio, anti-rabies, Td, HB, HA, MMR, MMRV, meningococcal ACWY, pneumococcal 23V, poliomyelitis, yellow fever, zoster, Japanese encephalitis, typhoid fever.[189]
- **Vaccines against COVID-19 SARS-CoV-2:** COVID-19 vaccines have been introduced globally, and millions of people are being vaccinated with various types of vaccines, many of which use new vaccine platforms.[22] Local reaction following immunization has been reported in clinical trials and by countries for different vaccines among AEFIs.[24]

MALAISE

Category: Systemic events

Rationale for inclusion: Possible side effects after receiving the COVID-19 vaccine.

About the AESI: Malaise is a symptom that can occur with almost any health condition. It may start slowly or quickly, depending on the type of disease.[212] The condition of not being in good health. "Her symptoms included fatigue and general malaise."[213]

Case definition: General feeling of discomfort, illness, or lack of well-being.[212] (Complete_casedefinition_malaise)

Malaise risk factors:

- **Diseases and other factors:** There are numerous possible causes of malaise, such as an injury, disease, or trauma, a musculoskeletal condition, arthritis, osteoarthritis or rheumatoid arthritis, acute viral disorders (HIV/AIDS, fibromyalgia, Lyme disease, hepatitis), or chronic fatigue syndrome (a complex disorder that is characterized by a feeling of overall pain). The chronic conditions that may cause malaise are severe anemia, congestive HF, chronic obstructive pulmonary disease, kidney disease, liver disease, diabetes, and mental health conditions. Other causes of malaise can include parasitic infections, influenza, mononucleosis, cancer, adrenal gland dysfunction, and diabetes.[214]
- **Medicines:** Medications that can also put a person at risk of malaise include anticonvulsants, some medications used to treat high blood pressure and heart disease, specifically beta-blockers, medications used to treat psychiatric conditions, and antihistamines. Some medications may not cause malaise on their own but can lead to malaise when combined with other medications.[214]
- **Vaccines in general:** Vaccines against typhoid, cholera, zoster, TDaP, Td, PPSV23, PCV13, meningococcal B, DTaP can cause the feeling of being sick (as an AEFI). Complemented by influenza, anti-rabies, anti-varicella immunoglobulin vaccines.[21]
- **Vaccines against COVID-19 SARS-CoV-2:** COVID-19 vaccines have been introduced globally, and millions of people are being vaccinated with various types of vaccines, many of which use new vaccine platforms.[22] Malaise following immunization has been reported in clinical trials and by countries for different vaccines among AEFIs.[24]

MUSCLE PAIN (MYALGIA)

Category: Systemic events

Rationale for inclusion: Possible side effects after receiving the COVID-19 vaccine.

About the AESI: Common pain that may involve more than one muscle.[215]

Case definition: It is described as muscle pain, pain associated with ligaments, tendons, and soft tissues that connect bones, organs, and muscles.[215] (Complete_casedefinition_musclepain)

Event rating scale[172]

Event rating scale	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potential life threat (Grade 4)
	Does not interfere with activity	Some interference with activity	Prevents routine daily activity	Emergency visit or hospitalization for new severe pain or worsening muscle pain

Muscle pain risk factors:

- **Diseases and other factors:** Not all muscle aches are related to stress, tension, and physical activity. Some medical explanations for myalgia include fibromyalgia, especially if aches and pains last longer than 3 months, chronic fatigue syndrome, myofascial pain syndrome (which causes inflammation in muscular connective tissues called fasciae), infections (such as the flu, polio, or bacterial infections), autoimmune disorders (such as lupus, dermatomyositis, and polymyositis), and thyroid problems (such as hypothyroidism or hyperthyroidism hypokalemia [low potassium]).[215]
- **Medicines:** Certain medications or drugs, such as statins, ACE inhibitors, or cocaine.[215]
- **Vaccines in general:** Vaccines against yellow fever, HZ, anthrax, influenza, ACWY, meningococcal B, and Japanese encephalitis can lead to muscle pain with AEFI.[189]
- **Vaccines against COVID-19 SARS-CoV-2:** COVID-19 vaccines have been introduced globally, and millions of people are being vaccinated with various types of vaccines, many of which use new vaccine platforms.[22] Muscle pain malaise following immunization has been reported in clinical trials and by countries for different vaccines among AEFIs.[24]

NAUSEA/VOMITING

Category: Systemic events

Rationale for inclusion: Possible side effects after receiving the COVID-19 vaccine.

About the AESI: Nausea and vomiting are symptoms of many different conditions, including early pregnancy, concussions, and stomach flu. Drinking cold drinks and eating bland, tasteless foods can help with nausea and vomiting in adults and children.[217]

Case definition: Nausea and vomiting are not diseases, but rather are symptoms of many different conditions, such as infection (stomach flu), food poisoning, motion sickness, overeating, blocked intestine, illness, concussion or brain injury, appendicitis, and migraines.[217] (Complete_casedefinition_NauseaVomiting)

Event rating scale[172]

Event rating scale	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potential life threat (Grade 4)
	1–2 times in 24 hours	> 2 times in 24 hours	Requires IV hydration	Emergency visit or hospitalization for hypotensive shock

Nausea and vomiting risk factors:

- **Diseases and other factors:** Nausea and vomiting can occur in both children and adults. People who are undergoing cancer treatments, such as radiation therapy or chemotherapy, have an increased risk of nausea and vomiting. Pregnant women in their first trimester may also experience nausea and vomiting, commonly referred to as "morning sickness." It is estimated that 50–90% of pregnant women experience nausea, while 25–55% experience vomiting. The causes of nausea and vomiting are quite similar: seasickness and other motion sicknesses, early pregnancy, intense pain, exposure to chemical toxins, emotional stress (fear), gallbladder disease, food poisoning, indigestion, various viruses, and certain smells or odors. The causes of vomiting differ according to age. For adults, vomiting is commonly a result of a viral infection and food poisoning, and occasionally a result of motion sickness and illnesses in which the person has a high fever. For children, it is common for vomiting to occur because of a viral infection, food poisoning, motion sickness, overeating or feeding, coughing, and illnesses in which the child has a high fever. Although rare, blocked intestines can cause vomiting, most typically in early infancy. Usually, vomiting is harmless, but it can be a sign of a more serious illness such as concussion, encephalitis, meningitis, intestinal blockage, appendicitis, migraine headaches, or brain tumors. Another concern with vomiting is dehydration.[217]
- **Medicines:** Vomiting associated with radiation therapy, anticancer drugs, alcohol, and morphine can often be treated with another type of drug therapy.[217]
- **Vaccines in general:** DTaP, rotavirus, typhoid, live-attenuated influenza vaccine, cholera, and zoster vaccines can lead to adverse events such as nausea and vomiting.[189]
- **Vaccines against COVID-19 SARS-CoV-2:** COVID-19 vaccines have been introduced globally, and millions of people are being vaccinated with various types of vaccines, many of which use new vaccine platforms.[22] Nausea/vomiting following immunization has been reported in clinical trials and by countries for different vaccines among AEFIs.[24]

NEUTROPENIA

Category: Systemic events

Rationale for inclusion: Possible side effects after receiving the COVID-19 vaccine.

About the AESI: Neutropenia is a reduction in the blood neutrophil count. If it is severe, the risk and severity of bacterial and fungal infections increases. Focal symptoms of infection may go unnoticed, but there is a fever during most serious infections. Diagnosis is made by leukocyte count with differential formulas, but evaluation requires identifying the cause. If fever is present, an infection is presumed, and immediate empirical treatment with broad-spectrum antibiotics is required, especially when neutropenia is severe. Treatment with granulocyte colony-stimulating factor is sometimes helpful.[218]

Case definition:

Transient neutropenia is associated with a transient fall in the neutrophil count, and many of the underlying causes are reversible.[218] (Complete_casedefinition_neutropenia)

Neutropenia risk factors:

- **Diseases and other factors:** Numerous factors may cause neutropenia through destruction, decreased production, or abnormal storage of neutrophils: cancer and cancer treatments, leukemia, chemotherapy, radiation therapy, infections, chickenpox, EBV, hepatitis A, B, or C, HIV/AIDS, measles, Salmonella infection, sepsis (an overwhelming bloodstream infection),

autoimmune diseases, granulomatosis with polyangiitis (formerly called Wegener's granulomatosis), lupus, rheumatoid arthritis, bone marrow disorders, aplastic anemia, myelodysplastic syndromes, myelofibrosis; conditions present at birth, such as Kostmann's syndrome (a disorder involving low production of neutrophils), unknown reasons (called chronic idiopathic neutropenia), vitamin deficiencies, abnormalities of the spleen. People can have neutropenia without an increased risk of infection. This is known as benign neutropenia.[219]

- **Medicines:** A common cause of neutropenia are the medications used to treat overactive thyroid, such as methimazole (Tapazole) and propylthiouracil; certain antibiotics, including vancomycin (Vancocin), penicillin G and oxacillin; antiviral drugs, such as ganciclovir (Cytovene) and valganciclovir (Valcyte); anti-inflammatory medication for conditions such as ulcerative colitis or rheumatoid arthritis, including sulfasalazine (Azulfidine); some antipsychotic medications, such as clozapine (Clozaril, Fazaclo, others), and chlorpromazine; drugs used to treat irregular heart rhythms, including quinidine and procainamide; levamisole — a veterinary drug that is not approved for human use in the United States, but may be mixed in with cocaine; cancer chemotherapy.[219]
- Vaccines in general: Clinical trials and literature review reported several cases of neutropenia in the first two weeks after vaccination, although it was usually transient, with a benign clinical outcome, with several new candidates or well-known licensed vaccines.[220]
- **Vaccines against COVID-19 SARS-CoV-2:** COVID-19 vaccines have been introduced globally, and millions of people are being vaccinated with various types of vaccines, many of which use new vaccine platforms.[22] Postimmunization neutropenia has been monitored by countries for different vaccines among AEFIs.[24]

ALLERGIC REACTIONS

Category: Systemic reactions

Rationale for inclusion: Possible side effects after receiving the COVID-19 vaccine.

About the AESI: A disorder characterized by an adverse local or general response from exposure to an allergen. A local or general reaction of an organism following contact with a specific allergen to which it has been previously exposed and to which it has become sensitized. Altered reactivity to an antigen, which can result in pathologic reactions upon subsequent exposure to that antigen.[221]

Case definition:

An allergic reaction of the skin including any one of the following: urticaria (hives), erythema, pruritus, prickling (or tingling) sensation, localized or generalized edema (in the deeper layers of the skin, subcutaneous tissues, or mucosa lining the throat, airways, and gut), which can occur 0–2 days following immunization.[222] (Complete_casedefinition_allergicreactions)

Allergic reactions risk factors:

- **Diseases and other factors:** Substances that often cause reactions are pollen, dust mites, mold spores, pet dander, food, insect stings, medicines. Genes and the environment have something to do this reaction. The immune system normally fights germs (body's defense system), but, in most allergic reactions, however, it is responding to a false alarm. An allergen induces type I IgE-mediated or type IV T-cell-mediated immune responses (house dust mite feces, animal dander, pollens [tree, grass, weeds], molds, foods, insect saliva and venom [transmitted by bites and stings], drugs, latex,

household chemicals). Allergic triggers are almost always low-molecular-weight proteins; many of them can become attached to airborne particles.[222]

- Medicines: Drug hypersensitivity is an immune-mediated reaction to a drug. Symptoms range from mild to severe and include rash, anaphylaxis, and serum sickness. Abacavir, allopurinol, carbamazepine, fosphenytoin, phenytoin, lamotrigine.[223]
- Vaccines in general: According to many IgE-mediated reactions and immediate-type allergic reactions, the primary allergens are proteins. Those most frequently implicated in vaccine allergies are egg and gelatin, with perhaps rare reactions to yeast or latex (the average rate of reactions of the immediate type in children and adolescents is 0.22 per 100,000 vaccine doses, 31% with reports of immediate-type reactions after the first vaccination). Vaccines cited as likely for allergic reactions are MMR, MMRV, rabies, typhoid, yellow fever, zoster, influenza, inactivated polio vaccine;[224] others such as diphtheria and tetanus, conjugated meningococcal C.[21]
- Vaccines against COVID-19 SARS-CoV-2: COVID-19 vaccines have been introduced globally, and millions of people are being vaccinated with various types of vaccines, many of which use new vaccine platforms.[22] Allergic reactions following immunization has been reported in clinical trials and by countries for different vaccines among AEFIs.[24]

COMPLETE CASE DEFINITIONS, PART A

Anaphylaxis
Complete case definition for AESI[13]

Level 1 of diagnostic certainty:

• ≥ 1 major dermatological **AND**

• ≥ 1 major cardiovascular **AND/OR** ≥ 1 major respiratory criterion.

Level 2 of diagnostic certainty:

• ≥ 1 major cardiovascular **AND** ≥ 1 major respiratory criterion **OR**

• ≥ 1 major cardiovascular **OR** respiratory criterion **AND**

• ≥ 1 minor criterion involving ≥ 1 different system (**other than** cardiovascular or respiratory systems) **OR**

• (≥ 1 major dermatologic) **AND** (≥ 1 minor cardiovascular **AND/OR** minor respiratory criterion).

Level 3 of diagnostic certainty:

• ≥ 1 minor cardiovascular **OR** respiratory criterion **AND**

• ≥ 1 minor criterion from each of ≥ 2 different systems/categories.

The case definition (CD) should be applied when there is no clear alternative diagnosis for the reported event to account for the combination of symptoms.

Major and minor criteria used in the case definition of anaphylaxis

Criteria	Major	Minor
Dermatologic or mucosal	• generalized urticaria (hives) or generalized erythema • angioedema, localized or generalized* • generalized pruritus with skin rash	• generalized pruritus without skin rash • generalized prickle sensation • localized injection-site urticaria • red and itchy eyes
Cardiovascular	• measured hypotension • clinical diagnosis of uncompensated shock, indicated by the combination of at least three of the following: tachycardia, capillary refill time > 3 s, reduced central pulse volume, decreased level of consciousness or loss of consciousness	• reduced peripheral circulation as indicated by the combination of at least two of: - tachycardia, - a capillary refill time of > 3 s without hypotension, and - a decreased level of consciousness
Respiratory	• bilateral wheeze (bronchospasm) • stridor • upper airway swelling (lip, tongue, throat, uvula, or larynx) • respiratory distress – 2 or more of the following: tachypnoea, increased use of accessory respiratory muscles (sternocleidomastoid, intercostals, etc.), recession, cyanosis, grunting	• persistent dry cough, hoarse voice • difficulty breathing without wheeze or stridor • sensation of throat closure • sneezing, rhinorrhea
Gastrointestinal		• diarrhea, abdominal pain, nausea, vomiting
Laboratory		• mast cell tryptase elevation > upper normal limit

* Not hereditary angioedema.

Return_to_Anaphylaxis

Thrombosis with thrombocytopenia syndrome (TTS) Complete case definition for AESI (interim)[26]

Level 1 BC thrombosis thrombocytopenia syndrome case criteria

• A platelet count of less than 150,000/ul of new onset without history of receipt of heparin within 100 days

AND

Imaging study, surgical, or pathology findings consistent with thrombosis/thromboembolism

- Imaging studies include any of the following, depending on the location of the lesion
- Ultrasound – Doppler
- Computed tomography (CT scan) – contrast/angiography
- Magnetic resonance venography (MRV) or arteriography (MRA)
- Echocardiogram
- Perfusion V/Q scan
- Conventional angiography / digital subtraction angiography

OR

- Procedure that confirms the presence of a thrombus (e.g., thrombectomy)

OR

- Pathology consistent with thrombosis/thromboembolism including biopsy or autopsy

Most appropriate imaging test depends on the location of the lesion. Any of the tests listed may be used as available. Based on radiologist/expert interpretation.

Beyond the presence of thrombocytopenia (TP), additional abnormal laboratory clotting study results are not required for confirmation as they can be normal in presence of thrombotic/thromboembolic events. When present, they can be supportive of the diagnosis, including:

- D-dimer elevated above the upper limit of normal for age;
- Shortened prothrombin time (PT), partial thromboplastin time (PTT) – below the lower limit of normal for age.

Level 1-H BC thrombosis thrombocytopenia syndrome case criteria are the same as Level 1 EXCEPT that the case has a history of heparin exposure within 100 days of symptom onset.

Level 2 BC thrombosis thrombocytopenia syndrome criteria (modified) – probable case

- A platelet count of less than 150,000/ ul of new onset without recent history of receiving heparin within 100 days.

AND

Clinical presentation consistent with thrombosis or thromboembolism event, including

- Specific clinical syndromes including any of the following
- Deep vein thrombosis (DVT) – symptoms will depend on the location of the thrombosis, for example: swelling, pain, redness, or warmth of an extremity; headache, visual disturbance, seizures for sinus vein thrombosis; abdominal pain for intra-abdominal thrombosis
- Pulmonary thromboembolism (PE) – sudden onset shortness of breath, pleuritic chest pain, sudden death / pulseless electrical activity arrest (Wells criteria for scoring – based on clinical findings)

- Stroke
- Myocardial infarction
- Arterial thrombosis

AND

- Supporting imaging or laboratory (D-dimer) findings suggestive but not definitive of thrombosis/ thromboembolism including any of the following
- Chest radiograph
- Echocardiogram
- CT scan without contrast

OR

- D-dimer – elevated above the upper limit of normal for age.

Level 2-H BC thrombosis thrombocytopenia syndrome case criteria are the same as Level 2 EXCEPT that the case has a history of heparin exposure within 100 days of symptom onset.

Level 2 BC thrombosis criteria – possible case (modified)

- A platelet count of less than 150,000/ul of new onset without recent history of receiving heparin within 100 days.

AND

Clinical presentation consistent with thrombosis or thromboembolism event, including any of the following specific clinical syndromes (see full list in the flow diagram below):

- DVT – symptoms will depend on the location of the thrombosis, for example: swelling, pain, redness, or warmth of an extremity; headache, visual disturbance, seizures for sinus vein thrombosis, abdominal pain for intra-abdominal thrombosis
- PE – sudden onset shortness of breath, pleuritic chest pain, sudden death/pulseless electrical activity arrest (Wells criteria for scoring – based on clinical findings)
- Stroke
- Myocardial infarction
- Arterial thrombosis.

Level 3-H BC thrombosis thrombocytopenia syndrome case criteria are the same as Level 3 EXCEPT that the case has a history of heparin exposure within 100 days of symptom onset.

According to BC, the decision-tree algorithm for case-finding of thrombocytopenia thrombosis syndrome (TTS).

Return_to_TTS

Thrombocytopenia
Complete case definition for AESI[37]

The case definition of Robert Wise et al. to BC:

Level 1 of diagnostic certainty: Platelet counta less than 150 × 109/L AND confirmed by blood smear examination OR the presence of clinical signs and symptoms of spontaneous bleedingb

Level 2 of diagnostic certainty: Platelet counta less than 150 × 109/L

Level 3 of diagnostic certainty: Not applicable

Notes:

[a] Measured by an automated hematology analyzer or assessed by hand count of platelets on a cell count slide.

[b] Presentations of spontaneous (i.e., non-traumatic) bleeding include purpura (i.e., petechiae, purpura sensu stricto, ecchymosis), hemorrhagic oozing of skin lesions including rashes, hematoma, bruising, hematemesis, hematochezia, occult bleeding per rectum, epistaxis, hemoptysis, hematuria, vaginal bleeding other than menstruation, conjunctival bleeding, intracranial bleeding.

The review CD of TP for SPEAC[41] presents key caveats for diagnosis, data analysis and presentation and key elements of the CD:

- There are only two levels of certainty based on the platelet count (150×10^9/L), regardless of whether there is a peripheral smear made to rule out agglomeration as a cause of TP and clinical evidence of spontaneous bleeding;
- The working group chose the limit of 150 instead of 100 based on the former being the reference value most used in the revised hematological literature.

The working group deliberately avoided defining idiopathic TP or idiopathic thrombocytopenic purpura because the observed event is TP with or without clinical manifestations. The labeling of an idiopathic TP event was considered to imply that a causal association with the vaccine had already been excluded.

Return_to_Thrombocytopenia

Generalized convulsion
Complete case definition for AESI[46]

Bonhoeffer et al. standardized as a case definition for generalized convulsive seizure as an AEFI:

Level 1 of diagnostic certainty: Witnessed sudden loss of consciousness

AND

Generalized, tonic, clonic, tonic–clonic, or atonic motor manifestations.

Level 2 of diagnostic certainty: History of unconsciousness

AND

Generalized, tonic, clonic, tonic–clonic, or atonic motor manifestations.

Level 3 of diagnostic certainty: History of unconsciousness

AND

Other generalized motor manifestations.

Return_to_Generalized_Convulsion

Guillain Barré syndrome (GBS)
Complete case definition for AESI[48]

Sejvar James et al. standardized as a case definition for Guillain-Barré syndrome (GBS):

Level 1 of diagnostic certainty:

Bilateral AND flaccid weakness of the limbs, AND decreased or absent deep tendon reflexes in weak limbs, AND monophasic illness pattern, AND interval between onset and nadir of weakness between 12 h and 28 days, AND subsequent clinical plateau, AND electrophysiological findings consistent with GBS, AND cytoalbuminologic

dissociation (i.e., elevation of cerebrospinal fluid [CS]F protein level above laboratory normal value AND CSF total white cell count < 50 cells/μl), AND absence of an identified alternative diagnosis for weakness.

Level 2 of diagnostic certainty:

Bilateral **AND** flaccid weakness of the limbs, **AND** decreased or absent deep tendon reflexes in weak limbs, **AND** monophasic illness pattern, **AND** interval between onset and nadir of weakness between 12 h and 28 days, **AND** subsequent clinical plateau, **AND** CSF total white cell count < 50 cells/μl l (with or without CSF protein elevation above laboratory normal value), OR if CSF not collected or results not available, electrophysiological studies consistent with GBS, **AND** absence of identified alternative diagnosis for weakness.

Level 3 of diagnostic certainty:

Bilateral **AND** flaccid weakness of the limbs, **AND** decreased or absent deep tendon reflexes in weak limbs, **AND** monophasic illness pattern, **AND** interval between onset and nadir of weakness between 12 h and 28 days, **AND** subsequent clinical plateau, **AND** absence of identified alternative diagnosis for weakness.[54]

Law stresses that chronic demyelinating inflammatory polyneuropathy should be differentiated from GBS; the clinical picture may be identical, but chronic demyelinating inflammatory polyneuropathy tends to appear within 8 weeks or more and weakness tends to remit and relapse. It is important to ensure that the degree and distribution of limb weakness are assessed, and that deep tendon reflexes are assessed in all weak limbs, and if possible, by obtaining an assessment from a neurologist (manual muscle testing using the Medical Research Council scale; deep tendon reflexes; examination of sensory and cranial nerves; presence or absence of ataxia, measures of functionality or impairment).

Typically, for GBS, there is a steady progression in weakness to a low point, followed by a plateau, fatal outcome, or gradual improvement. Therapies such as immunoglobulins or steroids can cause fluctuations in levels of weakness – all of which must be carefully documented. They usually occur within the first 9 weeks. Level 1 of certainty requires white blood count (WBC) and CSF protein results showing cytoalbumin dissociation (WBC < 50, elevated protein) and characteristic electrophysiological test results (electromyography, nerve conduction studies) as described.

It is important to note that electrophysiological tests may be normal if obtained within the first 7 days after symptom onset. If normal, the test should be repeated if possible. Level 2 of certainty can be achieved with CSF or electrophysiological tests instead of both. Nerve conduction studies may be normal if performed within 7 days of onset of weakness. If normal at that time, they should be repeated after 1–2 weeks. Level 3 depends exclusively on clinical findings, of which the most important are the requirements for the GBS (not the Miller variant of Fisher) that deep tendon reflexes are absent or diminished in the same limbs that are weak.

Return_to_GBS

Acute disseminated encephalomyelitis Complete case definition for AESI[59]

Sejvar James et al. standardized a CD for acute disseminated encephalomyelitis (ADEM).

Level 1 of diagnostic certainty:

(a) Demonstration of diffuse or multifocal areas of demyelination by histopathology

OR

(b) Focal or multifocal findings referable to the central nervous system (CNS), including one or more of the following:

1. Encephalopathy (see CD for encephalitis for specification of encephalopathy)
2. Focal cortical signs (including but not limited to aphasia, alexia, agraphia, cortical blindness)
3. Cranial nerve abnormality/abnormalities
4. Visual field defect/defects
5. Presence of primitive reflexes (Babinski's sign, glabellar reflex, snout/sucking reflex)
6. Motor weakness (either diffuse or focal, more often focal)
7. Sensory abnormalities (either positive or negative, sensory level)
8. Altered deep tendon reflexes (hypo- or hyper-reflexia, asymmetry of reflexes) or
9. Cerebellar dysfunction, including ataxia, dysmetria, cerebellar nystagmus

AND

(c) Magnetic resonance imaging (MRI) findings displaying diffuse or multifocal white matter lesions on T2-weighted, diffusion-weighted imaging, or fluid-attenuated inversion recovery sequences (± gadolinium enhancement on T1 sequences)

AND

(d) Monophasic pattern to illness (i.e., absence of relapse within a minimum of 3 months of symptomatic nadir).

Level 2 of diagnostic certainty:

(a) Focal or multifocal findings referable to the CNS, including one or more of the following:

1. Encephalopathy (see CD for encephalitis for specification of encephalopathy)
2. Focal cortical signs (including but not limited to aphasia, alexia, agraphia, cortical blindness)
3. Cranial nerve abnormality/abnormalities
4. Visual field defect/defects
5. Presence of primitive reflexes (Babinski's sign, glabellar reflex, snout/sucking reflex)
6. Motor weakness (either diffuse or focal, more often focal)
7. Sensory abnormalities (either positive or negative, sensory level)
8. Altered deep tendon reflexes (hypo- or hyper-reflexia, asymmetry of reflexes) or
9. Cerebellar dysfunction, including ataxia, dysmetria, cerebellar nystagmus

AND

(b) MRI findings displaying diffuse or multifocal white matter lesions on T2-weighted, diffusion-weighted imaging, or fluid-attenuated inversion recovery sequences (± gadolinium enhancement on T1 sequences)

AND

(c) Insufficient follow-up time achieved to document absence of relapse within a minimum period of 3 months following symptomatic nadir.

Level 3 of diagnostic certainty:

(a) Focal or multifocal findings referable to the CNS, including one or more of the following:

1. Encephalopathy (see CD for encephalitis for specification of encephalopathy)
2. Focal cortical signs (including but not limited to aphasia, alexia, agraphia, cortical blindness)
3. Cranial nerve abnormality/abnormalities
4. Visual field defect/defects
5. Presence of primitive reflexes (Babinski's sign, glabellar reflex, snout/sucking reflex)

6. Motor weakness (either diffuse or focal, more often focal)

7. Sensory abnormalities (either positive or negative, sensory level)

8. Altered deep tendon reflexes (hypo- or hyper-reflexia, asymmetry of reflexes) or

9. Cerebellar dysfunction, including ataxia, dysmetria, cerebellar nystagmus.

Level 3A of diagnostic certainty:

Insufficient information is available to distinguish case between acute encephalitis or ADEM; case unable to be definitively classified.

Exclusion criteria for all levels of diagnostic certainty:

- Presence of a clear alternative acute infectious or other diagnosis for illness. Recurrence or relapse of illness at any point following a 3-month period of clinical improvement from symptomatic nadir; or, if known, MRI findings or histopathologic data inconsistent with the diagnosis of ADEM.

Return_to_ADEM

Acute encephalitis
Complete case definition for AESI[59]

James J. Sejvar, et al. reviewed the definition with its guidelines.

Level 1 of diagnostic certainty: Encephalitis

(a) Demonstration of acute inflammation of CNS parenchyma (± meninges) by histopathology.

Level 2 of diagnostic certainty: Encephalitis

(a) Encephalopathy (e.g., depressed or altered level of consciousness, lethargy, or personality change lasting > 24 h).

AND INCLUDING

(b) **ONE OR MORE** of the following:

1. Decreased or absent response to environment, as defined by response to loud noise or painful stimuli

2. Decreased or absent eye contact

3. Inconsistent or absent response to external stimuli

4. Decreased arousability

5. Seizure associated with loss of consciousness

OR

(c) Focal or multifocal findings referable to the CNS, including one or more of the following:

1. Focal cortical signs (including but not limited to: aphasia, alexia, agraphia, cortical blindness)

2. Cranial nerve abnormality/abnormalities

3. Visual field defect/defects

4. Presence of primitive reflexes (Babinski's sign, glabellar reflex, snout/sucking reflex)

5. Motor weakness (either diffuse or focal, more often focal)

6. Sensory abnormalities (either positive or negative, sensory level)

7. Altered deep tendon reflexes (hypo- or hyper-reflexia, reflex asymmetry)

8. Cerebellar dysfunction, including ataxia, dysmetria, cerebellar nystagmus

AND (for both possibilities to reach Level 2)

(d) **TWO OR MORE** of the following indicators of inflammation of the CNS:

1. Fever (temperature ≥ 38 °C)
2. CSF pleocytosis (> 5 WBC/mm3 in children > 2 months of age; > 15 WBC/mm in children < 2 months of age)
3. Electroencephalogram findings consistent with encephalitis or
4. Neuroimaging consistent with encephalitis.

Level 3 of diagnostic certainty: Encephalitis

(a) Encephalopathy (e.g., depressed or altered level of consciousness, lethargy, or personality change lasting > 24 h)

AND INCLUDING

(b) **ONE OR MORE** of the following:

1. Decreased or absent response to environment, as defined by response to loud noise or painful stimuli
2. Decreased or absent eye contact
3. Inconsistent or absent response to external stimuli
4. Decreased arousability **OR**
5. Seizure associated with loss of consciousness

OR

(c) Focal or multifocal findings referable to the CNS, including one or more of the following:

1. Focal cortical signs (including but not limited to: aphasia, alexia, agraphia, cortical blindness)
2. Cranial nerve abnormality/abnormalities
3. Visual field defect/defects
4. Presence of primitive reflexes (Babinski's sign, glabellar reflex, snout/sucking reflex)
5. Motor weakness (either diffuse or focal, more often focal)
6. Sensory abnormalities (either positive or negative, sensory level)
7. Altered deep tendon reflexes (hypo- or hyperreflexia, reflex asymmetry) or
8. Cerebellar dysfunction, including ataxia, dysmetria, cerebellar nystagmus

AND (for both possibilities to reach Level 3)

(d) **ONE** of the following indicators of inflammation of CNS:

1. Fever (temperature ≥ 38 °C)
2. CSF pleocytosis (> 5 WBC/mm3 in children > 2 months of age; > 15 WBC/mm3 in children < 2 months of age)
3. Electroencephalogram findings consistent with encephalitis or
4. Neuroimaging consistent with encephalitis.

Level 3A of diagnostic certainty:

(a) Insufficient information is available to distinguish case between acute encephalitis or ADEM; case unable to be definitively classified.

Exclusion criterion for Levels 2 and 3 of diagnostic certainty:

(a) Other diagnosis for illness present.

Return_to_Acute_Encephalitis

Acute myelitis
Complete case definition for AESI[64]

Level 1 of diagnostic certainty: Myelitis

(a) Demonstration of acute spinal cord inflammation (± meninges) by histopathology.

Level 2 of diagnostic certainty: Myelitis

(a) Myelopathy (development of sensory, motor, or autonomic dysfunction attributable to the spinal cord, including upper and/or lower motor neuron weakness, sensory level, bowel and/or bladder dysfunction, erectile dysfunction)

AND

(b) TWO OR MORE of the following indicators suggestive of spinal cord inflammation:

1. Fever (temperature ≥ 38 °C)

2. CSF pleocytosis (> 5 WBC/mm3 in children > 2 months of age; > 15 WBC/mm3 in children < 2 months of age)

3. Neuroimaging findings demonstrating acute inflammation (± meninges), or demyelination of the spinal cord.

Level 3 of diagnostic certainty: Myelitis

(a) Myelopathy (development of sensory, motor, or autonomic dysfunction attributable to the spinal cord, including upper and/or lower motor neuron weakness, sensory level, bowel and/or bladder dysfunction, erectile dysfunction)

AND

(b) ONE of the following indicators suggestive of spinal cord inflammation:

1. Fever (temperature ≥ 38 °C)

2. CSF pleocytosis (> 5 WBC/mm3 in children > 2 months of age; > 15 WBC/mm3 in children < 2 months of age)

3. Neuroimaging findings demonstrating acute inflammation (± meninges), or demyelination of the spinal cord.

Exclusion criterion for Levels 2 and 3 of diagnostic certainty:

(a) Other diagnosis for illness present.

Cases fulfilling the criteria for both encephalitis and myelitis in any category would be classified as encephalomyelitis.

Return_to_Acute_Myelitis

Aseptic meningitis
Complete case definition for AESI[65]

Terhi Tapiainen et al. reviewed the definition with its guidelines:

Level 1 of diagnostic certainty: Clinical evidence of acute meningitis such as fever, headache, vomiting, bulging fontanelle, nuchal rigidity, or other signs of meningeal irritation, AND pleocytosis in CSF[a] determined as:

- > 5 leukocytes/mm3 (L) if patient is 2 months of age[b] or older,
- > 15 leukocytes/mm3 (L) in infants younger than 2 months;[b]

AND

Absence of any microorganism on Gram stain of CSF, **AND** negative routine bacterial culture of CSF in the absence of antibiotic treatment before obtaining the first CSF sample.

Level 2 of diagnostic certainty: Clinical evidence of acute meningitis such as fever, headache, vomiting, bulging fontanelle, nuchal rigidity, or other signs of meningeal irritation, **AND** pleocytosis in CSF[a] determined as:

- » > 5 leukocytes/mm3 (L) if patient is 2 months of age[b] or older,
- » > 15 leukocytes/mm3 (L) in infants younger than 2 months;[b]

AND

Absence of any microorganism on Gram stain of CSF, AND no bacterial culture of CSF obtained, OR negative culture in the presence of antibiotic treatment before obtaining the first CSF sample.

Level 3 of diagnostic certainty: Not applicable

If the case meets criteria for aseptic meningitis and encephalitis case definition, it should be reported only as encephalitis.

[a] In presumed traumatic lumbar puncture (i.e., erythrocytes in the CSF without other known cause such as head trauma, hemorrhagic stroke, or necrotizing encephalitis), CSF pleocytosis is defined as a > 1:1 ratio of observed and predicted leukocytes in CSF. Predicted CSF leukocytes are calculated by using the formula: predicted CSF leukocytes = CSF erythrocytes × (blood leukocytes/blood erythrocytes). In the absence of data on blood erythrocytes and leukocytes, pleocytosis can be defined as a > 1:500 ratio of CSF leukocytes and CSF erythrocytes.

[b] Chronological age (birth date).

Return_to_Aseptic_Meningites

Facial nerve palsy
Complete case definition for AESI[68]

Rath et al. reviewed the definition with its guidelines:

Level 1 of diagnostic certainty:

Manifests with the acute-onset decreased ability (paralysis **OR** paresis) to wrinkle the forehead **OR** to raise the eyebrows at the affected side.

Given the lack of consensus about the term Bell's palsy and the sometimes synonymous use with peripheral facial nerve palsy, the aim is not to describe a definition for Bell's palsy. Instead, an algorithm/decision tree has been developed that ultimately leads to a common definition of idiopathic facial nerve palsy by systematically excluding known causes of such palsies. This approach has been chosen as it is most relevant for vaccinologists to identify and confirm true cases of idiopathic palsies.

(a) Peripheral facial nerve palsy

Initially, the diagnosis of acute-onset peripheral facial nerve palsy needs to be confirmed. Peripheral facial nerve palsy is defined as a weakness of the facial muscles innervated by cranial nerve VII, which is either complete (paralysis) **OR** incomplete (paresis)[1, 2] and may manifest unilaterally OR bilaterally.[3]

Level 2 of diagnostic certainty: Not applicable

Level 3 of diagnostic certainty: Not applicable

(b) Idiopathic peripheral facial nerve palsy

For all levels of diagnostic certainty: Idiopathic peripheral facial nerve palsy has an **unknown etiology**, which has a sudden onset[4] **AND** shows initial rapid progression of symptoms and signs[5] **AND** shows resolution.[6]

Level 1 of diagnostic certainty: Remains unexplained after excluding known causes[7] by review of clinical history **AND** physical examination, **AND** laboratory investigations, **AND** radiological studies.

Level 2 of diagnostic certainty: Remains unexplained after excluding known causes7 by review of clinical history **AND** physical examination, **AND** laboratory investigations.

Level 3 of diagnostic certainty: Remains unexplained after excluding known causes7 by review of clinical history **AND** physical examination.

Notes for the CD:

[1] Facial muscle weakness: Weakness of facial muscle activity would include decreased movement of the corner of the mouth on the affected side, decreased ability to close the eye on the affected side, or decreased movement of the forehead skin on the affected side. In most cases of peripheral facial nerve palsy, the weakness would involve all branches of the facial nerve. In some cases of peripheral facial nerve palsy, there may be obvious involvement of only one or two branches of the facial nerve. Such cases will meet the case definition, if all of the remaining criteria are fulfilled.

[2] Decreased facial muscles movement: Decreased movement of facial muscles in infants and young children and other persons with limited ability to cooperate in an examination (e.g., persons with dementia) may be based on a period of observation for spontaneous or provoked movement of the affected muscles.

[3] Unilateral versus bilateral palsy: Bilateral peripheral facial nerve palsy is an unusual manifestation. All attempts to exclude an alternative cause for the bilateral facial weakness should be attempted in the setting of this clinical entity.

[4] Sudden onset: This criterion refers to an event that occurred unexpectedly and without warning leading to a marked change in a subject's previously stable condition.

[5] Rapid progression: This criterion refers to the worsening of disease over a short period of time.

[6] Resolution occurs: There is symptom and sign resolution, with or without treatment.

[7] Multiple causality: Known causes of facial nerve palsy include the diagnosis of an alternative illness (listed below).

Over half of all cases of acute-onset peripheral facial nerve palsy are considered Bell's palsy. The annual incidence rate is estimated to be 13–53 cases per 100,000 population. The prognosis of Bell's palsy is usually excellent.

Return_to_Facial_Nerve_Palsy

Vaccine associated enhanced disease (VAED) Complete case definition for AESI[72]

Vaccine-associated enhanced respiratory disease (VAERD).[77] Refers to the predominant lower respiratory tract presentation of vaccine-associated enhanced disease (VAED). The mechanisms of pathogenesis might be specific to the lower respiratory tract or part of a systemic process.

CD and levels of certainty (LOC) of VAED

Level 1 of diagnostic certainty (definitive case): The working group considers that a definitive case (LOC 1) of VAED cannot be ascertained with current knowledge of the mechanisms of pathogenesis of VAED.

Level 2 of diagnostic certainty (probable) rationale for Level 2: Ascertainment is based on confirmed infection, with known (2A, higher level of certainty [LOC]) or without previously known (2B, lower certainty) serostatus, clinical and epidemiologic criteria, and available histopathology.

Level 2A: A probable case of VAED is defined by the occurrence of disease in a previously seronegative vaccinated individual with: laboratory confirmed infection with the pathogen targeted by the vaccine **AND** clinical findings of disease involving one or more organ systems (a case of VAERD if the lung is the primarily affected organ) **AND** severe disease as evaluated by a clinical severity index/score (systemic in VAED or specific to the lungs in VAERD) **AND** increased frequency of severe outcomes (including severe disease, hospitalization, and mortality) when compared to a nonvaccinated population (control group or background rates) **AND** evidence of immunopathology in target organs involved by histopathology, when available, including any of the following:

- Present or elevated tissue eosinophils in tissue;
- Elevated pro-inflammatory Th2 cytokines in tissue (IL4, IL5, IL10, IL13);
- C4d tissue deposition (evidence for complement activation through immune complex deposition);
- C1q assessments of immune complexes in fluids;
- Low C3 levels as evidence complement consumption **AND** no identified alternative etiology.

Level 2B: A probable case of VAED is defined by the occurrence of disease in a vaccinated individual with no prior history of infection and unknown serostatus, with: laboratory confirmed infection with the pathogen targeted by the vaccine **AND** clinical findings of disease involving one or more organ systems (a case of VAERD if the lung is the primarily affected organ) **AND** severe disease as evaluated by a clinical severity index/score (systemic in VAED or specific to the lungs in VAERD) **AND** increased frequency of severe outcomes (including severe disease, hospitalization, and mortality) when compared to a nonvaccinated population (control group or background rates) **AND** evidence of immunopathology in target organs involved by histopathology, if available, including any of the following:

- Present or elevated tissue eosinophils in tissue.
- Elevated pro-inflammatory Th2 cytokines in tissue (IL4, IL5, IL10, IL13);
- C4d tissue deposition (evidence for complement activation through immune complex deposition);
- C1q assessments of immune complexes in fluids;
- Low C3 levels as evidence complement consumption **AND** no identified alternative etiology.

Level 3 of diagnostic certainty (possible) rationale for Level 3: Ascertainment is based on confirmed or suspected infection, known (3A higher LOC) or unknown (3B lower LOC) serostatus, clinical and epidemiologic criteria, but no histopathology findings.

Level 3A: A possible case of VAED is defined by the occurrence of disease in a previously seronegative vaccinated individual with: laboratory confirmed infection with the pathogen targeted by the vaccine **AND** clinical findings of disease involving one or more organ systems (a case of VAERD if the lung is the primarily affected organ) **AND** severe disease as evaluated by a clinical severity index/score (systemic in VAED or specific to the lungs in VAERD) **AND** increased frequency of severe outcomes (including severe disease, hospitalization, and mortality) when compared to a nonvaccinated population (control group or background rates) **AND** no identified alternative etiology.

Level 3B: A possible case of VAED is defined by the occurrence of disease in vaccinated individual with no prior history of infection and unknown serostatus, with: laboratory confirmed infection with the pathogen targeted by the vaccine **AND** clinical findings of disease involving one or more organ systems (a case of VAERD if the lung is the primarily affected organ) **AND** severe disease as evaluated by a clinical severity index/score (systemic in VAED or specific to the lungs in VAERD) **AND** increased frequency of severe outcomes (including severe disease, hospitalization, and mortality) when compared to a nonvaccinated population (control group or background rates) **AND** no identified alternative etiology.

Return_to_VAED

Multisystem inflammatory syndrome (MIS C/A) Complete case definition for AESI[74, 75]

Tiphanie Vogel et al. developed a consensus CD and defined levels of diagnostic certainty, after an exhaustive review of the literature and expert consultation.

Level 1 of diagnostic certainty – definitive case:

Age < 21 years (multisystem inflammatory syndrome in children [MIS-C][a]) **OR** ≥ 21 years (multisystem inflammatory syndrome in adults [MIS-A]) **AND** fever ≥ 3 consecutive days **AND** two or more of the following clinical features:

- Mucocutaneous (rash, erythema or cracking of the lips/mouth/pharynx, bilateral nonexudative conjunctivitis, erythema/edema of the hands and feet);
- Gastrointestinal (abdominal pain, vomiting, diarrhea);
- Shock/hypotension;
- Neurologic (altered mental status, headache, weakness, paresthesia, lethargy).

AND

Laboratory evidence of inflammation including any of the following:

Elevated C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), ferritin, or procalcitonin[b] **AND** two or more measures of disease activity:

- Elevated brain natriuretic peptide (BNP) or N-terminal proBNP (NT-proBNP) or troponin;[b]
- Neutrophilia, lymphopenia, or TP;[b]
- Evidence of cardiac involvement by echocardiographyc or physical stigmata of heart failure;[d]
- Electrocardiogram (ECG) changes consistent with myocarditis or myo-pericarditis[e]

AND

Laboratory confirmed SARS-CoV-2 infection[f] **OR** personal history of suspected COVID-19 within 12 weeks **OR** close contact with known COVID-19 case within 12 weeks **OR** following SARS-CoV-2 vaccination.[g]

Level 2 of diagnostic certainty – probable case:

Level 2a:

Same criteria as Level 1 except: One measure of disease activity **AND** within 12 weeks of a personal history of known or strongly suspected COVID-19 **OR** within 12 weeks of close contact with a person with known or strongly suspected COVID-19 **OR** following SARS-CoV-2 vaccination.[g]

Level 2b:

Same criteria as Level 1 except: Fever lasting 1–2 days and can be subjective.

Level 3 of diagnostic certainty – possible case:

Level 3a:

Age < 21 years (MIS-C) **OR** ≥ 21 years (MIS-A) AND fever ≥ 3 consecutive days **AND** two or more of the following clinical features:

- Mucocutaneous (rash, erythema or cracking of the lips/mouth/pharynx, bilateral nonexudative conjunctivitis, erythema/edema of the hands and feet);
- Gastrointestinal (abdominal pain, vomiting, diarrhea);
- Shock/hypotension;
- Neurologic (altered mental status, headache, weakness, paresthesia, lethargy);
- Physical stigmata of heart failure: gallop (**IF** diagnosed by expert) or rales, lower extremity edema, jugular venous distension, hepatosplenomegaly.

AND

No laboratory markers of inflammation or measures of disease activity available **AND** within 12 weeks of a personal history of known or strongly suspected COVID-19 **OR** within 12 weeks of close contact with a person with known or strongly suspected COVID-19 **OR** following SARS-CoV-2 vaccination.g

Level 3b:

Same criteria as Level 2a except: Fever lasting 1–2 days and can be subjective.

Level 4 of diagnostic certainty – insufficient evidence:

Reported MIS-C/A with insufficient evidence to meet Levels 1–3 in the case definition.

Example:

Two clinical features and history of COVID-19 within 12 weeks, but laboratory results and measures of disease activity are not available, and the fever criterion is not met.

Level 5 of diagnostic certainty – not a case of MIS-C/A:

Sufficient clinical and laboratory evidence exists to ascertain that a case is **NOT** MIS-C/A.

An alternative diagnosis has been ascertained.

Note: At all levels of certainty, minimal to mild respiratory symptoms may be present and their presence does not exclude a case of MIS-C/A. However, a case must be excluded if there is concern for acute COVID-19-related pulmonary disease. Further, one of the critical components of the CD is that it is only applied when there is no clear alternative diagnosis for the reported event.

[a] MIS-C = multisystem inflammatory syndrome in children; MIS-A = multisystem inflammatory syndrome in adults; CRP = C-reactive protein (detected by any measure); ESR = erythrocyte sedimentation rate; BNP = brain natriuretic protein; NT-proBNP = N-terminal proBNP; ECG = electrocardiogram; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2; COVID-19 = coronavirus disease 2019.

[B] Laboratory values are defined as low or high based on local laboratory normal ranges.

[c] Echocardiographic signs: dysfunction, wall motion abnormality, coronary abnormality (dilation, aneurysm, echo brightness, lack of distal tapering), valvular regurgitation, pericardial effusion, evidence of abnormal left ventricular strain.

[d] Physical stigmata of heart failure: gallop (IF diagnosed by expert) or rales, lower extremity edema, jugular venous distension, hepatosplenomegaly.

[e] ECG changes consistent with myocarditis or myo-pericarditis: abnormal ST segments and/or arrhythmia and/or pathologic Q waves and/or atrioventricular (AV) conduction delay and/or PR segment depression and/or low voltage QRS.

[f] Laboratory evidence of SARS-CoV-2 infection: serologic evidence of SARS-CoV-2 infection or SARS-CoV-2 nucleic acid amplification positivity or SARS-CoV-2 antigen positivity.

[g] If a known or suspected COVID-19 infection has not occurred within the preceding 12 weeks.

Return_to_MIS_C_A

Acute respiratory distress syndrome
Complete case definition for AESI[77]

Category	Adult	Pediatric
Level 1 confirmed acute respiratory distress syndrome (ARDS)	Berlin definition To make diagnosis, must meet ALL the following criteria: 1. Hypoxemia – P/F ratio ≤ 300 2. Positive pressure requirement: 3. – PEEP/CPAP ≥ 5 cmH2O 4. Imaging: Chest imaging with bilateral chest opacities not explained by other process 5. Origin of edema: not related to fluid overload or cardiogenic edema 6. Timing: within 1 week of known clinical insult*	Pediatric Acute Lung Injury Consensus Conference (PALICC) definition To make diagnosis, must meet ALL the following criteria: 1. Hypoxemia – P/F ≤ 300 or S/F ≤ 264 for non-intubated patients – OI ≥ 4 or OSI ≥ 5 for intubated patients 2. Positive pressure Requirement: 3. – PEEP/CPAP ≥ 5 cm H2O 4. Imaging: Chest imaging findings of new infiltrate(s) consistent with acute pulmonary parenchymal disease 5. Origin of edema: new infiltrate not related to fluid overload or cardiogenic edema 6. Timing: within 1 week of known clinical insult*

Category	Adult	Pediatric
Level 2 probable ARDS	Meet Berlin definition excluding positive predictive value requirement (#2) **AND** If PaO2 unavailable, then can classify as Level 2a using S/F criteria **OR** If CXR/CT unavailable, then can classify as Level 2b using chest US^	Meet PALICC definition excluding positive predictive value requirement (#2) **AND** If PaO2 unavailable, then can classify as Level 2a using S/F criteria **OR** If CXR/CT unavailable, then can classify as Level 2b using chest US^
Level 3 suspected ARDS	Strong clinical concern but CXR, CT, or US not available to meet Berlin Definition • Diagnosis based on clinical exam and assessment+	Strong clinical suspicion but CXR, CT, or US not available to meet all PALICC Definition • Diagnosis based on clinical exam and assessment
Level 4 clinical suspicion for ARDS	Clinical suspicion but insufficient data to classify as Level 1–3	Clinical suspicion but insufficient data to classify as Level 1–3
Level 5 Not a case of ARDS	Patients that do not meet above criteria for ARDS but may have hypoxemia and/ or chest imaging findings due to other pathologic process	Patients that do not meet above criteria for ARDS but may have hypoxemia and/ or chest imaging findings due to other pathologic process

Abbreviations: P/F ratio – PaO2 to FiO2 ratio (arterial oxygen pressure to inspired fraction of oxygen ratio); S/F ratio – saturation by pulse oximeter to FiO2 ratio; PEEP – positive end-expiratory pressure; CPAP – continuous positive airway pressure; CXR – chest X ray; CT = chest tomography; US = ultrasound; OI = oxygenation index; OSI = oxygen saturation index.

* Timing criteria for ARDS, may vary after vaccination.

^ Severity as defined by S/F: For adults, mild ≤ 315 but > 235, moderate ≤ 235 but > 144, severe S/F ≤ 144. For pediatrics, mild ≤ 264 but > 221, moderate ≤ 221 but > 150, severe S/F ≤ 150.

Return_to_ARDS

Sensorineural hearing loss
Complete case definition for AESI[80]

The definition can be applied to any subject, regardless of age or clinical presentation. While some subjects may present with self-recognized hearing loss or other clinical symptoms such as tinnitus, or because of concerns from contacts who have observed difficulty understanding everyday conversation, frequently asking others to repeat things, social avoidance, difficulty hearing with background noise, or turning up the volume of sound equipment, some individuals with sensorineural hearing loss (SNHL) might have no clinical symptoms or concerns. This is more likely to occur with milder severity or unilateral SNHL.

The criteria for ascertainment of a case of SNHL based on level of diagnostic certainty are described as:

SNHL is hearing loss of ≥ 30 dB in three sequential frequencies in the standard pure-tone audiogram.

Levels of diagnostic certainty:

Level 1 (definite case):

A physical examination excluding conductive hearing loss;

AND

Audiometry consistent with SNHL.

Level 2 (probable case):

A physical examination excluding conductive hearing loss;

AND

Auditory brainstem response test consistent with SNHL;

OR

Tuning fork exam consistent with SNHL.

Level 3 (possible case):

A physical examination excluding conductive hearing loss;

AND

Otoacoustic emissions test consistent with hearing loss;

OR

Behavioral or neurodevelopmental testing questionnaire concerning for hearing loss;

OR

Remote screening using telehealth technology concerning for hearing loss.

A physical examination that excludes possible causes of hearing loss includes the clinical observation and inspection of the ears to demonstrate that there are no anomalies or obstruction of the ear canal, and that the tympanic membrane is visible, intact, and mobile, with no evidence of middle ear disease. An audiometry consistent with SNHL is one that shows 30 dB or more hearing loss over 3 consecutive frequencies.
The audiometry can be a limiting factor for a definitive diagnosis when adequate equipment and appropriately trained personnel are not available. However, the diagnosis of SNHL may be established at a lower level of certainty (probable case), with a physical examination that excludes conductive hearing loss and by performing standard tests that can differentiate conductive vs. SNHL utilizing a an ABR or Tuning fork test, as described in this document.

Return_to_SNHL

Single organ cutaneous vasculitis Complete case definition for AESI[81]

For the case definition, Zanoni et al. adopted the term single organ cutaneous vasculitis (SOCV), which refers to small-vessel vasculitis of the skin where systemic involvement has been excluded. SOCV is a syndrome characterized by clinical and histological features of small-vessel vasculitis of the skin without involvement of other organ systems.[86]

For all levels of diagnostic certainty: Clinical features, hemorrhagic papules OR urticaria-like lesions OR purpuric rash involving the face, ears, and extremities AND edema AND low-grade fever (only for acute hemorrhagic edema of infancy).

Level 1 of diagnostic certainty: Histology

Perivascular inflammatory cells infiltrates dominated by neutrophils with fragmented nuclei (leukocytoclasia);

AND

Erythrocyte extravasation or hemorrhage into the dermis, **AND** fibrinoid necrosis or degeneration of the dermal postcapillary venules;

AND

Exclusion of other vasculitic organ system involvement:

- normochromic normocytic anemia, TP;

- renal involvement (proteinuria, hematuria, hypertension, increased serum creatinine);
- pulmonary involvement (dyspnea, cough, hemoptysis, patchy or diffuse alveolar infiltrates in chest X ray);
- gastrointestinal involvement (abdominal pain, vomiting, gastrointestinal bleeding);
- liver involvement (elevated liver enzymes and bilirubin);
- serosal involvement (pericardial and or pleural effusion) with ultrasound and/or X-ray examination in case of clinical suspicion;
- arthritis (synovitis) with synovial aspirate in case of clinical suspicion;
- central or peripheral nervous system involvement by neurologic physical examination;
- presence of antinuclear antibodies, antineutrophilic cytoplasmic antibody, rheumatoid factor, anticitrullinated peptides antibodies, cryoglobulins;
- reduced serum complements factors (C3, C4, C1q);
- serologic evidence of hepatitis C, hepatitis B, EBV, parvovirus B19 serology, antistreptolysin-O titer.

Level 2 of diagnostic certainty: Histology

Perivascular inflammatory cells infiltrates dominated by neutrophils with fragmented nuclei (leukocytoclasia);

AND

erythrocyte extravasation or hemorrhagic into the dermis, AND exclusion of other organ or systemic involvement (see Level 1).

Level 3 of diagnostic certainty: Histology – not available

AND

Exclusion of other organ or systemic involvement (see Level 1).

Return_to_SOCV

Acute aseptic arthritis
Complete case definition for AESI[83]

Woerner et al. define acute aseptic arthritis (AAA) as a clinical syndrome characterized by acute onset of signs and symptoms of joint inflammation for a period of no longer than 6 weeks, synovial increased leuk ocyte count, and the absence of microorganisms on Gram stain, routine culture, and/or PCR.[88]

All levels of diagnostic certainty: One or more of the following clinical signs and symptoms assessed by a healthcare provider: articular or periarticular swelling, articular effusion, articular or periarticular erythema, increased warmth palpable over capsular contour of the joint, restricted range of movement;

AND

- Duration of less than 6 weeks until complete resolution of symptoms;

AND

- Absence of recent articular trauma.

Level 1 of diagnostic certainty: Increased leuk ocyte count in synovial fluid determined as:

> 2,000 leukocytes/mm3 on aspirate regardless of age AND < 50% WBC polymorphonuclear leukocyte in synovial fluid

AND

- Absence of pathological synovial fluid cells;
- Absence of any microorganism on Gram stain, microscopy, or polymerase chain reaction (PCR) in synovial fluid;
- No bacterial growth on routine culture of synovial fluid;
- Absence of antibiotic treatment before obtaining the first synovial fluid sample.

Level 2 of diagnostic certainty:

- Negative bacterial blood cultures;

AND

- Negative routine bacterial culture of synovial fluid;

AND

- Absence of antibiotic treatment before obtaining the first synovial fluid sample;

AND

- Absence of fever.

Level 3 of diagnostic certainty:

- Absence of fever.

The BC definition really limits the amount of diagnosis that fits. The definition can mainly be used to look at a specific joint in the research setting to determine if it fits the AAA definition or not, it is not a diagnosis. This is the reason why AAA is hard to qualify.

AAA	Not AAA
Gouty arthritis	Rheumatoid arthritis (chronic)
Psoriatic arthritis	Osteoarthritis (chronic)
Viral arthritis	Spondyloarthropathies (chronic)
	Reactive arthritis (bacterial)
	Felty syndrome (part of rheumatoid arthritis)
	Juvenile idiopathic arthritis (chronic)
	Posttrauma
	Periarthritis (frozen shoulder) (caused by repetitive movements)
	Lyme arthritis (bacterial)

Return_to_AAA

Narcolepsy
Complete case definition for AESI[87]

The CD that Francesca Poli et al. developed for the standardized assessment of narcolepsy focused on narcolepsy as an adverse event following immunization (AEFI).[93]

Level 1: In the presence of: excessive daytime sleepiness[a] **OR** unambiguous cataplexyc **AND** CSF hypocretin-1 deficiency.[b]

Level 2: In the presence of: excessive daytime sleepinessa **AND** unambiguous cataplex[c] **AND**

Mean sleep latency (MSLT)[d] ≤ 8 min in adults **OR**

MSLT[d] ≤ 12 min in children and adolescents **OR**

MSLT[d] sleep-onset rapid eye movement periods ≥ 2.

Level 3: In the presence of: excessive daytime sleepinessa **AND**

MSLT[d] mean sleep latency ≤8 min in adults **OR**

MSLT[d] mean sleep latency ≤12 min in children and adolescents **AND**

MSLT[d] sleep-onset rapid eye movement periods ≥ 2

All levels: AND in the absence of other mimicking disorders, see[e]

[a] Excessive daytime sleepiness in adults (≥ 16 years): unintended sleep episodes during the day AND present almost daily for at least one month in children and adolescents (< 16 years). An increase in daytime sleep episodes AND present almost daily for at least one month.

Note: Usually in combination with feelings of subjective sleepiness and impaired concentration. Sleepiness may also be manifested as irritability or hyperactivity.

[b] CSF hypocretin-1 deficiency: hypocretin-1 concentration below 110 pg/ml in crude, unextracted CSF **AND** measured by the Phoenix radioimmunoassay **AND** performed in a laboratory according to published guidelines and by using the Stanford reference sample.

[c] Unambiguous cataplexy: In adults (≥ 16 years): sudden **AND** unexpected onset of episodes **AND** presence of all the following criteria during episodes (before initiation of treatment):

• Partial or generalized muscle weakness, preserved consciousness; clear emotional trigger in ≥ 2 episodes, duration of < 30 s; **OR**

• Episodes with documented, reversible areflexia **AND** duration of < 30 s, **NOT** partial or generalized seizure **OR** neuromuscular disorders.

In children and adolescents (< 16 years): Episodes of cataplexy that fulfill the criteria for adult cataplexy OR the following criteria of pediatric cataplexy.

Pediatric cataplexy: Sudden **AND** unexpected onset of episodes **AND** loss of muscle tone, e.g., falling during routine activity (i.e., while walking or running), wide-based gait, head droops, prominent facial involvement resulting in "cataplectic facies," eyelid ptosis, mouth opening, tongue protrusion, facial weakness, facial grimacing, abnormal postures, swaying of the head and trunk, stereotypic movements, or chorea-like patterns. Hypotonia and wide-based gait may also be disclosed at neurological examination **AND** preserved consciousness **AND** duration of episodes is a few seconds to several minutes (sometimes present in protracted clusters if emotional triggers continue).

Note: Cataplexy in children may or may not be triggered by "emotional" circumstances (e.g., watching funny cartoons, eating certain foods, playing games or videogames) NOT partial or generalized seizure OR neuromuscular disorders, any other known explanation.

[d] Four or five nap MSLT performed according to the American Academy of Sleep Medicine protocol.

[e] Exclusion of other conditions.

The following conditions must be clinically/instrumentally assessed, as they could either mimic one or more narcolepsy symptoms (mainly excessive daytime sleepiness) or constitute comorbidities with narcolepsy:

- Other sleep disorders, according to ICSD-2 criteria;
- Sleep-related breathing disorder;
- Behaviorally induced insufficient sleep;
- Circadian rhythm disorders;
- Recurrent hypersomnia secondary to medical or psychiatric conditions;
- Use of sedating medication and antidepressants;
- Focal cerebral lesions, indicated by neurological examination and/or brain imaging.

Return_to_Narcolepsy

COAGULATION DISORDERS
COMPLETE CASE DEFINITION FOR AESI[93]

Thrombosis_thromboembolism
Case definition and levels of diagnostic certainty of venous or arterial (draft)[94]

Level of certainty 1 – definitive case: Imaging study findings consistent with thrombosis/thromboembolism. Imaging studies include any of the following, depending on the location of the lesion:

- Ultrasound – Doppler, computed tomography (CT scan) – contrast/angiography, magnetic resonance venography (MRV) or arteriography (MRA), echocardiogram, perfusion V/Q scan, conventional angiography/digital subtraction angiography.

OR

• Procedure that confirms the presence of a thrombus (e.g., thrombectomy);

OR

- Pathology consistent with thrombosis/thromboembolism including biopsy or autopsy.

Notes: LOC 1 is independent of clinical findings or presence of risk factors. Most appropriate imaging test depends on the location of the lesion.

Any of the tests listed may be used as available. Based on radiologist/expert interpretation. Abnormal laboratory results are not required for confirmation, as they can be normal in presence of thrombotic/thromboembolic events. When present, they can be supportive of the diagnosis, including D-dimer elevated above the upper limit of normal for age; shortened PT, PTT – below the lower limit of normal for age; elevated fibrinogen.

Level of certainty 2 – probable case: Clinical presentation consistent with thrombosis or thromboembolism event, including specific clinical syndromes:

- DVT – symptoms will depend on the location of the thrombosis (swelling, pain, redness, or warmth of an extremity, headache, visual disturbance, seizures for sinus vein thrombosis, abdominal pain for intraabdominal thrombosis);
- Pulmonary thromboembolism (PE) – sudden onset shortness of breath, pleuritic chest pain, sudden death/ pulseless electrical activity arrest stroke, myocardial infarction;

OR

- Non-specific clinical symptoms: (LIST) edema, pain, ischemia, absent pulses, headaches.

AND

Presence of risk factors: History of immobilization, vascular catheter in place, recent surgery or trauma, obesity, previous thrombosis, cancer, oral contraceptive use, pregnancy, age > 65 years, family history of thrombosis, heart failure, inflammatory bowel disease or other inflammatory disorder.

AND

Supporting imaging findings suggestive but not definitive of thrombosis/thromboembolism, chest radiograph, ECG, computed tomography without contrast **OR** D-dimer – elevated above the upper limit of normal for age **AND** no alternative etiology.

Notes: LOC 2: Lower LOC when the gold standard imaging is not available, nor are procedural or pathology findings. Abnormal laboratory results are not required for confirmation, as they can be normal in presence of thrombotic/thromboembolic events. When present, they can be supportive of the diagnosis, including D-dimer elevated above the upper limit of normal for age, PT, PTT, international normalized ratio (INR) – elevated above the upper limit of normal for age.

Level of certainty 3 – possible case: Clinical presentation consistent with thrombosis or thromboembolism event, including specific clinical syndromes:

- DVT – symptoms will depend on the location of the thrombosis (swelling, pain, redness, or warmth of an extremity; headache, visual disturbance, seizures for sinus vein thrombosis; abdominal pain for intraabdominal thrombosis);

- PE – sudden onset shortness of breath, pleuritic chest pain, sudden death/pulseless electrical activity arrest, stroke, myocardial infarction;

OR

- Non-specific clinical symptoms: (LIST) edema, pain, ischemia, absent pulses, headaches.

AND

Presence or risk factors (high risk criteria): History of immobilization, recent surgery or trauma, vascular catheter in place, obesity, previous thrombosis, cancer, oral contraceptive use, pregnancy, age > 65 years, family history of thrombosis, heart failure, inflammatory bowel disease or other inflammatory disorder.

AND

No alternative etiology.

Notes: LOC 3 Lower LOC based on clinical findings; presence of risk factors increases likelihood. Abnormal laboratory results are not required for confirmation, as they can be normal in presence of thrombotic/thromboembolic events. When present, they can be supportive of the diagnosis, including D-dimer elevated above the upper limit of normal for age, PT, PTT, INR – the upper limit of normal for age.

Level 4: Insufficient information available to confirm a possible, probable, or definitive case of venous thrombosis/thromboembolism.

Level 5: Sufficient information to determine that it is NOT a case of venous thrombosis/thromboembolism.

Return_to_Thrombosis_Thromboembolism

Pulmonary thromboembolism
Complete case definition for AESI[93]

Synonyms for pulmonary thromboembolism (PE) / lay terms for the event: Lung infarction, blockage of the pulmonary artery, pulmonary thrombosis.

Laboratory tests that are specific for event: Laboratory tests are not diagnostic, but alter the clinical suspicion for PE, confirm the presence of alternative diagnoses, and provide prognostic information if PE is diagnosed:

- **Complete blood count and serum chemistries:** Routine laboratory findings include leukocytosis, increased ESR, and elevated serum lactate dehydrogenase and aspartate aminotransferase;
- **Arterial blood gas:** Unexplained hypoxemia in the setting of a normal chest radiograph should raise the clinical suspicion for PE and prompt further evaluation;
- **BNP:** Elevated BNP has limited diagnostic value in patients suspected of having PE. However, elevated BNP or its precursor, NT-proBNP, may be useful for prognostic risk stratification of patients diagnosed with acute PE;
- **Troponin:** Similarly, serum troponin I and T levels are useful prognostically but not diagnostically.
- **D-dimer:** An elevated D-dimer alone is insufficient to make a diagnosis of PE, but a normal D-dimer can be used to rule out PE in patients with a low or intermediate probability of PE.

Return_to_PE

Stroke
Complete case definition for AESI[93]

Acute stroke is defined as the acute onset of focal neurological findings in a vascular territory because of underlying cerebrovascular disease. This can happen in two ways. One is an ischemic stroke, where a small thrombus becomes trapped in a blood vessel transporting blood to the brain. Ischemic stroke accounts for 85% of all acute strokes. The other 15% of strokes are hemorrhagic strokes, which are caused by bursting of a blood vessel i.e., acute hemorrhage. There are numerous causes of stroke, such as prolonged hypertension, arteriosclerosis, and emboli that have formed in the heart because of atrial fibrillation or rheumatic heart disease.

Synonyms for cerebrovascular stroke / lay terms for the event: Stroke, cerebral stroke, acute stroke, apoplexy, cerebrovascular apoplexy, collapse, shock, attack, seizure (this is actually epilepsy), fit, transient ischemic attack, cerebrovascular accident, brain vascular accident, brain infarction.

Laboratory tests that are specific for event: A number of blood tests may be indicated in select patients with brain ischemia or hemorrhage, including: blood glucose, complete blood count including hemoglobin, hematocrit, white blood cell count, and platelet count; PT, INR, and activated partial thromboplastin time. Thrombin time and/or ecarin clotting time if patient is known or suspected to be taking a direct thrombin inhibitor or a direct factor Xa inhibitor, blood lipids including total, high-density lipoprotein, and low-density lipoprotein cholesterol, and triglycerides and toxicology screen to detect cocaine and other sympathomimetic drugs.

Return_to_Stroke

Limb ischemia
Complete case definition for AESI[93]

Another word for limb ischemia is peripheral artery disease (PAD) or peripheral occlusive artery disease. The decrease in perfusion is due to an occlusion of the artery leading to the leg or arm. Occlusion of the upper limb is rare, so the focus is on the lower limbs. The clinical presentation depends upon the etiology and whether the patient has underlying PAD. Patients who present later than two weeks after the onset of the acute event are considered to have chronic lower extremity ischemia.

If a patient has symptoms of PAD, the ankle-brachial index should be obtained. This is a measure for the severity of the PAD. A value < 0.4 is indicative of severe ischemia.

Synonyms for limb ischemia/ lay terms for the event: PAD, peripheral occlusive artery disease, intermittent claudication, limb infarction.

Laboratory tests that are specific for event: There is no laboratory testing specific for limb ischemia.

Return_to_Limb_Ischemia

Hemorrhagic disease
Complete case definition for AESI[93]

The cause of this bleeding lies within a problem in hemostasis. Hemostasis consists of two parts, primary and secondary hemostasis. Primary hemostasis consists of the production of an initial blood clot with thrombocytes sticking together. After this process, in secondary hemostasis, this blood clot is secured with fibrin through a cascade of multiple coagulation factors. Problems within the primary hemostasis result in excessive bleeding when a wound occurs. Whenever there is a problem within the secondary hemostasis, an initial blood clot is formed and the wound might be dry, but the blood clot is weak and might break from time to time resulting in recurrent bleeding.

To focus on specific diseases to be able to obtain incidence rates about hemorrhagic diseases, it was decided to focus on acquired TP for primary hemostasis and acquired hemophilia for secondary hemostasis. Hemophilia is the absence of coagulation factors necessary for making fibrin within a primary blood clot.

Acquired hemophilia occurs rarely, with an incidence of approximately 1–4 cases per million/year, with severe bleeds in up to 90% of affected patients, and high mortality of 8–22%. Most often, factor VIII is inhibited by neutralizing antibodies. This form is called acquired hemophilia A.

TP can be caused in many ways. For example, within pregnancy, by medication, because of an autoimmune reaction, due to infection, heavy alcohol consumption, and some types of anemia. In this situation of a possible connection between the coronavirus vaccination and hemorrhagic disease, it was decided to exclude causes such as pregnancy, cancers, infections, and inherited causes. The best representation for a possible vaccine-induced TP is immune TP. Immune TP happens when the immune system mistakenly attacks and destroys platelets. This effect can be triggered after an infection.

Another distinction that is possible to make within hemorrhagic disease is between major, minor, and trivial bleeding. Major bleeding is a hemorrhagic stroke or bleeding that requires transfusion, minor bleeding is any bleeding severe enough to disturb social activities, and trivial bleeding is no clinically unusual bleeding.

Synonyms for hemorrhagic disease / lay terms for the event: Excessive bleeding, hemophilia, bleeding disorder, bleeding problems, spontaneous bleeding, hemorrhaging, hemorrhagic disease, hemorrhagic disorder, coagulopathy, coagulation disorder.

Laboratory tests that are specific for event: General complete blood count including platelet count and morphology, fibrinogen level; genetic testing: genetic testing for known platelet function disorders in certain individuals with a suspected platelet disorder of genetic origin.

- Secondary hemostasis: PT and activated PTT: The INR is used to normalize the PT result across all testing laboratories;
- Thrombin time and reptilase time: The thrombin time and reptilase time both measure the final step in the clotting cascade (cleavage of fibrinogen to fibrin);
- Specific clotting factor assays: e.g., factor VIII primary hemostasis;
- Von Willebrand disease: This includes von Willebrand factor antigen, tests for von Willebrand function, and factor VIII activity;
- Platelet function: The platelet count and platelet morphology should be reviewed from the complete blood count. Additional testing can be done using platelet aggregation studies or the platelet function analyzer (PFA-100).

Return_to_Hemorrhagic_Disease

COMPLETE CASE DEFINITION FOR AESI ACUTE CARDIAC INJURY

Myocarditis
Complete case definition for AESI[103]

Level of certainty – 1 (definitive case): Histopathologic examination of myocardial tissue (autopsy or endomyocardial biopsy) showed myocardial inflammation **OR** elevated myocardial biomarkers (at least one of the following findings) – troponin T **AND** troponin I.

AND

Abnormal imaging study; abnormal cardiac magnetic resonance study (at least one of the following findings): edema on T2 weighted study, typically patchy in nature; late gadolinium enhancement on T1 weighted study with an increased enhancement ratio between myocardial and skeletal muscle typically involving at least one nonischemic regional distribution with recovery (myocyte injury) **OR** abnormal ECG (at least one of the following findings): new focal or diffuse left or right ventricular function abnormalities (e.g., decreased ejection fraction); segmental wall motion abnormalities; global systolic or diastolic function depression/abnormality; ventricular dilation; wall thickness change; intracavitary thrombi.

Level of certainty – 2 (probable case): Clinical symptoms: Cardiac symptoms (at least one of the following findings): acute chest pain or pressure; palpitations; dyspnea after exercise or lying down; diaphoresis; sudden death OR nonspecific symptoms (at least two of the following findings): fatigue, gastrointestinal symptoms (nausea, vomiting, abdominal pain), dizziness/syncope, edema, cough OR infants and young children (at least two of the following findings): irritability, vomiting, poor feeding, tachypnea, lethargy.

AND

Testing supporting diagnosis (biomarkers, echocardiogram [ECHO], and ECG); elevated myocardial biomarkers (at least one of the following findings): troponin T and troponin I, and creatine kinase (CK) myocardial band.

OR

Echocardiogram (ECHO) abnormalities (at least one of the following findings): new focal or diffuse left or right ventricular function abnormalities (e.g., decreased ejection fraction), segmental wall motion abnormalities, global systolic or diastolic function depression/abnormality, ventricular dilation, wall thickness change, intracavitary thrombi.

OR

ECG abnormalities (at least one of the following findings): ST-segment or T-wave abnormalities, elevation or inversion), paroxysmal or sustained atrial or ventricular arrhythmias (premature atrial or ventricular beats, and/or supraventricular or ventricular tachycardia, interventricular conduction delay, abnormal Q waves, low voltages), AV nodal conduction delays or intraventricular conduction defects (AV block [grade I–III]), new bundle branch block), continuous ambulatory electrocardiographic monitoring that detects frequent atrial or ventricular ectopy.

AND

No alternative etiology for symptoms.

Clinical symptom: Cardiac symptoms (at least one of the following findings): acute chest pain or pressure, palpitations, dyspnea after exercise or lying down, diaphoresis, sudden death.

OR

Nonspecific symptoms (at least two of the following findings): fatigue, abdominal pain, dizziness/syncope, edema, cough.

OR

Infants/young children (at least two of the following findings): irritability, vomiting, poor feeding, tachypnea, lethargy.

AND

Biomarkers supporting evidence of inflammation (at least one of the following findings): elevated CRP, elevated ESR, elevated D-dimer.

AND

Nonspecific ECG abnormalities (at least one of the following findings): ST-segment or T-wave abnormalities (elevation or inversion), premature atrial contractions (PACs), premature ventricular complex (PVCs).

AND

No alternative etiology for symptoms.

Level of certainty – 3 (probable case):

Clinical symptoms. Cardiac symptoms (at least one of the following findings): acute chest pain or pressure, palpitations, dyspnea after exercise, at rest, or lying down, diaphoresis, sudden death.

OR

Nonspecific symptoms (at least two of the following findings): fatigue, abdominal pain, dizziness/syncope, edema, cough.

OR

Infants/young children (at least two of the following findings): irritability, vomiting, poor feeding, tachypnea, lethargy.

AND

Biomarkers supporting evidence of inflammation (at least one of the following findings): elevated CRP, elevated ESR, elevated D-dimer.

AND

Nonspecific ECG abnormalities that are new and/or normalize on recovery (at least one of the following findings):

ST-segment or T-wave abnormalities (elevation or inversion), PACs and PVCs.

AND

No alternative diagnosis for symptoms

Return_to_Myocarditis

Pericarditis
Complete case definition for AESI[104, 105]

Level of certainty – 1 (definitive case): Histopathologic examination of pericardial tissue (autopsy or pericardial biopsy) showed pericardial inflammation.

OR

Abnormal testing needs at least two of three of the following: evidence of abnormal fluid collection or pericardial inflammation by imaging (ECHO, MR, cardiac magnetic resonance [CMR], CT).

OR

ECG abnormalities that are new and/or normalize on recovery (must have all findings): diffuse concave-upward ST-segment elevation, ST-segment depression in aVR, PR-depression throughout the leads without reciprocal ST-segment changes.

OR

Physical examination findings (at least one finding): pericardial friction rub, distant heart sounds (infants/children), pulsus paradoxus.

Level of certainty – 2 (probable case): Clinical symptoms. Cardiac symptoms (at least of the following findings): acute chest pain or pressure, palpitations, dyspnea after exercise or lying down, diaphoresis, sudden death.

OR

Infants/children (at least two of the following findings): irritability, vomiting, poor feeding, sweating.

AND

Physical examination findings (at least one of the following findings): pericardial friction rub; pulsus paradoxus.

OR

Evidence of abnormal fluid collection or pericardial inflammation by imaging (Echo, MR, CMR, CT).

OR

ECG abnormalities that are new and/or normalize on recovery (at least one of the following findings): diffuse concave-upward ST-segment elevation, ST-segment depression in aVR, PR-depression throughout the leads without reciprocal ST-segment changes.

AND

No alternative diagnosis for symptoms (e.g., myocardial infarction, PE, mediastinitis, etc.).

Level of certainty – 3 (possible case):

Clinical symptoms. Cardiac symptoms (at least one of the following findings): new onset cardiac chest pain or pressure, palpitations, dyspnea after exercise, at rest, or lying down.

AND

Nonspecific symptoms (at least one of the following findings): cough, weakness, gastrointestinal – nausea, vomiting diarrhea, shoulder/upper back pain, cyanosis, low-grade intermittent fever, altered mental status, edema, fatigue.

OR

Infants/children (at least two of the following findings): irritability, vomiting, poor feeding, back pain, tachypnea, lethargy.

AND

Abnormal testing: abnormal chest radiograph showing enlarged heart.

OR

ECG abnormalities.

Nonspecific changes that are new and/or normalize in recovery.

AND

No alternative diagnosis for symptoms (e.g., myocardial infarction, PE, mediastinitis, etc.).

Return_to_Pericarditis

Microangiopathy
Complete case definition for AESI[106]

Small vessel disease is a condition in which the walls of the small arteries of the heart do not work properly. This reduces the flow of oxygen-rich blood to the heart, causing chest pain (angina), shortness of breath, and other signs and symptoms of heart disease. The condition is usually diagnosed after finding little or no narrowing in the main arteries of the heart, despite the presence of symptoms that suggest heart disease.

Small vessel disease is more common in women and in people with diabetes or hypertension. Warns for chest pain, tightness, or discomfort (angina), which can worsen with activity or emotional stress, discomfort in the left arm, jaw, neck, back or abdomen along with chest pain, shortness of breath, tiredness and lack of energy and when treating coronary artery disease with angioplasty and stents and persistent signs and symptoms.

Return_to_Microangiopathy

Heart failure
Complete case definition for AESI

Heart failure can involve the left, right, or both sides of the heart, but it usually affects the left side first. It is a chronic, progressive condition in which the heart muscle is unable to pump enough blood to meet the body's blood and oxygen needs. The heart can no longer handle its workload and to compensate, the heart initially stretches to contract more forcefully and keep up with the demand to pump more blood. Over time, this causes the heart to dilate, building more muscle mass, because the contracting cells in the heart get bigger, allowing the heart to pump harder, at least initially, pumping faster. This helps to increase cardiac output.

The body also tries to compensate by narrowing blood vessels to keep blood pressure high, trying to compensate for the loss of strength in the heart. The body diverts blood from less important tissues and organs (such as the kidneys), the heart and brain. These temporary measures mask the problem of heart failure but do not solve it. Heart failure continues and worsens until these compensatory processes no longer work. Eventually, the heart and body just can't keep up, and the person experiences fatigue, breathing problems, or other symptoms.[110]

Definition of heart failure with preserved (HFpEF), mid-range (HFmrEF) and reduced ejection fraction (HFrEF) [109]

Type of HF		HFrEF	HFmrEF	HFpEF
Criteria	1	Symptoms ± signs[a]	Symptoms ± signs[a]	Symptoms ± signs[a]
	2	LVEF < 40%	LVEF 40–49%	LVEF ≥ 50%
	3	–	1. Elevated levels of natriuretic peptides[b] 2. At least one additional criterion: a. relevant structural heart disease (LVH and/or LAE) b. diastolic dysfunction	1. Elevated levels of natriuretic peptides[b] 2. At least one additional criterion: a. relevant structural heart disease (LVH and/or LAE) b. diastolic dysfunction

CD of HF (in all cases): Presence of symptoms and/or signs of HF **AND** an LVEF <40% **OR** a "preserved" LVEF (defined as LVEF as LVEF ≥ 50% for HFmrEF or 40–49% for HFmrEF); **AND** elevated levels of natriuretic peptides

(BNP > 35 pg/mL and/or NT-proBNP > 125 pg/mL); **AND** objective evidence of other cardiac functional and structural alterations underlying HF.

Return_to_HF

Stress cardiomyopathy
Complete case definition for AESI[114]

Stress cardiomyopathy is a condition in which intense emotional or physical stress can cause rapid and severe heart muscle weakness. The pattern of left ventricular dysfunction was first described in Japan and has been referred to as “takotsubo cardiomyopathy,” named after the fishing pot with a narrow neck and wide base that is used to trap octopus. “Takotsubo cardiomyopathy”, also known as “apical ballooning syndrome”, “ampulla cardiomyopathy”, “stress cardiomyopathy” or “brokenμheart syndrome” is now increasingly recognized. “Transient left ventricular apical ballooning” has also been used to describe similar cardiac contractile function in patients after physical or emotional stress. This condition can occur following a variety of emotional stressors such as grief, fear, extreme anger, and surprise. On the other hand, numerous physical stressors such as stroke, seizure or acute asthma can also trigger the condition. Common presenting signs of this syndrome are chest pain, Takotsubo segment elevation in the precordial leads, mild elevation of cardiac enzyme and biomarker levels, and transient apical systolic left ventricular dysfunction in the absence of obstructive epicardial coronary disease. From the available medical literature so far, women—especially middle aged or elderly—are the most affected. While it can also occur in young women and men, most of these patients are postμmenopausal women. Indeed, more than 90% of patients suffering from stress cardiomyopathy are females. The basis for this predisposition is unknown. Sex hormones exert important influences on the sympathetic neurohormonal axis as well as on coronary vasoreactivity, but sexμrelated differences in catecholamine metabolism and responsiveness are complex and remain poorly understood. Reversible myocardial dysfunction can develop in critically ill patients without any primary heart disease. This syndrome is associated with systolic dysfunction, segmental contractile disturbance, and electrocardiographic changes.

Return_to_Stress_Cardiomyopathy

Coronary artery disease
Complete case definition for AESI[115]

ECG or EKG (electrocardiogram) to measure electrical activity, frequency and regularity of heartbeats.

Echocardiogram Uses ultrasound (special sound wave) to create an image of the heart.

Exercise stress testing to measure heart rate while the patient walks on a treadmill (helps determine how well the heart is working when it needs to pump more blood).

Chest X-ray Uses X-rays to create an image of the heart, lungs, and other organs in the chest.

Cardiac catheterization to check for blockage inside the arteries by inserting a thin, flexible tube through an artery in the groin, arm, or neck to reach the heart.

Coronary angiography that monitors blockage and blood flow through the coronary arteries. It uses X-rays to detect dye injected through cardiac catheterization.

Coronary Artery Calcium Scan A computed tomography (CT) scan that examines the coronary arteries for calcium buildup and plaque

Return_to_Coronary_Artery

Arrhythmia
Complete case definition for AESI [118]

CG: history and physical examination may detect an arrhythmia and suggest possible causes, but diagnosis requires a 12-lead ECG or, less reliably, a rhythm strip, preferably obtained during symptoms to establish the relationship between symptoms and rhythm. The ECG is approached systematically; calipers measure intervals and identify subtle irregularities. The key diagnostic features are:

- Rate and regularity of atrial activation
- Rate and regularity of ventricular activation
- The relationship between the two

Irregular activation signals are classified as regularly irregular or irregularly irregular (no detectable pattern). Regular irregularity is intermittent irregularity in an otherwise regular rhythm (eg, premature beats) or a predictable pattern of irregularity (eg, recurrent relationships between groups of beats).

A **narrow QRS complex** (< 0.12 seconds) indicates a supraventricular origin (above the His bundle bifurcation). A **wide QRS complex** (≥ 0.12 seconds) indicates a ventricular origin (below the His bundle bifurcation) or a supraventricular rhythm conducted with an intraventricular conduction defect or with ventricular.

Bradyarrhythmias: ECG diagnosis of bradyarrhythmias depends on the presence or absence of P waves, morphology of the P waves, and the relationship between P waves and QRS complexes. **AV block** is indicated by a bradyarrhythmia with no relationship between P waves and QRS complexes and more P waves than QRS complexes; the escape rhythm can be:

- Junctional with normal AV conduction (narrow QRS complex)
- Junctional with aberrant AV conduction (wide QRS complex)
- Ventricular (wide QRS complex)

Absence of AV block is indicated by a regular QRS bradyarrhythmia with a 1:1 relationship between P waves and QRS complexes. P waves preceding QRS complexes indicate sinus bradycardia (if P waves are normal) or sinus arrest with an escape atrial bradycardia (if P waves are abnormal). P waves after QRS complexes indicate sinus arrest with a junctional or ventricular escape rhythm and retrograde atrial activation. A ventricular escape rhythm results in a wide QRS complex; a junctional escape rhythm usually has a narrow QRS (or a wide QRS with bundle branch block or preexcitation).

When the QRS rhythm is irregular, P waves usually outnumber QRS complexes; some P waves produce QRS complexes, but some do not (indicating 2nd-degree AV block). An irregular QRS rhythm with a 1:1 relationship between P waves and the following QRS complexes usually indicates sinus arrhythmia with gradual acceleration and deceleration of the sinus rate (if P waves are normal).

Pauses in an otherwise regular QRS rhythm may be caused by blocked P waves (an abnormal P wave can usually be discerned just after the preceding T wave or distorting the morphology of the preceding T wave), sinus arrest, or sinus exit block, as well as by 2nd-degree AV block.

Tachyarrhythmias: may be divided into 4 groups, defined by the QRS complexes:

- Visibly regular vs irregular
- Narrow vs wide QRS complexes

Irregular, narrow QRS complex tachyarrhythmias include the following 4 rhythms. Differentiation is based on atrial ECG signals, which are best seen in the longer pauses between QRS complexes.

- Atrial fibrillation (AF): Atrial ECG signals (usually best seen in lead V1) that are continuous, irregular in timing and morphology, and very rapid (> 300 beats/minute) without discrete P waves
- Atrial flutter with variable AV conduction: Regular, discrete, uniform atrial signals (usually best seen in leads II, III, and aVF) without intervening isoelectric periods, usually at rates > 250 beats/minute
- True atrial tachycardia with variable AV conduction: Regular, discrete, uniform, abnormal atrial signals with intervening isoelectric periods (usually at rates < 250 beats/minute)
- Multifocal atrial tachycardia: Discrete P waves that vary from beat to beat with at least 3 different morphologies

Irregular, wide QRS complex tachyarrhythmias include

- The above 4 irregulars, narrow atrial tachyarrhythmias conducted with either bundle branch block or ventricular preexcitation
- Polymorphic ventricular tachycardia (VT)

Differentiation is based on atrial ECG signals and the presence in polymorphic VT of a very rapid ventricular rate (> 250 beats/minute).

Regular, narrow QRS complex tachyarrhythmias include

- Sinus tachycardia
- Atrial flutter with a consistent AV conduction ratio
- True atrial tachycardia with a consistent AV conduction ratio
- Paroxysmal supraventricular tachycardias ([SVT] such as AV nodal reentrant SVT, orthodromic reciprocating AV tachycardia in the presence of an accessory AV connection, and SA nodal reentrant SVT)

Vagal maneuvers or pharmacologic AV nodal blockade can help distinguish among these tachycardias. With these maneuvers, sinus tachycardia is not terminated, but it slows, or AV block develops, disclosing normal P waves. Similarly, atrial flutter and true atrial tachycardia are usually not terminated, but AV block discloses flutter waves or abnormal P waves. The most common forms of paroxysmal SVT (AV nodal reentry and orthodromic reciprocating tachycardia) must terminate if AV block occurs.

Regular, wide QRS complex tachyarrhythmias include

- The above 4 regular, narrow QRS complex tachyarrhythmias conducted with bundle branch block or ventricular preexcitation
- Monomorphic VT

Vagal maneuvers can help distinguish among them. ECG criteria to distinguish between VT and SVT with an intraventricular conduction defect are often used (see figure Modified Brugada criteria for ventricular tachycardia). When in doubt, the rhythm is assumed to be VT because some drugs for SVTs can worsen the clinical state if the rhythm is VT; however, the reverse is not true.

Return_to_Arrhytmia

Acute kidney injury
Complete case definition for AESI[119]

Acute kidney injury (AKI) case definitions: In Europe, the definition/guideline of Kidney Disease: Improving Global Outcomes (KDIGO) is the leading one.

The guideline defines AKI as follows (not graded): Increase in serum creatinine (SCr) by X0.3 mg/dl (X26.5 lmol/l) within 48 hours;

OR

Increase in SCr to X1.5 times baseline, which is known or presumed to have occurred within the prior 7 days;

OR

Urine volume < 0.5 ml/kg/h for 6 hours.

AKI is staged for severity according to different criteria. The first classification system is risk, injury, failure, loss of kidney function, and end-stage kidney disease (RIFLE), from the Acute Dialysis Quality Initiative.

RIFLE incorporated three categories of injury and two outcomes that varied by severity. The outcomes (loss, and end-stage kidney disease) were eliminated from the subsequent Acute Kidney Injury Network and KDIGO definitions.

The Acute Kidney Injury Network definition incorporated smaller changes in SCr concentration, and the KDIGO definition added more definitive time frames to the definition. A key concept for the SCr-based definitions of AKI is the identification of baseline SCr concentration. Although the initial RIFLE criteria recommended the use of an SCr concentration that would equate to an estimated glomerular filtration rate of 75 mL/min/1.73 m2 by the Modification of Diet in Renal Disease (MDRD) study equation (MDRD-75) if no baseline were available, this definition does not account for chronic kidney disease if present.

It is essential to look for a prior baseline/reference SCr concentration, ideally from the 365 days before hospital admission from a clinical context in which there was not concern for AKI (e.g., a stable clinic visit). This concept is discussed in detail in the KDIGO AKI clinical practice guideline.

Return_to_AKI

Anosmia ageusia
Complete case definition for AESI[124]

Anosmia: Absent smell function. Two causes for anosmia: conductive and/or traumatic **AND** sensorineural.

1) Obstructive nasal diseases, such as chronic rhinosinusitis (CSR), nasal polyposis, allergic rhinitis, and nasal masses, can obstruct the nasal airflow to the olfactory cleft. However, chronic rhinosinusitis is not considered a cause of decreased odor, but it is considered possible after immunization.

Approximately 20-30% of patients who suffer traumatic brain injury develop some degree of olfactory dysfunction, while up to 5% have anosmia. In the diagnosis, recent trauma must be excluded.

2) A recent history of upper respiratory infection is reported by 20–30% of patients with acquired olfactory dysfunction. Excluding congenital anosmia: Kallmann syndrome (congenital), which can be distinguished by the presence of hypogonadotropic hypogonadism, must be ruled out in similar cases because the presentation can be similar. Damage to the olfactory bulb can also be seen with many neurodegenerative diseases, such as Alzheimer's disease and Parkinson's disease. Exclusion of anosmia as a part of another disease: numerous

commonly prescribed medications, such as antihypertensive and antihyperlipidemic drugs, are associated with smell disturbance. Exclusion of anosmia caused using specific medication: angiotensin-converting-enzyme inhibitors, diuretics, calcium channel blockers, and statins.

Ageusia: Absent taste function. Staging system to assess whether the patient has ageusia or dysgeusia: a scale that ranges from 0, which refers to no taste, to 4, which refers to total taste loss, may be useful in evaluation.

Return_to_Anosmia_Ageusia

Chilblain like lesions
Complete case definition for AESI[129]

Chilblain-like lesions manifest as multiple red-violet edematous lesions with papules and macules located in the acral regions, such as toes, feet (heel, sole) and/or toes, asymptomatic or associated with itching or mild pain . They appear in places of exposure to cold and humid environments (idiopathic chilblains). Because of the presentation as chilblains, they are referred to as chilblain-like lesions pseudo-chicken. Lesions disappear after a few weeks without treatment. It is described as perniosis or pernio-type chilblains.

The most common sites of involvement are the fingers and toes, and the condition is often accompanied by a sensation of itching, burning, or pain. It is postulated that the pernio results from an abnormal vascular response to exposure to cold. Cold-induced vasoconstriction or vasospasm resulting in hypoxemia that stimulates an inflammatory response is a potential mechanism for the formation of skin lesions. There are reports of a causal correlation between systemic diseases and chilblains. The most frequently reported and studied relationship is the relationship between (chronic) chilblains and lupus erythematosus, also known as chilblain lupus erythematosus. Acute and idiopathic cases of pernio usually resolve in 1–3 weeks. Chronic pernio (due to systemic disease) can present as recurrent acute episodes or episodes that persist for more than several weeks.

Return_to_Chilblain_Like_Lesions

Erythema multiforme
Complete case definition for AESI[135]

The definition of the event has been revised by the contributing authors of ACCESS.

Erythema multiforme (EM) is an acute self-limited disease, usually associated with hypersensitivity reactions to viruses, as well as to medications. It is characterized by target erythematous lesions with a predominant acral location and can be subdivided into isolated cutaneous and combined mucocutaneous forms. It is defined by the morphology of individual lesions and by the distribution pattern and is included only in its main form called erythema multiforme major.

In EM, skin detachment affects < 10% of the body surface area and typical and atypical / elevated localized targets are present. Typical targets are defined as lesions less than 3 cm in diameter and characterized by three different concentric zones. Elevated atypical targets usually contain only two zones. In typical and elevated atypical targets, the central zone may show the formation of bubbles as a sign of epidermal involvement. Clinically, EM patterns can be classified into EM with and without mucosal involvement. MS was subdivided into less MS (involvement of ≤1 mucosal site) and larger MS (involvement of ≥ 2 mucosal sites) by some authors.

Consensus classification of Erythema multiforme

Criterion	Erythema multiforme major
Skin detachment (body surface area affected)	< 10%
Target lesions	Typical and/or atypical
Raised lesions	Yes
Distribution	Predominantly affects the extremities; in children, frequently affects the trunk
Progression to toxic epidermal necrolysis	No

Return_to_Erythema_Multiforme

Acute liver injury
Complete case definition for AESI[138]

The clinical course of acute liver failure (ALF) starts with a severe acute liver injury (ALI). This is characterized by a two- to three-fold increase in transaminases (liver damage marker) associated with impaired liver function, such as jaundice or coagulopathy in a patient without previous chronic disease. The coagulation disorders necessary to define ALF are determined by an extension of the INR, usually > 1.5 or an extension of the PT.

Severe ALI defines a syndrome characterized by markers of liver damage (elevated serum transaminases) and impaired liver function (jaundice and INR > 1.5) that usually precedes clinical encephalopathy. The group cite a systematic review that investigated the clarity and extent of variability in ALF definitions used in the ALF prognosis literature. Gathered in the table below are four different definitions that deserve special mention.

Classification systems of acute liver failure

	Bernuau system	O'Grady system	International Association for the Study of the Liver system	Japanese system
Definition of ALF	> 50% decrease in factor II or V with hepatic encephalopathy (HE)	Severe liver injury with HE without prior liver disease	Severe liver disfunction with HE within 4 wk without prior liver disease	INR ≥ 1.5 or PT ≤ 40% within 8 wk of symptoms without prior liver disease
Requirement for HE	Yes	Yes	Yes	No
Subclasses	Fulminant Subfulminant	Hyperacute Acute Subacute	Hyperacute Fulminant	With hepatic coma: • Acute • Subacute Without hepatic coma
Duration between symptoms and HE	Fulminant < 2 wk Subfulminant 2–12 wk	Hyperacute < 1 wk Acute 1–4 wk Subacute 4–12 wk	Hyperacute Fulminant	With hepatic coma: • Acute < 10 d • Subacute 10–56 d Without hepatic coma NA

Abbreviations: ALF, acute liver failure; HE, hepatic encephalopathy; INR, International Normalized Ratio; NA, not applicable; PT, prothrombin time.

The Catalan Society of Digestology defines ALF as liver injury in the context of acute, but potentially reversible, liver disease affecting a previously healthy liver. However, it also includes other etiologies in which the condition

is the acute manifestation of a chronic liver disease (Wilson's disease, reactivation of hepatitis B virus in a noncirrhotic liver, usually in the context of immunosuppression induced by chemotherapy, acute Budd-Chiari, and autoimmune hepatitis) and describes the accepted diagnostic criteria as being essentially as follows: acute liver disease; reduction of the prothrombin rate below 40% or INR ≥ 1.5 as a biological sign of liver failure; less than 28 weeks since onset (24 weeks according to the 1999 definition from the International Association for the Study of the Liver); onset of hepatic encephalopathy [HE] as a clinical sign of liver failure (not considered essential in pediatric patients); previously healthy liver (with the exceptions previously mentioned).

Drug-induced liver injury: CDs for drug-induced liver injury (DILI) include one of the following thresholds: ≥ 5x upper limit of normal (ULN) elevation in alanine transaminase (ALT); ≥ 2 ULN elevation in alkaline phosphatase (ALP) (particularly with accompanying elevations in concentrations of gamma-glutamyl transferase in the absence of known bone pathology driving the rise in ALP level); ≥ 3x ULN elevation in ALT and simultaneous elevation of total bilirubin level concentration exceeding 2x ULN.

In patients with abnormal liver tests prior to starting treatment with the implicated drug, ULN is replaced by the mean baseline values obtained prior to DILI onset, and increases should be proportionate to this modified baseline. Three patterns of DILI are determined using earliest identified elevation of liver enzymes levels. Initially, ALT activity (patient's ALT/ULN of ALT) and ALP activity (patient's ALP/ULN of ALP) are calculated. Then, the ALT/ALP ratio is determined: hepatocellular, when there is a fivefold or higher rise in ALT alone or when the ratio of serum activity (activity expressed as a multiple of ULN) of ALT to ALP is 5 or more; cholestatic, when there is a twofold or higher rise in ALP alone or when the ratio of serum activity of ALT to ALP is 2 or less; mixed, when the ratio of the serum activity of ALT to ALP is between 2 and 5.

Return_to_ALI

Subacute thyroiditis
Complete case definition for AESI[141]

Subacute thyroiditis is a diagnosis made clinically. Anterior neck pain, preceded by an upper respiratory inflammation, alerts the clinician to the classic painful (De Quervain's; granulomatous) thyroiditis (PFSAT). Differential diagnostic considerations include acute (suppurative, thyroid abscess) thyroiditis, which is usually a painful nodular enlargement of the thyroid or unusual presentations of Graves' or nodular thyroid disease with pain generated by capsular stretching. Thyroid function tests during the painful (initial) phase of subacute thyroiditis (SAT) often reveal a suppressed thyroid-stimulating hormone and elevation of total T4 and T3 levels consistent with the thyrotoxic state. The T3 (ng/dl) to T4 (ug/dl) ratio is less than 20 in all forms of SAT.

The ESR is almost always greater than 50, and WBC and CRP levels are usually elevated in PFSAT. Painless SAT (including postpartum thyroiditis) is typically associated with the presence of anti-thyroid peroxidase (TPO-ab) and thyroglobulin (Tg-ab) antibodies, both of which are usually absent, and present only in low titers in PFSAT. Thyrotropin receptor antibodies are usually positive in Graves' disease and absent or low level in patients with PFSAT as well as postpartum thyroiditis. Radioactive iodine uptake and scan typically reveals a low radioactive iodine uptake and poor visualization of the thyroid in PFSAT and painless (silent, autoimmune) SAT, whereas significant uptake is expected in Graves' disease or toxic nodular goiters. Painless (silent, autoimmune) SAT must be differentiated from other forms of low uptake thyrotoxicosis, iatrogenically (factitious [l-thyroxine (LT4), l-triiodothyronine (LT3) or T4/T3 combination (animal extract)]) induced thyrotoxicosis results in a suppressed thyroglobulin level.

Ectopic thyroid hormone production in a Struma ovarii or functional metastatic thyroid cancer can be detected with total body scanning. Iodine contamination after a contrast-enhanced CT scan obliterates the radioactive

iodine uptake and obscures the presence of the more frequently encountered Graves' disease or a toxic multinodular goiter. A recent CT scan will frequently alert the clinician to this artifact. Urine iodine measurement can quantify the degree of iodine contamination present.

Thyroid ultrasound typically shows a heterogeneously hypoechoic pattern and has a suppressed vascular pattern in SAT, while patients with Graves' disease demonstrate hypervascularity. The presence of thyroid nodules supports the presence of a toxic nodular goiter. Localized PFSAT can be suggestive of thyroid cancer. Usually, the pain, elevated ESR and leukocytosis, and clinical remission or spread to other parts of the gland make clinical differentiation possible but may require a fine needle aspiration for definitive diagnosis.

Return_to_SAT

Rhabdomyolysis
Complete case definition for AESI[148]

The classic triad is observed in < 10% of patients only, and > 50% of patients do not complain of muscle pain or weakness.

Systemic manifestations may include tachycardia, general malaise, fever, nausea, and vomiting, and as such are nonspecific. The clinical manifestations of acute renal failure disseminated intravascular coagulation and multiorgan failure may subsequently appear.

To accurately diagnose rhabdomyolysis, there must be a high index of suspicion and a thorough history and physical examination. With the classic triad being observed in only < 10% of patients, any patient with known risk factors – including trauma, sepsis, muscular disease, and immobilization – should be suspected of rhabdomyolysis.

Other indirect clues include the presence of muscle injury with an unexpected rise in serum phosphate or aspartate transaminase. A neuromuscular examination focusing on the extremities can also give important physical clues.

Color, pulse, sensation, muscle power, and size are all informative, even in nonverbalizing patients. The gold standard for laboratory diagnosis is the determination of plasma CK. Although a cut-off threshold has not been established, a concentration five times the upper limit of the normal reference range (i.e., 1,000 IU/L) is commonly used.

CK level is generally considered predictive of the likelihood of developing acute renal failure, and a concentration > 5,000 IU/L is closely related to the development of kidney damage. CK has a half-life of 1.5 days.

Consequently, CK blood levels remain increased longer than the concentration of myoglobin, which has a half-life of 2–4 hours. Myoglobin concentrations tend to normalize within 6–8 hours following muscle injury. Plasma myoglobin is not as sensitive as CK for diagnosis because of its short half-life, resulting in false-negative tests. Urine myoglobin will show erythrocyte positivity on the urine dipstick because the ortho-toluidine portion of the dipstick turns blue in the presence of myoglobin.

Return_to_Rhabdo

Acute pancreatitis
Complete case definition for AESI[154]

Diagnosis is based on clinical symptoms, a three-times increase in pancreatic enzymes, and radiologic evaluation.

A. In the patient's history, ask about acute abdominal pain in left upper quadrant that radiates to the back or right upper quadrant and is associated with nausea and vomiting. This may be with or without fever.

B. In the physical examination, note abdominal distention with or without peritoneal signs, and ascites. There may be signs of an ileus with absent bowel sounds. Discoloration around the umbilicus or flank suggests pancreatic necrosis (Cullen's sign). Note signs of respiratory distress associated with pleural effusions or pneumonitis. Assess circulatory status and peripheral perfusion to identify intravascular volume loss secondary to third spacing. Note purpura or bleeding that suggests disseminated intravascular coagulation.

C. Laboratory findings of pancreatitis include increases in serum amylase and lipase levels. Comprehensive metabolic panel including liver function test results may be abnormal when choledocholithiasis or hepatitis is present. Glucose may be increased, and calcium decreased with severe disease. The WBC is often increased (10,000–25,000 K/ml).

D. Assess degree of illness. For mild degree of illness, observe the patient. Provide hydration and symptomatic treatment. Start with a clear or low-fat diet. For severe pain, the patient should be hospitalized. For very severe illness that may include respiratory distress and shock, admit the patient to the intensive care unit.

E. Provide fluid resuscitation intravenously and correct electrolyte abnormalities. Control pain with narcotics. Prevent stress ulcer with a proton pump inhibitor (1–3 mg/kg IV every 24 hours) or use an H2-receptor antagonist (ranitidine 1 mg/kg intravenously every 8 hours).

F. Consider evaluation with ultrasound or abdominal CT scan if increased liver function tests or physical examination give findings of shock or peritonitis. In severe cases, treat with octreotide (1–10 mg/kg/day IV divided every 12 hours). In severe cases, use nasogastric decompression.

G. Follow-up by re-evaluation over 24–72 hours. If improved with decreased amylase and lipase, consider feeds. If not improved clinically and with increased amylase and lipase, consider repeat ultrasound or CT and consider nasojejunal feeds or total parenteral nutrition.

Severity of illness in pancreatitis

Severe	Very severe
Severe abdominal pain with nausea and vomiting **And** Increased serum amylase or lipase	Signs of shock **Or** Disseminated intravascular coagulation **Or** Severe respiratory distress / impending respiratory failure **Or** Signs of pancreatic necrosis **Or** Signs of peritonitis

Return_to_Acute_Pancreatitis

Lymphadenopathy
Complete case definition for AESI[161]

Collections of superficial lymph nodes are present in the neck, axillae, and inguinal region; a few small (< 1 cm) nodes often are palpable in those areas in healthy people.

Lymphadenopathy is palpable enlargement (> 1 cm) of ≥ 1 lymph nodes and is categorized as localized (present in only one body area) or generalized (present in ≥ 2 body areas).

Lymphadenitis is lymphadenopathy with pain and/or signs of inflammation (e.g., redness, tenderness), and other symptoms may be present depending on the underlying disorder.

Vital signs are reviewed for fever, palpation in areas of specific lymph node concentration in the neck (including occipital and supraclavicular areas), armpits, and inguinal region.

Knot size (knot > 2 cm, knot that is draining, rigid or attached to tissue). Underlying sensitivity and consistency are noted.

The skin is inspected for rashes and lesions, with special attention to areas drained by the affected nodules. The oropharynx is inspected and palpated for signs of infection and any lesions that might be cancerous. The thyroid gland is palpated for enlargement and nodularity.

The breasts (also in males) are palpated for lumps. The lungs are listened to for rales (suggesting sarcoidosis or infection). The abdomen is palpated for hepatomegaly and splenomegaly. The genitals are examined for cancers, blisters, and other lesions, and for urethral discharge. The joints are examined for signs of inflammation.

Return_to_Lymphadenopathy

Appendicitis
Complete case definition for AESI[166]

Classic signs and symptoms of appendicitis present; the diagnosis of appendicitis is clinical.

In patients with atypical or equivocal findings, imaging studies should be performed without delay (using contrast-enhanced CT).

The cause of appendicitis is uncertain, and prevailing theories center on luminal obstruction of the appendix blind as the primary pathology. When goblet cell secretions are prevented from escaping by luminal obstruction, intraluminal pressure within the appendix increases and leads to ischemia of the appendix wall. Translocation of bacteria from the lumen through the compromised mucosa causes transmural inflammation. Ongoing tissue ischemia and inflammation can then lead to infarction and appendix perforation (complicated appendicitis). Free perforation causes the intraperitoneal cavity to be fouled with pus or feces. A perforation can also be involved by the surrounding soft tissue (omentum, mesentery, or intestine), leading to the development of an inflammatory mass. This inflammatory mass may contain pus (abscess) or not (phlegmon). There is some debate as to whether perforated appendicitis is a distinct disease process from uncomplicated appendicitis.

Graduated compression ultrasound – can be done quickly and does not use radiation. Laparoscopy can be used for diagnosis as well as definitive treatment of appendicitis; may be especially helpful in women with lower abdominal pain of unclear etiology.

Laboratory studies usually show leukocytosis (12,000–15,000/mcL [12.00 to 15.00 × 10^9/L]), but this finding is highly variable; a normal WBC count should not be used to exclude appendicitis.

Return_to_Appendicitis

Herpes zoster
Complete case definition for AESI[168]

According to the CD document for varicella-zoster (herpes zoster) infection used in Australia, the steps to be followed should determine whether a case should be reported.

Reporting

Both **confirmed cases** and **probable cases** should be notified.

Confirmed case

A confirmed case requires **laboratory definitive evidence AND clinical evidence**.

Laboratory definitive evidence

1. Isolation of varicella-zoster virus (VZV) from a skin or lesion swab.

OR

2. Detection of VZV by nucleic acid testing from a skin or lesion swab.

OR

3. Detection of VZV antigen by direct fluorescent antibody from a skin or lesion swab.

Clinical evidence

A vesicular skin rash with a dermatomal distribution that may be associated with pain in skin areas supplied by sensory nerves of the dorsal root ganglia.

Probable case

A probable case requires **clinical evidence** only.

Note: Laboratory confirmation should be strongly encouraged for vaccinated cases. If positive, samples should be referred for identification as a vaccine or wild-type strain.

Return_to_Herpes_Zoster

COMPLETE CASE DEFINITIONS, PART B

Complete case definition for fever following immunization

The definition of a fever case has been standardized by the Brighton Collaboration (BC) group to be globally accepted as guidelines for data collection, analysis, and presentation. The case definition (CD) of fever as an AEFI is presented at three levels of diagnostic certainty:

Level 1 of diagnostic certainty: Fever is defined as the endogenous elevation of at least one measured body temperature of ≥ 38 °C.

Levels 2 and 3 of diagnostic certainty: Not applicable.[170]

The same working group presents in another publication a table with selected temperature measurement guidelines to facilitate data comparability. They detail that the developed definition of fever as an adverse event following immunization (AEFI) is as a temperature rise to ≥ 38 °C (100.4 °F) measured at any location using any validated device. They recognize that the somewhat arbitrary defined value is based on a conservative interpretation of the definitions proposed and used over the years by physicians, researchers, and the public.[171]

Selected temperature measurement guidelines to facilitate data comparability[171]

Temperature elevation to > 38 °C (100.4 °F)	Measured at any site, using any validated device
Temperature measurement of a vaccine recipient	Should be available before immunization
Tactile determinations of fever	Are not acceptable forms of measurement unless confirmed by thermometry, and terms to describe fever (e.g., low-grade, mild, moderate, high, severe, or significant) are highly subjective and prone to wide interpretation, and, therefore, should be avoided
Temperature measurement in clinical trials	Should be performed wherever fever is suspected, but no less than once a day even in the absence of suspected fever. If fever is detected, temperature should be measured at least twice a day (in the morning and evening) or as clinically appropriate until two consecutive measurements are > 38 °C
Any device validated to provide accurate and reproducible results	Is acceptable for measuring body temperature. Appropriate anatomic site(s), duration of measurement, and maintenance/standardization schedules should be specified for each such device and recorded on the diary card
For all cases and/or all study participants, as appropriate, the following information should be recorded:	Temperature: method of temperature measurement (i.e., route and device), detailed clinical description of the pattern of elevated temperature. Concurrent signs, symptoms, and diseases. Laboratory examination and/or pathological findings and diagnoses. Person reporting and/or measuring the temperature (e.g., medical provider, parent/patient, and other third-party reporter), including contact information. Placement of measuring device within or upon the anatomic site. Level of prior activity and relationship to a meal. Time of day and environment conditions. Duration of measurement
The device, route, method, and duration of measurement, and time of day	Should be consistent within and between study groups, if applicable
Temperature measurement in clinical trials – and wherever possible, in surveillance systems –should be analyzed in defined time increments	These may vary according to the biological activity of the vaccine under consideration. The time interval between immunization and fever should be determined by using the date of immunization and the date of diagnosis
The duration of fever	Should be analyzed as the number of days with > 38 °C
Temperature measurement	Should be analyzed in 0.5 °C increments and as the percentage of subjects whose highest temperature decreased within that increment during a specified time span

Return_to_Fever

Complete case definition for fatigue[175]

CD of fatigue elaborated by the BC group:

Level 1 of diagnostic certainty (persons ≥ 5 years of age)[a, b]

Level 1a (fatigue state): A new symptom[c, d] of fatigue (or a synonym),[e] **that is** the primary complaint,[f] **and is** not relieved by rest,[g] and interferes with an individual's function.[h]

Level 1b (specified fatigue syndrome): A new symptomc of fatigue (or a synonym),[e] **that is** the primary complaint,[f] **and** is not relieved by rest,[g] **and** interferes with an individual's function,[h] **and which is** accompanied by any of the following specified new symptoms[c] including postexertion malaise,[i] impaired memory or concentration, unrefreshing sleep, sore throat, tender cervical or axillary lymph nodes, muscle pain, multi-joint pain, or new headaches.[j]

Level 1c (other fatigue syndrome): A new symptom[c, d] of fatigue (or a synonym),[e] **that is** the primary complaint,[f] **and is** not relieved by rest,[g] **and** interferes with an individual's function,[h] **and which is** accompanied by other new symptomsc not specified in Level 1b.[k]

Further criteria required to achieve Levels 1a, 1b, and 1c: The fatigue has been confirmed by a valid and reliable self-report measured, and the functional impairment has been confirmed by a valid and reliable measure.

Exclusion criteria required to achieve Levels 1a, 1b, and 1c: Concurrent onset of medical or psychiatric disorders of which fatigue is a recognized symptom, which have been identified by appropriate laboratory tests and a standardized psychiatric interview **and** concomitant use of a medicine or recreational drug recognized to cause fatigue.

Level 2 of diagnostic certainty (all age groups)[a, b]

Level 2a (fatigue state): A new symptomc, d of fatigue (or a synonym).[e]

Level 2b (specified fatigue syndrome): A new symptom[c, d] of fatigue (or a synonym),[e] **which is** accompanied by any of the following specified new symptoms[c] including postexertion malaise,[i] impaired memory or concentration, unrefreshing sleep, sore throat, tender cervical or axillary lymph nodes, muscle pain, multi-joint pain, or new headaches.[j]

Level 2c (other fatigue syndrome): A new symptom[c, d] of fatigue (or a synonym),[e] which is accompanied by other new symptoms[c] not specified in Level 2b.[k]

Exclusion criteria required to achieve Levels 2a, 2b, and 2c: Known concurrent onset of known medical or psychiatric disorders of which fatigue is a recognized symptom and known concomitant use of a medicine or recreational drug recognized to cause fatigue.

Level 3 of diagnostic certainty (all age groups)[a, b]

Level 3a (fatigue state): A new symptom[c, d] of fatigue (or a synonym).[e]

Level 3b (specified fatigue syndrome): A new symptom[c, d] of fatigue (or a synonym),[e] **which is** accompanied by any of the following specified new symptoms[c] including postexertion malaise,[i] impaired memory or concentration, unrefreshing sleep, sore throat, tender cervical or axillary lymph nodes, muscle pain, multi-joint pain, or new headaches.[j]

Level 3c (other fatigue syndrome): A new symptom[c, d] of fatigue (or a synonym),[e] **which is** accompanied by other new symptoms[c] not specified in Level 3b.[k]

Exclusion criteria required to achieve Levels 3a, 3b, and 3c: Any information about a concurrent medical or psychiatric disorder of which fatigue is a recognized symptom, **and/or** any information about concomitant use of a medicine or recreational drug known to cause fatigue.

[a] The working group considered that recognition of an unexplained fatigue state in children < 5 years of age was problematic; hence, only Levels 2 and 3 of the CDs can be

reached in that age group.

[b] Review of all criteria (inclusion AND exclusion) prior to categorization of a case is necessary.

[c] Symptom is defined as "a phenomenon experienced by an individual as a departure from normal function, sensation, or appearance, generally indicating disease or disorder." A "new" symptom implies a change from normal, or if the symptom was a preexisting condition, then a change in character or severity is implied.

[d] Investigators must describe the method(s) of collection. Symptoms can be collected as a spontaneous narrative, through clarifying questions, or actively solicited. The methods of data collection may differ depending on the research setting. The frequency of the symptoms reported likely varies significantly depending on the method of data collection used. In all children (< 18 years of age), the parent or caregiver should ideally report on fatigue or synonyms for fatigue based on observation of the child, in addition to the child's self-report which should also be collected in children 5–17 years of age.

[e] Synonyms for fatigue may include verbs, adjectives, or nouns such as worn out, pooped, run down, lassitude, tiredness, exhausted, loss or lack of energy, lethargy. Synonyms are also culture- and language-specific and can be adjusted accordingly.

[f] Primary complaint is equivalent to the principal or main complaint.

[g] Rest may result in partial relief of the fatigue state but return to pre-morbid status is not achieved.

[h] Interference with individual's function means a reduction in daily function at work, school, social, or personal activities.

[i] Postexertion malaise needs to be out of proportion to the degree of exertion and may last > 24 h.

[j] One of the outcomes of adherence to the definition as described in Level 1b is the identification of chronic fatigue syndrome as defined by Fukuda et al. Specifically, unexplained fatigue of greater than 6 months duration that is not relieved by rest and interferes with work, school, personal, and/or social activities and is accompanied by four of the eight specified symptoms would be required to fulfill this definition.

[k] If one or more specified symptoms as well as nonspecific symptoms are identified, the case should be coded as Level b.

Return_to_Fatigue

Complete case definition for joint pain

Joint pain (arthralgia) or joint inflammation with swelling, redness, and/or warmth (arthritis) that is associated with limitation of regular activities and lasts 24 hours or longer. The temporal criteria for arthritis/arthralgia occur 0–30 days following immunization with an inactivated vaccine, or 0–42 days following immunization with a live vaccine.

Arthralgia means pain in a joint. Polyarthralgia means pain in several joints (two or more for the purposes of this discussion). Arthritis is a diagnosis and is not a symptom; its diagnosis requires the physical signs of articular inflammation or the physical or roentgenographic signs of osteoarthritis.

Rheumatic pain syndrome – located in one or more joints, has the need for additional historical data and establishment of the nature of the onset of pain. It should be determined whether other signs of inflammation (of the joint) have been observed by the patient, whether redness, heat ("fever"), and especially swelling. These must be dealt with specifically. If the arthralgia has a recent and rapid onset, the syndrome can be considered acute, and a specific differential diagnosis is suggested. Regardless of the nature of the onset, arthralgia that has persisted for a month or more can be considered chronic or persistent, and other differential diagnoses are suggested depending on whether one joint or more than one joint has been symptomatic.[178]

About arthritis – a CD that includes arthritis and other rheumatic conditions that may not technically be arthritis by healthcare providers, but they are close enough to include in a simplified term "arthritis."[179]

Return_to_Joint_Pain

Complete case definition for diarrhea[185]

The proposed CD contributes to the improvement of data comparability allowing a better understanding of diarrhea as an AEFI. The CD is structured in two levels of diagnostic certainty, that, although potentially applicable in a clinical setting, the level of diagnostic certainty is primarily intended for epidemiological purposes and not as a criterion for treatment. It is defined as an increase of three or more bowel movements (defecation),

above normal or baseline, occurring in a period of 24 hours and with liquid consistency stools, and at a second level due to an increase in the frequency of bowel movements with a liquid consistency.

Level 1 of diagnostic certainty: Diarrhea is defined as an increase of three or more stools (above normal or baseline) occurring within a 24-hour time.

AND

A liquid or liquid consistency of these stools.

Level 2 of diagnostic certainty: Diarrhea is defined as an increase in the frequency of bowel movements (above normal or baseline).

AND

A liquid or liquid consistency of these stools.

Return_to_diarrhea

Complete case definition for chills[192]

Chills are the subjective reports of shivering or shaking associated with rapid changes in body temperature. They result from involuntary muscle contractions that occur in response to a sudden lowering of body temperature below the prevailing set point. Although not a diagnosis, fever curves can sometimes be suggestive. Acute fevers, due to wide variations in temperature, are often associated with chills and sweating.

Chills are a sign that the body is trying to regulate its core temperature, it may shiver or tremble, move; teeth chatter (it feels like the jaw is chattering, sometimes with teeth chattering); goose bumps (small bumps like a rash in the skin), also known as pimples. These are involuntary body responses (which a person cannot consciously control). Tremors cause the muscles to contract and relax, which warms the body.

Return_to_chills

Complete case definition for headache[198]

Headache is pain in any region of the head.

Headaches can occur on one or both sides of the head, be isolated to a particular location, radiate through the head from one point, or have a sensation of screw pressure.

Headaches can appear as a sharp pain, a throbbing sensation, or a dull ache. They can last from less than an hour to several days.

A primary headache can be caused by overactivity of or problems with pain-sensitive structures in the head.

A primary headache is not a symptom of an underlying disease. Chemical activity in the brain, the nerves or blood vessels surrounding the skull, or the muscles of the head and neck (or some combination of these factors) can play a role in primary headaches.

Some people may also carry genes that make them more likely to develop such headaches. A few headache patterns are also generally considered types of primary headaches but are less common. These headaches have distinct features, such as an unusual duration or pain associated with a certain activity.

Return_to_Headache

Complete case definition for local reactions[202]

The general definition: It was developed by the BC group to allow for an improvement in the comparability of data and to allow a better understanding of the injection site and related local reactions and serves three different purposes: [1] to determine whether a local reaction can be present, that is, act as a screening tool for the presence of any local reaction; [2] a local reaction present must be decided which specific local reaction is present; and [3] along with the guidelines to serve as a tool to collect, analyze and present the information necessary to allow a standardized assessment of a local reaction.

Level 1 of diagnostic certainty: Any description of morphological or physiological change at or near the injection site,

THAT IS, described or identified by a healthcare provider.

Level 2 of diagnostic certainty: Any description of morphological or physiological change at or near the injection site,

THAT IS, described or identified by any other person.

Level 3 of diagnostic certainty: Not applicable.

Exclusion criteria: A systemic reaction that includes the injection site, e.g., generalized urticaria, **OR** other distinct entities or conditions such as lymphadenopathy that may be near the injection site.

Return_to_Local_Reactions

Complete case definition for nodule[204]

The discrete (i.e., well-demarcated) clinical feature of a nodule at the injection site sufficiently differentiates it from the more common clinical picture of acute induration and swelling, which are more diffuse and of shorter duration. Moreover, no clear cut-off time based on duration and onset of a nodule at the injection site versus acute induration and swelling could be identified based on the current understanding of these reactions.
A nodule is a solid formation (lump) of more than 2.5 cm in diameter that persists for more than a month, caused by epidermal thickening, inflammatory infiltration of the skin or subcutaneous tissues, or by deposits of substances at the administration site. Nodules are firm and may include increased sensitivity, pain, and itching.

Case definition for nodule at the injection site as an AEFI: A nodule at injection site is defined by:

Level 1 of diagnostic certainty: The presence of a discrete or well-demarcated soft-tissue mass or lump

THAT IS firm,

AND is at the injection site.

There may be additional less-discrete, softer swelling surrounding the nodule at the injection site, especially early in its development. There may also be tenderness and pruritus. In the absence of abscess formation,

AND erythema, **AND** warmth.

Levels 2 and 3 of diagnostic certainty: Not applicable.

Return_to_Nodule

Complete case definition for cellulitis[205]

Cellulitis is defined[a] as an acute, infectious,[b] and expanding inflammatory condition of the skin that is characterized by the following inclusion and exclusion criteria. Of note, cellulitis may be accompanied by fever[c] and/or regional lymphadenopathy; however, their presence or absence does not influence the level of diagnostic certainty. The clinical manifestations of cellulitis are related to the infecting organism and the vaccination technique, and not the vaccine administered. Because cellulitis as an AEFI is usually a bacterial infection, it is commonly treated empirically with antimicrobial agents. However, identification of the etiological agent is useful in adapting therapy and avoiding overtreatment with antimicrobial agents of large noninfectious local reactions.

Level 1a of diagnostic certainty: At least three of the following four signs/symptoms: localized pain or tenderness[d] (pain to touch), erythema,[d] induration[d] or swelling,[e] warmth,[d]

AND reaction is at the injection site [f],

AND laboratory confirmation by culture.[g]

If known,h exclusion criteria are spontaneous rapid resolution,[l] **AND/OR** fluctuance.[j]

OR

Level 1b of diagnostic certainty: A diagnosis of cellulitis by a qualified healthcare provider,[k]

THAT IS at the injection site;[f]

AND laboratory confirmation by culture.[g]

If known,[h] exclusion criteria are spontaneous rapid resolution,[l]

AND/OR fluctuance.[j]

Level 2 of diagnostic certainty: At least three of the following four signs/symptoms: localized pain or tenderness[d] (pain to touch), erythema,[d] indurationd or swelling,[e] warmth,[e]

AND reaction is at the injection site,[f]

AND has been diagnosed by a qualified healthcare provider.[g]

If known,[h] exclusion criteria are spontaneous rapid resolution,[l]

AND/OR fluctuance.[j]

Level 3 of diagnostic certainty: At least three of the following four signs/symptoms localized pain or tenderness[d] (pain to touch), erythema,[d] induration[d] or swelling,[e] warmth,[d]

AND reaction is at the injection site,[f]

AND has been reported by any person (not specified as a qualified healthcare provider).[g]

If known,[h] exclusion criteria are spontaneous rapid resolution,[i]

AND/OR fluctuance.[j]

[a] All criteria (inclusion and exclusion) apply to the time of diagnosis, and review of all criteria (inclusion and exclusion) prior to categorization of a case is necessary. Follow-up information can be considered if sufficiently documented and reported in a timely manner.

[b] The infectious agent is not to solely include the vaccine antigen itself.

[c] Fever is defined as ≥ 38 °C.

[d] Cellulitis at injection site is distinguished from postinjection erythema, tenderness, and induration by the more intense erythema, tenderness to light touch, at least moderate induration, and substantial local warmth.

[e] See respective BC CDs for swelling and induration at injection site. Cellulitis is typically accompanied by induration and not swelling. However, for reporting and coding purposes, either is acceptable.

[f] In subcutaneous tissue, fat, fascia, or muscle.

[g] The diagnosis of cellulitis may be clinical, or laboratory confirmed. An aspirate from the involved area should be done for a laboratory culture confirmation of the etiological agent. It is less common but more definitive in confirming cellulitis of infectious etiology. Similarly, a positive recovery of a recognized pathogen such as S. aureus or group A beta-hemolytic Streptococcus from a blood culture in the presence of at least three listed signs/symptoms would confirm the presence of cellulitis. Laboratory confirmation facilitates the differentiation of cellulitis from postimmunization erythema or induration. In the absence of laboratory confirmation, diagnosis of cellulitis by a qualified

healthcare provider or treatment with antimicrobial agents may increase the likelihood of the correctness of the diagnosis. Healthcare provider is not further defined, because of country-specific differences; qualifying professionals will have to be decided upon in the respective country.

[h] Lack of information on exclusion criteria does not preclude the diagnosis of cellulitis; however, if exclusion criteria are present, the event needs to be rejected as cellulitis at injection site.

[i] Cellulitis at injection site is associated with a prolonged duration; erythema and induration at injection site usually resolve spontaneously within 2 days, whereas cellulitis does usually not resolve spontaneously.

[j] See "Brighton" CD for abscess at injection site (http://www.brightoncollaboration.org/internet/en/index.html): if the involved area develops fluctuance, or ultrasound evidence of abscess, then the event should be reported as an abscess.

[k] A qualified healthcare provider diagnosis alone with laboratory confirmation is acceptable as Level 1 evidence, because healthcare providers typically report a diagnosis rather than individual symptoms.

Return_to_Cellulitis

Complete case definition for abscess[206]

Abscess at the injection site is a localized soft tissue collection of material, occurring at the site of immunization and is defined by:

Level 1 of diagnostic certainty: Abscess of infectious etiology: spontaneous or surgical drainage of material from the mass, **AND** laboratory confirmation (Gram stain, culture, or other tests) of microbiological organisms with or without polymorphonuclear leukocytes in material drained or aspirated from mass. Abscesses of infectious etiology may be accompanied by fever and/or regional lymphadenopathy. Sterile abscess: spontaneous or surgical drainage of material from the mass, **AND** material obtained from the mass prior to initiating antimicrobial therapy, but with negative evaluation for infectious etiology (which may include Gram stain, cultures, or other tests). Sterile abscesses are typically not accompanied by fever and/or regional lymphadenopathy.

Level 2 of diagnostic certainty: In settings where laboratory evaluation for infectious etiology (Gram stain, cultures, or other technique) was either not performed, performed after starting antimicrobial therapy, or not reported.

A. Abscess of infectious etiology: Spontaneous or surgical drainage of purulent material from the mass, **OR** collection of material diagnosed by an imaging technique (e.g., sonogram, CT, MRI, or another modality) or fluctuance, **AND** localized sign(s) of inflammation including at least one of the following: erythema, pain to light touch, or warm to touch at the injection site, **AND** resolution/improvement temporally related to antimicrobial therapy. Abscesses of infectious etiology may be accompanied by fever and/or regional lymphadenopathy.

B. Sterile abscess: Spontaneous or surgical drainage of nonpurulent material from the mass, **OR** collection of material e.g., fluid diagnosed by imaging technique (e.g., sonogram, CT, MRI, or another modality) or fluctuance, **AND** the absence of signs of local inflammation such as erythema, pain to light touch, and warm to touch at the injection site, **OR** no resolution/improvement temporally related to antimicrobial therapy. Sterile abscesses are typically not accompanied by fever and/or regional lymphadenopathy.

Type indeterminant: Insufficient information to determine whether abscess is of infectious etiology or a sterile abscess, i.e., report of incision and drainage of the injection site mass but no culture results reported, or report of the collection of material at the injection site demonstrated by an imaging technique but clinical symptoms or response to antimicrobial therapy not reported.

Level 3 of diagnostic certainty: Not applicable.

For all levels listed above, the following in and of themselves do not constitute abscesses at the injection site: superficial vesicles or pustules on the skin; suppurative lymph nodes adjacent to the site of immunization; septic joints adjacent to the site of immunization, or cellulitis and nodule at injection site.

Return_to_Abscess

Complete case definition for induration[207]

Induration and swelling at the injection site are commonly reported local reactions following immunization. However, there are no standardized definitions of swelling and induration, and it may be that the term induration is used as a synonym for swelling in some reports. Sometimes, swelling and induration are used interchangeably in the literature, and sometimes both are mentioned, either separately or combined, but with no further description of their differences.

Case definition for induration at or near injection site:

Level 1 of diagnostic certainty: Palpable thickening, firmness, or hardening of soft tissue,[a]

AND is assessed and reported by a healthcare provider.[b]

Level 2 of diagnostic certainty: Palpable thickening, firmness or hardening of soft tissue,[a]

AND is assessed and reported by any person (not specified as a healthcare provider).

Level 3 of diagnostic certainty: Not applicable.

Notes: For all levels – induration should be described as follows for each level of diagnostic certainty: (a) induration clearly includes the injection site(s) (approximate point of needle entry), OR (b) local induration not clearly including the injection site(s). Induration needs to be carefully distinguished from abscess, nodule, cellulitis, and swelling. It is recognized that distinguishing them clinically can sometimes be difficult. Moreover, induration can exist independently of, concomitantly to, or as part of, the other event. Focus should be given to differentiate swelling from induration. Swelling is typically caused by fluid infiltration in tissue, and, although swelling may be either soft (typically) or firm (less typical) depending on the space available for fluid to disperse, it can best be described by looking and measuring. Induration is usually well demarcated with palpable borders, can be visible (raised or sunken compared to surrounding skin), is often "woody" to touch, and has a flat shape (versus the rounder shape of a nodule); it can best be described by palpation. The appropriate BC documents (http://www.brightoncollaboration.org/en/index/aefi.html) defining these conditions could be consulted, and the local reaction(s) that best fits the description should be considered.

[a] In subcutaneous tissue, fat, fascia, or muscle.

[b] Healthcare provider is not further defined, because of country-specific differences; qualifying professionals will have to be decided upon in the respective country.

Return_to_Induration

Complete case definition for swelling[208]

Swelling at injection site is the most frequent AEFI reported and in vaccine clinical trials. The definition of swelling at or near injection site is as an increase in size or volume at the injection site that may extend to the entire limb according to severity. It is currently unknown whether localized swelling at or near the injection site and "whole or upper or extensive limb swelling" are pathophysiologically different events.

Level 1 of diagnostic certainty:[a] Visible enlargement of an injected limb with or without objective measurement,

AND assessed by a healthcare provider. [b]

Level 2 of diagnostic certainty:a Visible enlargement of an injected limb with or without objective measurement.

AND Assessed by any person (not specified as a healthcare provider).[b]

Level 3 of diagnostic certainty: Not applicable

For all levels: Extension of swelling should be described as follows for each level of diagnostic certainty:

(a) Swelling clearly including the injection site(s) (approximate point of needle entry);

(b) Local swelling, near to, but not clearly including the injection site(s);

(c) "Joint to joint" or "crossing-joint" – joint to joint means that the swelling includes the entire portion of the limb between joints, e.g., upper limb (i.e., from shoulder to elbow), and crossing joints means that the swelling crosses at least one joint (e.g., the elbow joint).

The swelling may be accompanied by erythema and tenderness.

Swelling needs to be carefully distinguished from abscess, nodule, cellulitis, and induration. It is recognized that distinguishing them clinically can sometimes be difficult. Moreover, swelling can exist independently of, concomitantly to, or as part of, the other event. Focus should be given to differentiate swelling from induration. Swelling is typically caused by fluid infiltration in tissue, and although swelling may be either soft (typically) or firm (less typical) depending on the space available for fluid to disperse, it can best be described by looking and measuring. Induration usually has well-demarcated palpable borders, can be visible (raised or sunken compared to surrounding skin), is often "woody" to touch, and has a flat shape (versus the rounder shape of a nodule); it can best be described by palpation.

[a] Where possible, the swelling should be measured using valid instruments. It is considered that a valid measurement could be difficult to obtain outside the context of the controlled conditions of a clinical trial or prospective epidemiological study with a predefined protocol. Standardized and pre-tested tools and methods could be used, such as a caliper or pre- and post-injection measurement of the limb circumference at the injection site and/or at mid-limb. Caution should be used in the interpretation of tape measurements of the ipsi- and contra-lateral limbs given natural differences due to single handedness.

[b] Healthcare provider is not further defined, because of country-specific differences; qualifying providers will have to be decided upon in the respective country.

Return_to_Swelling

Complete case definition for immunization site_pain[209]

It is an unpleasant sensory and emotional experience associated with actual or potential tissue damage and is the most frequent local AEFI. Pain results from the stimulation of nociceptive sensory neurons at the time of vaccine administration or inflammatory process in the damaged tissue afterwards.

Level 1 of diagnostic certainty: Presence of an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage,

AND occurring at the immunization site with or without involvement of surrounding tissue,

AND at the time of vaccine administration or following such a procedure,

AND self-report of pain or distress as assessed by a subject (self-report) using validated or verified instruments.

- For pre- or non-verbal subjects, observer report using validated tools (specific method depends on age).

Level 2 of diagnostic certainty: Presence of an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage,

AND occurring at the immunization site with or without involvement of surrounding tissue,

AND at the time of vaccine administration or following such a procedure,

AND other observer or reporter of pain or distress in a subject capable of self-report, whereby pain is assessed by an observer using a validated or verified instrument on behalf of the subject.

Level 3 of diagnostic certainty: Presence of an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage,

AND occurring at the immunization site with or without surrounding tissue,

AND at the time of vaccine administration or following such a procedure,

WITHOUT additional description of pain and distress or assessment with a validated method.

Return_to_Site_Pain

Complete case definition for redness[7, 21]

Redness can occur at the injection site; in general, it is a mild and well-tolerated manifestation, lasting 24–48 hours.

Local inflammatory sign that usually subsides within the first 24 hours following vaccine application.

Redness at the injection site is a common and expected reaction to vaccine administration. The injection of foreign material into the tissues and irritation of the tissues by the process of injection can produce a localized inflammatory response.

Return_to_Redness

Complete case definition for malaise[212]

An indefinite feeling of debility or lack of health often indicative of or accompanying the onset of an illness. A vague sense of mental or moral ill-being, a malaise of cynicism and despair.

Sometimes, malaise happens suddenly. Other times, it may develop gradually and persist for a long period. The reason behind malaise can be extremely difficult to determine because it can be the result of so many conditions.

Malaise and fatigue: Fatigue often occurs along with malaise. When experiencing malaise, a person will often also feel exhausted or lethargic in addition to a generalized feeling of being unwell.

Like malaise, fatigue has many possible explanations. It can be due to lifestyle factors, illnesses, and certain medications.

Return_to_Malaise

Complete case definition for muscle pain[215]

Muscle pain is described as pain associated with ligaments, tendons, and soft tissue that connect bones, organs, and muscles.

Return_to_Muscle_Pain

Complete case definition for nausea and vomiting[217]

Nausea and vomiting are not diseases, but rather are symptoms of many different conditions, such as infection ("stomach flu"), food poisoning, motion sickness, overeating, blocked intestine, illness, concussion or brain injury, appendicitis, and migraines.

Nausea and vomiting can sometimes be symptoms of more serious diseases such as heart attacks, kidney or liver disorders, CNS disorders, brain tumors, and some forms of cancer.

Nausea is an uneasiness of the stomach that often accompanies the urge to vomit but does not always lead to vomiting. Vomiting is the forcible voluntary, forced, or involuntary emptying ("throwing up") of stomach contents through the mouth.

Some triggers that may result in vomiting can come from the stomach and intestines (infection, injury, and food irritation), the inner ear (dizziness and motion sickness), and the brain (head injury, brain infections, tumors, and migraine headaches).

Return_to_Nausea_Vomiting

Complete case definition for neutropenia[218]

Neutropenia occurs when a person has too few neutrophils, a type of white blood cell. While all white blood cells help the body fight infections, neutrophils are important for fighting certain infections, especially those caused by bacteria. People often only find out about the problem when they have had blood tests done for other reasons.

A single blood test showing low levels of neutrophils does not necessarily mean a person has neutropenia. These levels can vary from day to day, so if a blood test shows a person has neutropenia, it needs to be repeated for confirmation. Neutropenia can make the person more vulnerable to infections. When neutropenia is severe, even the normal bacteria from the mouth and digestive tract can cause serious illness.

Severity of neutropenia relates to the relative risk of infection and is classified as follows:

- Mild: 1,000–1,500/mcL ($1–1.5 \times 10^9$/L);
- Moderate: 500–1,000/mcL ($0.5–1 \times 10^9$/L);
- Severe: < 500/mcL ($< 0.5 \times 10^9$/L).

When the neutrophil counts fall to < 500/mcL, endogenous microbial flora (e.g., in the mouth or gut) can cause infections. If the count falls to < 200/mcL ($< 0.2 \times 10^9$/L), the inflammatory response may be muted and the usual inflammatory findings of leukocytosis or white blood cells in the urine or at the site of infection may not occur.

Acute, severe neutropenia, particularly if another factor (e.g., cancer) is present, significantly impairs the immune system and can lead to rapidly fatal infections. The integrity of the skin and mucous membranes, the vascular supply to tissue, and the nutritional status of the patient also influence the risk of infections.

Return_to_Neutropenia

Complete case definition for an allergic reaction[222]

An allergic reaction of the skin including any one of the following: urticaria (hives), erythema, pruritus, prickle (**or tingling**) sensation, localized or generalized edema (in the deeper layers of the skin, subcutaneous tissues, or mucosa lining the throat, airways, and gut), which can occur 0–2 days following immunization. An allergic reaction is an acquired hypersensitivity to an antigen that does not normally produce such a reaction.

Antigen-antibody complexes stimulate the release of chemicals, such as histamine, that produce overt signs and symptoms of hypersensitivity.

An allergic reaction can occur in response to a component of a vaccine in a person previously sensitized (i.e., antibodies must be present from a previous exposure to the antigen).

Return_to_Allergic_Reaction

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This reference document lists and provides internationally standardized case definitions of adverse events of special interest and adverse events following immunization for COVID-19 vaccines. It is based on publications, documents, and information on the subject, and also lists other risks related to diseases, medicines, and vaccines that are part of routine vaccination schedules in countries. It offers healthcare professionals and decisionmakers in public health a tool with the primary objective of strengthening the pharmacovigilance of vaccines against COVID-19, reinforcing the importance of standardizing the definitions of adverse events and guidelines, to allow comparability of data and a better understanding of adverse events, considering the extreme importance of surveillance of the safety of COVID-19 vaccines. It aims to facilitate the recognition of adverse events following immunization, especially serious and/or uncommon ones, improving case analysis and the dissemination of high-quality information on vaccine safety. Conventional vaccine safety surveillance and pharmacovigilance systems need to adapt to new surveillance techniques and ensure that post-vaccination safety and exposure information is collected and processed quickly and in a standardized manner. Licensed vaccines and those that are in clinical trial and that have received emergency authorization for use will require close monitoring by multiple stakeholders to ensure that their use remains as safe and effective in the field as in clinical trials.

PAHO Pan American Health Organization World Health Organization Regional Office for the Americas