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Anaphylaxis: Case definition and guidelines for data collection, analysis, and presentation of immunization safety data☆

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1. Preamble

1.1. Need for developing case definitions and guidelines for data collection, analysis, and presentation for anaphylaxis as an adverse event following immunization

Anaphylaxis is an acute hypersensitivity reaction with multi-organ-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 [1–4].

Anaphylaxis is triggered by the binding of allergen to specific immunoglobulin E (IgE). It implies previous exposure and sensitization to the triggering substance or a cross reactive allergen. When an allergen binds to the IgE receptors on

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the surface of mast cells and basophils this results in cellular activation and degranulation. These cells release preformed mediators such as histamine and tryptase that elicit the signs and symptoms of anaphylaxis. This mechanism is also known as the Type 1 immediate hypersensitivity reaction in the Gel and Coombs classification [1,3].

"Anaphylactoid" reactions are clinically indistinguishable, but differ from anaphylaxis by their immune mechanism, being characterized by mast cell activation due to a range of chemical or physical triggers *independently* of IgE. This mechanism is less well understood. As distinction between anaphylaxis and anaphylactoid reaction is impossible on the basis of clinical signs and symptoms alone, a clinical definition cannot differentiate between the two. This position is consistent with recent suggestions for a revised nomenclature for allergy, issued by the European Association for Allergy and Clinical Immunology (EAACI) and the World Allergy Organization, referring to anaphylactoid reactions simply as "non-allergic anaphylaxis" [5–7].

Anaphylaxis following immunization is a serious, but rare occurrence—estimates are in the range of 1–10 per 1 million doses distributed depending on the vaccine studied [8–10], but accurate estimates are hampered by limited data and lack of standard case definitions. Some studies had to extrapolate their estimates from small absolute case numbers. Most publications on anaphylaxis following immunization are case reports or series, which do not use case definitions. Few publications dealing with larger case numbers have used strict, but quite different case definitions [8,10–18].

The Council for International Organizations of Medical Sciences (CIOMS) provides a case definition of anaphylaxis as a drug reaction [19]. It differentiates between anaphylactic reaction, anaphylactic shock, and anaphylactoid reaction, which is no longer in keeping with current allergy terminology (see above). With "anaphylactic reaction" requiring the presence of just a single skin, respiratory, or cardiovascular symptom, the specificity of the CIOMS definition may also be low. The criteria of anaphylactic shock also overlap to some degree with those of simple anaphylactic reactions.

An international symposium recently acknowledged that even a widely accepted definition of anaphylaxis in general is lacking, thus contributing to a wide variation in standards of diagnosis and management [7]. This symposium also developed a very useful preliminary definition, based on proposed diagnostic criteria, which has recently been modified [20]. This definition reflects a very similar understanding of anaphylaxis as the one presented herein, but it does not allow for different levels of evidence and it makes assumptions about "known allergens for the patient", which renders it less suitable for a vaccination setting.

There is hence no uniformly accepted definition of anaphylaxis following immunizations. This is a missed opportunity, as data comparability across trials or surveillance systems would facilitate data interpretation and promote the scientific understanding of the event.

1.2. Methods for the development of the case definition and guidelines for data collection, analysis, and presentation for anaphylaxis as an adverse event following immunization

Following the process described in the overview paper [21] as well as on the Brighton Collaboration Website http://www.brightoncollaboration.org/internet/en/index/process.html, the Brighton Collaboration *Anaphylaxis Working Group* was formed in 2003 and included members of clinical and academic, but also public health and industry background. The composition of the working and reference group as well as results of the web-based survey completed by the reference group with subsequent discussions in the working group can be viewed at: http://www.brightoncollaboration.org/internet/en/index/working_groups.html.

To guide the decision-making for the case definition and guidelines, a literature search was performed using Medline, Embase and the Cochrane Libraries, including the terms *vaccines, vaccination*, or *immunization* (*or terms beginning with vaccin-, immuni-, inoculat-*), and [*drug or delayed or immediate*] *hypersensitivity* (*or allerg-, hypersensit-, anaphyla-*). The search resulted in the identification of 9547 references. All abstracts were screened for possible reports of anaphylaxis following immunization. Two hundred and fifty-nine articles with potentially relevant material were reviewed in more detail, in order to identify studies using case definitions or, in their absence, providing clinical descriptions of the case material. This review resulted in a detailed summary of 110 articles, including information on the study type, the vaccine, the diagnostic criteria or case definition put forth, the time interval since time of immunization, and any other symptoms. Most publications were case reports of single cases. The terminology was very inconsistent. Very few used case definitions at all, and no two studies used the same definition. Multiple general medical, paediatric and infectious disease text books were also searched. An inventory comprising 14 relevant case definitions of anaphylaxis was made available to working group members.

1.3. Rationale for selected decisions about the case definition of anaphylaxis as an adverse event following immunization

1.3.1. The term anaphylaxis

Several related terms are commonly used in clinical practice, like "anaphylaxis", "anaphylactic reaction", "anaphylactoid reaction", and "anaphylactic shock". The working group refrained from using the term "anaphylactic reaction", due to its inference of a causal relation to a given exposure. Such a term is methodologically misleading when used in studies aiming to evaluate a potential causal relation to a given exposure. As current allergy terminology does not distinguish between "anyphylactic" and "anaphylactoid" events, the proposed Brighton definition refers to "anaphylaxis" only.

The term anaphylaxis has been used in some contexts primarily to denote an *immunological* principle (i.e., type I reaction according to Coombs/Gel) while in other contexts it has been reserved to denote the life-threatening character of a *clinical* event, thus implying a degree of clinical severity. The Brighton Collaboration case definition refers to the latter usage of the term, in keeping with the European Academy of Allergology and Clinical Immunology (EAACI's) and the American Academy of Pediatrics' use of the term [5,22]. In the definition presented here, severity is implied by the presence of cardiovascular and/or respiratory involvement in the presence of multi-system findings. Within the definition context, however, the three diagnostic levels must not be misunderstood as reflecting different grades of clinical severity. They instead reflect diagnostic certainty (see below).

1.3.2. The term "anaphylactic shock"

In its definition, the Brighton Collaboration Working Group refers to "anaphylactic shock" as the most severe manifestation of anaphylaxis. The Working Group has aimed to reflect the clinical syndrome of marked tissue hypoperfusion with signs and symptoms of haemodynamic failure in the definition.

1.3.3. Anaphylaxis as a multi-system disorder

Anaphylaxis is set apart from simple allergic reactions (e.g., urticaria, allergic rhinitis, asthma) by the simultaneous involvement of several organ systems. The combination of cardio-respiratory signs with mucosal and/or skin changes (urticaria, angioedema, etc.) is most specific. The presence of (muco-) cutaneous signs is key to differentiating anaphylaxis from similar clinical syndromes of different etiology (e.g., septic shock, syncope, myocardial infarction, hypotonic-hyporesponsive episode). Evidence of skin involvement is therefore required at Level One of the anaphylaxis definition.

In some patients, the clinical picture may be incomplete and cutaneous signs may be absent. This may even include the most acute and severe clinical cases, with rapid progression to asystole and death. The definition is designed to capture such cases under Level Two or Level Three. In order to retain sufficient specificity, involvement of two or more organ systems is indispensable at any level of the definition, always including the cardiovascular and/or respiratory system.

1.3.4. Formulating a case definition that reflects diagnostic certainty: weighing specificity versus sensitivity

As anaphylaxis is a medical emergency, the number of symptoms and/or signs that will be documented for each case may vary considerably. The case definition 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 One down to Level Three, while retaining an acceptable level of specificity at all levels. In this way it is hoped that all possible cases of anaphylaxis can be captured.

It needs to be re-emphasized that the grading of definition levels is entirely about diagnostic certainty, not clinical severity of an event. Thus, a clinically very severe event may appropriately be classified as Level Two or Three rather than Level One if it could reasonably be of non-anaphylactic etiology. Detailed information about the severity of the event should additionally always be recorded, as specified by the data collection guidelines.

1.3.5. Influence of treatment on fulfilment of case definition

The Working Group decided against using "treatment" or "treatment response" towards fulfillment of the anaphylaxis case definition, in contrast to some previous definitions of anaphylaxis [10,15].

A treatment response or its failure is not in itself diagnostic, and may depend on variables like clinical status, time to treatment, and other clinical parameters. Epinephrine is part of the treatment of any type of shock (allergic, septic, vascular, etc.). It may equally improve or mask symptoms in acute asthma, fainting spells, vasovagal syncope, etc. Prompt and early treatment of anaphylaxis may prevent the development of symptoms in other organ systems [23]. This may most commonly occur in controlled settings where anaphylaxis is anticipated and treatment is delivered promptly, such as specialized allergy clinics. Hence, we designed the Level 2 and Level 3 definitions to be broad enough to include cases presenting differently due to appropriate and early treatment initiation. For those cases where signs and symptoms remain limited to one body system we suggest using an alternative label specific to the organ system involved, such as rash, urticaria, asthma, etc.

1.3.6. The meaning of "sudden onset" and "rapid progression" in the context of anaphylaxis

The term "sudden onset" refers to an event that occurred unexpectedly and without warning leading to a marked change in a subject's previously stable condition.

The term "rapid progression" is a conventional clinical term. An exact timeframe should not be offered since it would have to refer to a wide range of signs and symptoms without a scientific evidence base. Using an arbitrarily restrictive setpoint might bias future data collection unnecessarily.

1.3.7. Timing post-immunization

Specific time frames for onset of symptoms following immunization are not included for the following main reasons: clinical manifestations of anaphylaxis are typically described as starting within seconds to minutes of exposure to a given substance. Most cases start within 1 h of exposure

[9,24,25], but in a minority of cases, symptoms may present up to 12 h after exposure. Biphasic presentation up to 72 h has also been described [23,26–28]. Clinical manifestations may also vary depending on the route of exposure to the allergen (intravenous versus oral, intramuscular, subcutaneous, etc.) [29].

Many authors have used time criteria as part of their definition of an allergic event, supporting the authors' contention that the cases described by them may have been *caused* by immunization [8,10,12,13,16]. We postulate, however, that a definition designed to be a suitable tool for testing causal relationships requires ascertainment of the outcome (e.g., anaphylaxis) independent from the exposure (e.g., immunizations). Therefore, to avoid selection bias, a restrictive time interval from immunization to onset of anaphylaxis should not be an integral part of such a definition. Instead, where feasible, details of this interval should be assessed and reported as described in the data collection guidelines.

Further, anaphylaxis most often occurs outside the controlled setting of a clinical trial or hospital. In some settings it may be impossible to obtain a clear timeline of the event, particularly in less developed or rural settings. In order to avoid selecting against such cases, the Brighton Collaboration definition avoids setting arbitrary time frames.

1.3.8. Pathology findings—mast cell tryptase

The measurement of serum mast cell tryptase (MCT) has been used as a marker of anaphylaxis [30]. MCT is increased in patients with hypotensive anaphylaxis following injected antigens [30]. Levels peak between 15 and 120 min from the onset of symptoms and are best determined within 6 h of the event [31]. However, because of uncertainties regarding the specificity of MCT in the diagnosis of anaphylaxis, as well as the absence of vaccine-specific data, the Working Group decided that MCT merits inclusion, but only as a minor criterion at the present stage. Investigators are nonetheless encouraged to determine MCT in cases of suspected anaphylaxis.

1.3.9. Pathology findings—IgE levels

The presence of antigen specific serum-IgE is not necessarily predictive of clinical allergic manifestations [32]. Neither does the absence of specific IgE rule out anaphylaxis, as the mechanism of anaphylaxis may well be non-IgE-mediated. There is therefore no role for specific IgE measurement in this case definition. The potentially useful role of specific IgE for *causality assessment* is undisputed, but it is not an approriate tool for *case ascertainment* and is not a criterion of the Brighton Collaboration case definition.

1.3.10. Pathology findings—autopsy

Anaphylaxis does not produce pathognomonic post-mortem features [29]. Post-mortem findings are therefore not included in the case definition of anaphylaxis proposed here.

1.3.11. Sudden unexplained death

The working group is aware that in settings with limited resources and access to health care a patient with anaphylaxis might not uncommonly present as a sudden, unexplained death. Although it is appreciated that this may be an important occurrence in such settings, the absence of specific criteria for the post-mortem diagnosis of anaphylaxis [29] would not permit a diagnosis of anaphylaxis at any acceptable level of diagnostic certainty. If anaphylaxis is strongly suspected as being the cause of death, such events may have to be categorized as "Reported anaphylaxis with insufficient evidence to meet the case definition" (see Section 3.2).

1.3.12. Oculo-respiratory syndrome

Among differential diagnoses of anaphylaxis as defined by us and others, the recently described "oculo-respiratory-syndrome" (ORS) requires special mention. This entity is defined by the presence of bilateral conjunctivitis in association with a wide range of mucosal and/or respiratory manifestations, some of which are also characteristic of allergic reactions [33,34]. Its pathophysiology is not well understood, hampering its differentiation from anaphylaxis, particularly non-IgE-mediated anaphylaxis. There are hence no highly specific ORS definitions to date. Capture of ORS cases under the anaphylaxis definition might be reduced by omitting eye symptoms from the list of minor dermatological/mucosal symptoms. However, eye symptoms are relevant clinical clues towards possible anaphylaxis. As the pathophysiological and clinical picture of ORS becomes better understood, future case definitions of both syndromes will need to take account of these findings. At present, excluding cases with ocular involvement from the anaphylaxis definition would seem an arbitrary distinction and has been decided against.

1.3.13. Guidelines for data collection, analysis, and presentation

As mentioned in the overview paper, the case definition is accompanied by guidelines, which are structured according to the steps of conducting a clinical trial, i.e., data collection, analysis, and presentation. Neither case definition nor guidelines are intended to guide or establish criteria for management of ill infants, children, or adults. Both were developed to improve data comparability.

1.3.14. Periodic review

Similar to all Brighton Collaboration case definitions and guidelines, review of the definition with its guidelines is planned on a regular basis (i.e., every 3–5 years), or more often, if needed.

2. Case definition of anaphylaxis

For all levels 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

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 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

Major criteria

Dermatologic or mucosal	• generalized urticaria (hives) or generalized erythema • angioedema*, localized or generalized • generalized pruritus with skin rash
Cardiovascular	• measured hypotension • clinical diagnosis of uncompensated shock, indicated by the combination of at least 3 of the following: • tachycardia • capillary refill time >3 s • reduced central pulse volume • decreased level of consciousness or loss 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

* Not hereditary angioedema.

Minor criteria

dermatologic or mucosal	• generalized pruritus without skin rash • generalized prickle sensation • localized injection site urticaria • red and itchy eyes
Cardiovascular	• reduced peripheral circulation as indicated by the combination of at least 2 of • tachycardia and • a capillary refill time of >3 s without hypotension • a decreased level of consciousness
Respiratory	• persistent dry cough • hoarse voice • difficulty breathing without wheeze or stridor • sensation of throat closure • sneezing, rhinorrhea
Gastrointestinal	• diarrhoea • abdominal pain • nausea • vomiting
Laboratory	• Mast cell tryptase elevation > upper normal limit

3. Guidelines for data collection, analysis, and presentation of anaphylaxis

It was the consensus of the Brighton Collaboration *Allergic Reactions* Working Group for anaphylaxis to recommend the following guidelines to enable meaningful and standardized collection, analysis, and presentation of information about anaphylaxis. However, implementation of all guidelines might not be possible in all settings. The availability of information may vary depending upon resources, geographical region, and whether the source of information is a prospective clinical trial, a post-marketing surveillance or epidemiologic study, or an individual report of anaphylaxis. Also, as explained in more detail in the overview paper in this volume, these guidelines have been developed by this working group for guidance only, and are not to be considered a mandatory requirement for data collection, analysis, or presentation.

3.1. Data collection

These guidelines represent a desirable standard for the collection of data on anaphylaxis following immunization to allow for comparability of data, and are recommended as an addition to data collected for the specific study question and setting. The guidelines are not intended to guide the primary reporting of anaphylaxis to a surveillance system or study monitor. Investigators developing a data collection tool based on these data collection guidelines also need to refer to the criteria in the case definition, which are not repeated in these guidelines.

Guidelines 2, 5, 6,10, 16–18, 21–23 below have been developed to address data elements for the collection of adverse event information as specified in general drug safety guidelines by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use [35], and the form for reporting of drug adverse events by the Council for International Organizations of Medical Sciences [36]. These data elements include an identifiable reporter and patient, one or more prior immunizations, and a detailed description of the adverse event, in this case, of anaphylaxis following immunization. The additional guidelines have been developed as guidance for the collection of additional information to allow for a more comprehensive understanding of anaphylaxis following immunization.

3.1.1. Source of information/reporter

For all cases and/or all study participants, as appropriate, the following information should be recorded:

(1) Date of report.
(2) Name and contact information of person reporting[4] and/or diagnosing the anaphylaxis as specified by country-specific data protection law.
(3) Name and contact information of the investigator responsible for the subject, as applicable.
(4) Relation to the patient (e.g., immunizer [clinician, nurse], family member [indicate relationship], other).

3.1.2. Vaccinee/Control

3.1.2.1. Demographics. For all cases and/or all study participants, as appropriate, the following information should be recorded:

(5) Case/study participant identifiers (e.g., first name initial followed by last name initial) or code (or in accordance with country-specific data protection laws).
(6) Date of birth, age, and sex.
(7) For infants: gestational age and birth weight.

3.1.2.2. Clinical and immunization history. For all cases and/or all study participants, as appropriate, the following information should be recorded:

(8) Past medical history including hospitalizations, underlying diseases/disorders, pre-immunization signs and symptoms including identification of indicators for, or the absence of, a history of allergy to vaccines, vaccine components, or medications; food allergy; allergic rhinitis; eczema; or asthma.
(9) Any medication history (other than treatment for the event described) prior to, during, and after immunization including prescription and non-prescription medication as well as medication or treatment with long half-life or long term effect (e.g., immunoglobulins, blood transfusion, and immunosuppressants).
(10) Immunization history (i.e., previous immunizations and any adverse event following immunization [AEFI]), in particular occurrence of anaphylaxis after a previous immunization.

3.1.3. Details of the immunization

For all cases and/or all study participants, as appropriate, the following information should be recorded:

(11) Date and time of immunization(s).
(12) Description of vaccine(s) (name of vaccine, manufacturer, lot number, dose [e.g., 0.25 mL, 0.5 mL, etc.] and number of dose if part of a series of immunizations against the same disease).
(13) The anatomical sites (including left or right side) of all immunizations (e.g., vaccine A in proximal left lateral thigh, vaccine B in left deltoid).
(14) Route and method of administration (e.g., intramuscular, intradermal, subcutaneous, and needle-free [including type and size], other injection devices).
(15) Needle length and gauge.

3.1.4. The adverse event

(16) For all cases at any level of diagnostic certainty and for reported events with insufficient evidence, the criteria fulfilled to meet the case definition should be recorded.

Specifically document:

(17) Clinical description of signs and symptoms of anaphylaxis, and if there was medical confirmation of the event (i.e., patient seen by physician).
(18) Date/time of onset[5], first observation[6], and diagnosis[7], end of episode[8], and final outcome[9].
(19) Concurrent signs, symptoms, and diseases.
(20) Measurement/testing.

- Values and units of routinely measured parameters (e.g., °C, blood pressure)—in particular those indicating the severity of the event.
- Method of measurement (e.g., type of thermometer, oral or other route, duration of measurement, etc.).
- Results of laboratory examinations, surgical and/or pathological findings and diagnoses if present.

[4] If the reporting center isdifferent from the vaccinating center, appropriate and timely communication of the adverse event should occur.

[5] The date and/or time of onset is defined as the time post-immunization, when the first sign or symptom indicative for anaphylaxis occurred. This may only be possible to determine in retrospect.

[6] The date and/or time of first observation of the first sign or symptom indicative for anaphylaxis can be used, if date/time of onset is not known.

[7] The date of diagnosis of an episode is the day post-immunization when the event met the case definition at any level.

[8] The end of an episode is defined as the time the event no longer meets the case definition at the lowest level of the definition.

[9] E.g., recovery to pre-immunization health status, spontaneous resolution, therapeutic intervention, persistence of the event, sequelae, and death.

(21) Treatment given for anaphylaxis, especially epinephrine, steroids, volume, antihistamines.
(22) Outcome[9] at last observation.
(23) Objective clinical evidence supporting classification of the event as "serious"[10].
(24) Exposures other than the immunization 24 h before and after immunization (e.g., foods, environmental) considered potentially relevant to the reported event.

3.1.5. Miscellaneous/general

(25) The duration of surveillance for anaphylaxis should be predefined based on

- Biologic characteristics of the vaccine e.g., live attenuated versus inactivated component vaccines;
- Biologic characteristics of the vaccine-targeted disease;
- Biologic characteristics of anaphylaxis including patterns identified in previous trials (e.g., early-phase trials); and
- Biologic characteristics of the vaccinee (e.g., nutrition, underlying disease like immunodepressing illness).

(26) The duration of follow-up reported during the surveillance period should be predefined likewise. It should aim to continue to resolution of the event.
(27) Methods of data collection should be consistent within and between study groups, if applicable.
(28) Follow-up of cases should attempt to verify and complete the information collected as outlined in data collection guidelines 1–24.
(29) Investigators of patients with anaphylaxis should provide guidance to reporters to optimize the quality and completeness of information provided.
(30) Reports of anaphylaxis should be collected throughout the study period regardless of the time elapsed between immunization and the adverse event. If this is not feasible due to the study design, the study periods during which safety data are being collected should be clearly defined.

3.2. Data analysis

The following guidelines represent a desirable standard for analysis of data on anaphylaxis to allow for comparability of data, and are recommended as an addition to data analyzed for the specific study question and setting.

(31) Reported events should be classified in one of the following five categories including the three levels of diagnostic certainty. Events that meet the case definition should be classified according to the levels of diagnostic certainty as specified in the case definition. Events that do not meet the case definition should be classified in the additional categories for analysis.

Event classification in 5 categories[11]

Event meets case definition

(1) Level 1: Criteria as specified in the anaphylaxis case definition.
(2) Level 2: Criteria as specified in the anaphylaxis case definition.
(3) Level 3: Criteria as specified in the anaphylaxis case definition.

Event does not meet case definition
Additional categories for analysis

(4) Reported anaphylaxis with insufficient evidence to meet the case definition[12].
(5) Not a case of anaphylaxis[13].

(32) The interval between immunization and reported anaphylaxis could be defined as the date/time of immunization to the date/time of onset[5] of the first symptoms and/or signs consistent with the definition. If few cases are reported, the concrete time course could be analyzed for each; for a large number of cases, data can be analyzed in the following increments:

Subjects with anaphylaxis by Interval to Presentation		
Interval	**Number**	**Percentage**
<30 min after immunization		
30 ≤ 60 min after immunization		
60 ≤ 90 min after immunization		
90 ≤ 120 min		
Hourly increments thereafter		
Total		

(33) The duration of a possible anaphylactic event could be analyzed as the interval between the date/time of onset[4] of the first symptoms and/or signs consistent with the definition and the end of episode[8] and/or final

[10] An AEFI is defined as serious by international standards if it meets one or more of the following criteria: (1) it results in death, (2) is life-threatening, (3) it requires inpatient hospitalization or results in prolongation of existing hospitalization, (4) results in persistent or significant disability/incapacity, (5) is a congenital anomaly/birth defect, and (6) is a medically important event or reaction.

[11] To determine the appropriate category, the user should first establish, whether a reported event meets the criteria for the lowest applicable level of diagnostic certainty, e.g., Level 3. If the lowest applicable level of diagnostic certainty of the definition is met, and there is evidence that the criteria of the next higher level of diagnostic certainty are met, the event should be classified in the next category. This approach should be continued until the highest level of diagnostic certainty for a given event could be determined. Major criteria can be used to satisfy the requirement of minor criteria. If the lowest level of the case definition is not met, it should be ruled out that any of the higher levels of diagnostic certainty are met and the event should be classified in additional categories 4 or 5.

[12] If the evidence available for an event is insufficient because information is missing, such an event should be categorized as "Reported anaphylaxis with insufficient evidence to meet the case definition".

[13] An event does not meet the case definition if investigation reveals a negative finding of a necessary criterion (necessary condition) for diagnosis. Such an event should be rejected and classified as "Not a case of anaphylaxis".

outcome[9]. Whatever start and ending are used, they should be used consistently within and across study groups.

(34) If more than one measurement of a particular criterion is taken and recorded, the value corresponding to the greatest magnitude of the adverse experience could be used as the basis for analysis. Analysis may also include other characteristics like qualitative patterns of criteria defining the event.

(35) The distribution of data (as numerator and denominator data) could be analyzed in predefined increments (e.g., measured values, times), where applicable. Increments specified above should be used. When only a small number of cases is presented, the respective values or time course can be presented individually.

(36) Data on anaphylaxis obtained from subjects receiving a vaccine should be compared with those obtained from an appropriately selected and document control group(s) to assess background rates of hypersensitivity in non-exposed populations, and should be analyzed by study arm and dose, where possible, e.g., in prospective clinical trials.

3.3. Data presentation

These guidelines represent a desirable standard for the presentation and publication of data on anaphylaxis following immunization to allow for comparability of data, and are recommended as an addition to data presented for the specific study question and setting. Additionally, it is recommended to refer to existing general guidelines for the presentation and publication of randomized controlled trials, systematic reviews, and meta-analyses of observational studies in epidemiology (e.g., statements of Consolidated Standards of Reporting Trials [CONSORT], of improving the quality of reports of meta-analyses of randomized controlled trials [QUORUM], and of Meta-analysis Of Observational Studies in Epidemiology [MOOSE], respectively) [37–39].

(37) All reported events of anaphylaxis should be presented according to the categories listed in guideline 31.

(38) Data on possible anaphylactic events should be presented in accordance with data collection guidelines 1–24 and data analysis guidelines 31–36.

(39) Terms to describe anaphylaxis such as "low-grade", "mild", "moderate", "high", "severe", or "significant" are highly subjective, prone to wide interpretation, and should be avoided, unless clearly defined.

(40) Data should be presented with numerator and denominator (n/N) (and not only in percentages), if available.

Although immunization safety surveillance systems denominator data are usually not readily available, attempts should be made to identify approximate denominators. The source of the denominator data should be reported and calculations of estimates be described (e.g., manufacturer data like total doses distributed, reporting through Ministry of Health, coverage/population based data, etc.).

(41) The incidence of cases in the study population should be presented and clearly identified as such in the text.

(42) If the distribution of data is skewed, median and range are usually the more appropriate statistical descriptors than a mean. However, the mean and standard deviation should also be provided.

(43) Any publication of data on anaphylaxis should include a detailed description of the methods used for data collection and analysis as possible. It is essential to specify:
- The study design;
- The method, frequency, and duration of monitoring for anaphylaxis;
- The trial profile, indicating participant flow during a study including drop-outs and withdrawals to indicate the size and nature of the respective groups under investigation;
- The type of surveillance (e.g., passive or active surveillance);
- The characteristics of the surveillance system (e.g., population served, mode of report solicitation);
- The search strategy in surveillance databases;
- Comparison group(s), if used for analysis;
- The instrument of data collection (e.g., standardized questionnaire, diary card, report form);
- Whether the day of immunization was considered "day one" or "day zero" in the analysis;
- Whether the date of onset[5] and/or the date of first observation[6] and/or the date ofdiagnosis[7] was used for analysis; and
- Use of this case definition for anaphylaxis, in the abstract or methods section of a publication[14].

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[14] Use of this document should preferrably be referenced by referring to the respective link on the Brighton Collaboration website (http://www.brightoncollaboration.org).

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Appendix A. Tool to aid identification of appropriate level of diagnostic certainty

As an alternative format, the algorithm below provides a tool to aid identification of the appropriate definition level for a given case of suspected anaphylaxis.

Step 1): Select the diagnostic categories represented by the clinical symptoms and signs of the suspected case.

Major	Minor
☐ Dermatologic & MUCOSAL	☐ Dermatologic & mucosal
☐ Cardiovascular	☐ Cardiovascular
☐ Respiratory	☐ Respiratory
	☐ Gastrointestinal
	☐ Laboratory

Step 2) Select the **column** from the table representing the highest-ranking diagnostic category present (i.e., major > minor, dermatology > laboratory).
Step 3) Select a **row** from the table indicating the second highest ranking diagnostic category present.
Step 4) The intersection gives the level of diagnostic certainty of the case based on the Brighton definition. Blank intersections do not fulfil the case definition at any level.

Algorithm for calculating the diagnostic certainty of a suspected case of anaphylaxis

		Symptom One				
		DERM	CVS	RESP	Cvs	Resp
Symptom Two	CVS	1	-	2	-	2
	RESP	1	2	-	2	-
	Derm	-	2	2	3*	3*
	Cvs	2	-	2	-	3*
	Resp	2	2	-	3*	-
	GI	-	2	2	3*	3*
	Lab	-	2	2	3*	3*

Capitals: 1 or more MAJOR criteria in that system; Lower case: 1 or more minor criteria. Columns or rows in **CAPITALS** indicate that 1 or more MAJOR criteria are present in that category. Columns or rows in **Lower case** indicate that 1 or more minor criteria are present. Level 3 diagnostic certainty requires 2 *or more* rows to be present *in either the "cvs" or "resp" minor criteria column.*

1—Level 1 diagnostic certainty
2—Level 2 diagnostic certainty
3*—Level 3 diagnostic certainty requires *two or more* minor criteria to be present *in this column*

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