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Acute aseptic arthritis: Case definition & guidelines for data collection, analysis, and presentation of immunisation safety data

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1. Preamble

1.1. Need for developing a case definition and guidelines for data collection, analysis, and presentation for acute aseptic arthritis as an adverse event following immunisation (AEFI)

Acute aseptic arthritis (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 different inflammatory conditions directly affecting the synovium of a joint space. The term aseptic arthritis has been used to differentiate the clinical entity from infectious arthritides with a known viable infectious agent being or having been present in the synovial fluid and/or positive blood cultures [1]. However, the differential diagnosis of joint inflammation is broad [2] and a clear delineation of peri-, post- and noninfectious joint inflammation is challenging based on current literature [3]. Furthermore, arthritis may 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 [4,5].

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In recent years, the diagnostic use of polymerase chain reaction (PCR) has become more common in addition to standard and specialized culture techniques to exclude infectious agents in synovial fluid. Other laboratory tests aiming to substantiate or exclude an existing or preceding joint infection include synovial membrane biopsy, synovial immunofluorescence microscopy or synovial fluid leucocyte investigations [6].

1.1.1. Aseptic arthritis as AEFI

An overview of the available literature on aseptic arthritis as an AEFI is provided in the systematic review in the same issue of this journal [55]. In brief, 343 articles were reviewed. 62 studies reported arthritis alone as an AEFI, 236 studies reported arthralgia alone, 14 studies reported both arthritis and arthralgia as separate outcomes, and 17 studies used arthritis and arthralgia as a composite outcome.

However, outcome definitions for arthritis or arthralgia in these studies were scarce. The large majority (n = 221) used physician-verified or patient reports based on symptom diaries to describe the outcome. 74 studies provided a description of clinical characteristics with or without laboratory, histopathology, or imaging results.

Only 5 studies reported pre-defined arthritis criteria, of whom two used the American College of Rheumatology criteria [7,8], two used the International League of Associations for Rheumatology criteria [9,10], and one applied the American Rheumatism Association 1956 criteria [11]. Therefore, the Brighton Collaboration Working Group set out to meet the need of developing a standardized case definition for AAA as an AEFI.

1.2. Methods for the development of the case definition and guidelines for data collection, analysis, and presentation for acute aseptic arthritis as an AEFI

Following the standard process described in the overview paper [12] as well as on the Brighton Collaboration Website,[3] the Brighton Collaboration *Acute Aseptic Arthritis Working Group* was formed in 2015 and included members with clinical, academic, public health, regulatory, and vaccine manufacturer background.

To guide decision-making during case definition and guideline development, a literature search was performed using Medline via PubMed, Embase and the Cochrane Libraries, including terms related to "vaccine", "immunisation", "inoculation", "arthralgia", "arthritis", and "joint pain". The search resulted in the identification of 13,039 references after the duplicates were removed. All abstracts were screened for possible reports of arthritis or arthralgia following immunisation. Nine-hundred thirty 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 145 original articles, including information on the study type, the vaccine, the diagnostic criteria or case definition put forth, the time interval since time of immunisation, and any other symptoms [55].

1.3. Rationale for selected decisions about the case definition of acute aseptic arthritis as an AEFI

1.3.1. The term acute aseptic arthritis

The term 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 non-infectious immunological etiology, as well as para- and post-infectious inflammatory responses which may theoretically be induced or promoted by wild type infections or immunisation. Delineation between these different acute clinical entities and differentiation from post-traumatic, septic and chronic arthritis is paramount both for causality assessment as well as for clinical management of AEFI [13].

1.3.2. Differentiation of acute aseptic arthritis from trauma

In the presence of a swollen joint or periarticular tissue, recent articular trauma has to be excluded. Injury to various intra-articular structures or to the articular capsule may be the cause of increased synovial fluid or articular or periarticular tissue swelling. Depending on the type, severity and localisation of the trauma, a positive history of a traumatic event increases the probability of a non-inflammatory arthralgia or posttraumatic arthritis [14].

1.3.3. Differentiation of acute aseptic arthritis from septic arthritis

The concept of septic arthritis is based on presence and replication of bacteria in the synovial fluid with subsequent inflammation and joint destruction, potentially leading to sepsis and death, if left untreated. The inflammatory response is led by polymorphonuclear leukocytes, and the causative organism (e.g., *Staphylococcus aureus*) can be cultured in most of the cases.

Systemic signs of illness (e.g. fever, malaise, vomiting) commonly accompany septic arthritis. Arthritis may be only one site of a more generalized infection which might include other organ systems [15]. There is a common misconception that septic arthritis affects one joint only, but evidence suggests that in up to 22% of cases the presentation is polyarticular. Large joints are more commonly affected than small joints and in up to 60% of cases the hip or the knee is involved [16]. Risk factors of septic arthritis have been largely unchanged over time. They include, the elderly and children, pre-existing joint disease, 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 [17].

Laboratory evaluation of septic arthritis focuses on synovial fluid analysis. Depending on the duration and severity of symptoms and the causative agent, the WBC is often markedly elevated, with high neutrophil predominance, accompanied by low synovial fluid viscosity, high protein content, high synovial fluid lactate dehydrogenase and low synovial fluid glucose.

1.3.3.1. Laboratory differentiation between aseptic versus septic arthritis.
1.3.3.1.1. Synovial fluid leucocyte accuracy measures for acute aseptic versus septic arthritis. The synovial fluid WBC is the test most relied upon in the acute setting to classify an articular process as inflammatory or non-inflammatory [18]. The synovial fluid WBC count and differential (% polymorphonuclear [PMN]) perform well in discriminating between inflammatory and non-inflammatory disease. Still, they do not necessarily distinguish among the various types and causes of inflammatory disease [18,19]. There is wide variability among cell counts in infectious arthritis and other inflammatory arthritides. A WBC count > 50,000/mm^3 with >75% PMN, however, should be considered highly suggestive for a septic joint. In well-established bacterial infections, it is not uncommon to have synovial fluid WBC counts of 100,000–200,000/mm^3. Many studies underscore that the higher the cut-off point, the higher the specificity and the positive predictive value for septic arthritis [18–26]. The most used cut-offs[4] are 20000, 25000, 50000, and 100000 WBCs in mm^3. Among these cut-offs, 50000 is sometimes

[3] https://brightoncollaboration.org/public/what-we-do//setting-standards/case-definitions/process.html.

[4] Ascending order of value, not frequency of being mentioned.

called the "traditional" cut-off for septic arthritis [18], or simply specified as the WBC cut-off for septic arthritis [27–30].[5]

1.3.3.1.2. Synovial fluid biochemistry accuracy measures for Acute Aseptic versus septic arthritis. Synovial fluid consists of a filtrate of plasma, originating from subsynovial capillaries, and hyaluronic acid, secreted by the synoviocytes. In normal synovial fluid, small molecules such as glucose are similar to those in plasma, and total protein content ranges around 1.7–2.1 g/dl [1]. Measuring biochemistry parameters in synovial fluid such as glucose, protein and lactate dehydrogenase has been performed during routine analysis [31], but recent systematic publications failed to discriminate septic from non-septic arthritis [21].[6]

1.3.4. Differentiation from chronic inflammatory diseases with articular involvement

Chronic inflammatory conditions such as rheumatoid arthritis (RA), connective tissue diseases, vasculitis or spondylarthropathies may present or have to present by definition with arthritis. For RA, the minimal duration of arthritis has been defined lasting at least 6 weeks by the 1987 American Rheumatism Association criteria [32]; the 2010 ACR/EULAR criteria also define a minimal 6 weeks' duration for the diagnosis of RA [32,33]. A common finding of chronic inflammatory diseases and acute aseptic arthritis is the absence of any microbial agent associated with the occurence of arthritis. In contrast to AAA, other organ systems are frequently affected by chronic inflammation in rheumatic diseases, and autoantibodies are frequently present. In spondyloarthritis, a heterogenous group of chronic inflammatory arthropathies, the human leucocyte antigen (HLA) B-27 is positive in the majority of the cases and is part of the classification criteria established by the Assessment of SpondyloArthritis International Society (ASAS) [34]. Because of the large spectrum of symptoms, ASAS and the European Spondyloarthropathies Study Group (ESSG) require a specific list of criteria for the diagnosis of spondylarthropathy.

1.3.5. Differentiation of acute aseptic arthritis from reactive arthritis

Reactive arthritis is commonly defined by an aseptic peripheral arthritis occurring within four weeks of a primary gastrointestinal or genitourinary infection, mostly associated with *Yersinia, Campylobacter, Salmonella, Shigella,* and *Chlamydia trachomatis* [6]. However, the search for infections potentially contributing to the diagnosis of reactive arthritis is often delayed. Thus, the pathogen may no longer be detectable and elevated serum antibodies may indicate recent or persistent infection, but also reflect the prevalence of such antibodies among healthy individuals and may this be misleading without a clear correlate in the patient history [1].

Reactive arthritis may be found in systemic inflammatory disease: First, gastrointestinal involvement is frequent, including different forms of inflammatory bowel disease. Second, ocular involvement occurs; conjunctivitis and acute anterior uveitis can manifest in about 50% of men with urogenital reactive arthritis syndrome and about 75% of men with enteric reactive arthritis syndrome. Third, skin symptoms may manifest in various forms, mainly psoriasis.

Laboratory results for reactive arthritis are nonspecific. The erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are elevated in at least 50% of patients. P-ANCA positivity is detected in 20–30% of patients, but this finding is not specific. Both synovial fluid and synovial membrane biopsies do not contribute substantially to the diagnosis.

1.3.5.1. Radiology findings. Plain radiographs, ultrasound or MRI may reveal various articular structural changes. However, in the context of AAA, they are only helpful in identifying articular effusion or periarticular soft tissue swelling, and to exclude traumatic lesions [35,36].

1.3.5.2. Other laboratory findings. There are no specific laboratory tests diagnostic of AAA. Erythrocyte sedimentation rate and C-reactive protein may be normal or slightly elevated. Presence of HLA-B27 does not exclude AAA, as it is found in up to 8% of healthy individuals [37].

1.3.5.3. Timing post immunisation. We postulate that a case definition designed to be a suitable tool for testing causal relationships requires ascertainment of the outcome (e.g. acute aseptic arthritis) independent from the exposure (e.g. immunisations). Therefore, to avoid selection bias, a restrictive time interval from immunisation to onset of acute aseptic arthritis should not be an integral part of such a definition. Further, AAA 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. In order to avoid selecting against such cases, the Brighton Collaboration case definition avoids setting arbitrary time frames. However, the diagnosis of acute aseptic arthritis later than 6 weeks after immunisation would seem unlikely to be attributable to immunisation. Where feasible, details of this interval should be assessed and reported as described in the data collection guidelines.

1.3.5.4. Formulating a case definition that reflects diagnostic certainty: weighing specificity versus sensitivity. It needs to be re-emphasised 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-acute aseptic arthritis aetiology. Detailed information about the severity of the event should additionally always be recorded, as specified by the data collection guidelines.

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 1 down to Level 3, while retaining an acceptable level of specificity at all levels. In this way it is hoped that all possible cases of AAA can be captured.

1.4. Guidelines for data collection, analysis and presentation

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.

1.5. 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 three to five years) or more often if needed.

[5] Benchmarks for cut-off points in synovial fluid white blood cell counts that provide the best differentiation between aseptic and septic arthritis are shown in Table S1.

[6] Benchmarks for cut-off points in synovial fluid biochemistry values are shown in the appendix, Table S2.

2. Case definition of acute aseptic arthritis

AAA is a clinical syndrome characterised by acute onset of signs and symptoms of joint inflammation for a period of no longer than 6 weeks, synovial increased leucocyte count and the absence of microorganisms on Gram stain, routine culture and/or PCR.

All levels of diagnostic certainty

- One or more of the following clinical signs and symptoms assessed by a health care provider
- Articular or peri-articular swelling[7]
- Articular effusion[8]
- Articular or peri-articular erythema[9]
- Increased warmth palpable over capsular contour of the joint[10]
- Restricted range of movement[11]

AND

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

AND

- Absence of recent articular trauma

Level 1 of diagnostic certainty

- Increased leucocyte count in synovial fluid determined as[12,13]:
  - >2000 leukocytes/mm^3 on aspirate regardless of age AND
  - <50% white blood count PMN in synovial fluid

AND

- Absence of pathological synovial fluid cells
- Absence of any microorganism on Gram stain, microscopy or 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[14]

Level 3

- Absence of fever.[14]

3. Guidelines for data collection, analysis and presentation of acute aseptic arthritis

It was the consensus of the Brighton Collaboration *Acute Aseptic Arthritis Working Group* for Acute Aseptic Arthritis to recommend the following guidelines to enable meaningful and standardized collection, analysis, and presentation of information about Acute Aseptic Arthritis. 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 epidemiological study, or an individual report of Acute Aseptic Arthritis. 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 following immunisation 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 aseptic arthritis 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.

The guidelines 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 [51], and the form for reporting of drug adverse events by the Council for International Organizations of Medical Sciences (https://cioms.ch/wp-content/uploads/2017/05/cioms-form1.pdf). These data elements include an identifiable reporter and patient, one or more prior immunisations, and a detailed description of the adverse event, in this case, of Acute Aseptic Arthritis following immunisation. The additional guidelines have been developed as guidance for the collection of additional information to allow for a more comprehensive understanding of Acute Aseptic Arthritis following immunisation.

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[15] and/or diagnosing the Acute Aseptic Arthritis as specified by country-specific data protection law.

[7] Articular swelling is defined as an visible enlargement in articular and/or capsular volume with or without objective measurement without articular trauma within the preceding 6 weeks. Periarticular swelling includes an visible enlargement of the periarticular soft tissue volume with or without objective measurement. Where possible, the swelling should be measured using validated 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 pre-defined 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.

[8] Articular effusion is defined either as a palpable increase in synovial fluid or an amount of synovial fluid above the upper normal age-corrected limits as detected by ultrasound, MRI or CT.

[9] Articular and periarticular erythema is defined as an increase in skin redness over the capsular contour of the joint and the joint-surrounding soft tissue, respectively.

[10] Warmth is defined as an increased skin temperature over the capsular contour of the joint.

[11] Restricted range of movement (ROM) is defined as an restricted joint mobility in at least one movement dimension as compared to age-corrected normal values [38]. Reese NB. Joint range of motion and muscle length testing St. Louis, Missouri: Saunders Elsevier; 2010). Restricted ROM may be due to pain on movement, increased synovial fluid or capsular or periarticular tissue swelling.

[12] See Table S1.

[13] Exclude crystal arthritis: absence of crystals in synovial fluid.

[14] Fever is defined as the endogenous elevation of at least one measured body temperature of ≥38 °C [39]. Fever may be absent in young children, older patients and with underlying immunodeficiency.

[15] If the reporting centre is different from the vaccinating centre, appropriate and timely communication of the adverse event should occur.

(3) Name and contact information of the investigator responsible for the subject, as applicable.
(4) Relation to the patient (e.g., immuniser [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 immunisation history. For all cases and/or all study participants, as appropriate, the following information should be recorded:

(8) Past medical history, including hospitalisations, underlying diseases/disorders, pre-immunisation 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; asthma.
(9) Any medication history (other than treatment for the event described) prior to, during, and after immunisation 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) Immunisation history (i.e. previous immunisations and any adverse event following immunisation (AEFI)), in particular occurrence of Acute Aseptic Arthritis after any previous immunisation(s).

3.1.3. Details of the immunisation

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

(11) Date and time of immunisation(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 immunisations against the same disease).
(13) The anatomical sites (including left or right side) of all immunisations (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).

3.1.4. Adverse event

(15) 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:

(16) Clinical description of signs and symptoms of Acute Aseptic Arthritis, and if there was medical confirmation of the event (i.e. patient seen by physician).
(17) Date/time of onset,[16] first observation[17] and diagnosis,[18] end of episode[19] and final outcome.[20]
(18) Concurrent signs, symptoms, and diseases.
(19) Measurement/testing
(20) Treatment given for Acute Aseptic Arthritis, especially specify what and dosing.
(21) Outcome26 at last observation.
(22) Objective clinical evidence supporting classification of the event as "serious".[21]
(23) Exposures other than the immunisation 24 h before and after immunisation (e.g. food, environmental) considered potentially relevant to the reported event.

3.1.5. Miscellaneous/general

(24) The duration of surveillance for Acute Aseptic Arthritis should be predefined based on
(25) The duration of follow-up reported during the surveillance period should be predefined likewise. It should aim to continue to resolution of the event.
(26) Methods of data collection should be consistent within and between study groups, if applicable.
(27) Follow-up of cases should attempt to verify and complete the information collected as outlined in data collection guidelines 1 to 23.
(28) Investigators of patients with Acute Aseptic Arthritis should provide guidance to reporters to optimise the quality and completeness of information provided.
(29) Reports of Acute Aseptic Arthritis should be collected throughout the study period regardless of the time elapsed between immunisation 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 Acute Aseptic Arthritis to allow for comparability of data, and are recommended as an addition to data analysed for the specific study question and setting.

(30) 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.

[16] The date and/or time of onset is defined as the time post immunisation, when the first sign or symptom indicative for Acute Aseptic Arthritis occurred. This may only be possible to determine in retrospect.
[17] The date and/or time of first observation of the first sign or symptom indicative for Acute Aseptic Arthritis can be used if date/time of onset is not known.
[18] The date of diagnosis of an episode is the day post immunisation when the event met the case definition at any level.
[19] 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.
[20] E.g. recovery to pre-immunisation health status, spontaneous resolution, therapeutic intervention, persistence of the event, sequelae, death.
[21] 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 hospitalisation or results in prolongation of existing hospitalisation, (4) results in persistent or significant disability/incapacity, (5) is a congenital anomaly/birth defect, (6) is a medically important event or reaction.

3.3. Event classification in 5 categories[22]

3.3.1. Event meets case definition

(1) Level 1: Criteria as specified in the Acute Aseptic Arthritis case definition
(2) Level 2: Criteria as specified in the Acute Aseptic Arthritis case definition
(3) Level 3: Criteria as specified in the Acute Aseptic Arthritis case definition.

3.3.2. Event does not meet case definition

Additional categories for analysis.

(4) Reported Acute Aseptic Arthritis with insufficient evidence to meet the case definition[23]
(5) Not a case of Acute Aseptic Arthritis.[24]

(31) The interval between immunisation and reported Acute Aseptic Arthritis could be defined as the date/time of immunisation to the date/time of onset[4] of the first symptoms and/or signs consistent with the definition. If few cases are reported, the concrete time course could be analysed for each; for a large number of cases, data can be analysed by stratifying absolute numbers of cases in the following increments: <24 h, 2–3 days, 4–7 days.
(32) The duration of a possible Acute Aseptic Arthritis could be analysed as the interval between the date/time of onset[24] of the first symptoms and/or signs consistent with the definition and the end of episode25 and/or final outcome26. Whatever start and ending are used, they should be used consistently within and across study groups.
(33) 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.
(34) The distribution of data (as numerator and denominator data) could be analysed 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.
(35) Data on Acute Aseptic Arthritis obtained from subjects receiving a vaccine should be compared with those obtained from an appropriately selected and documented control group(s) to assess background rates of hypersensitivity in non-exposed populations, and should be analysed by study arm and dose where possible, e.g. in prospective clinical trials.

3.4. Data presentation

These guidelines represent a desirable standard for the presentation and publication of data on Acute Aseptic Arthritis following immunisation 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 randomised 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 randomised controlled trials (QUORUM), and of Meta-analysis Of Observational Studies in Epidemiology (MOOSE), respectively) [52–54].

(36) All reported events of Acute Aseptic Arthritis should be presented according to the categories listed in guideline 31 (verify numbers).
(37) Data on possible Acute Aseptic Arthritis events should be presented in accordance with data collection guidelines 1–24 (verify numbers) and data analysis guidelines 31–36 (verify numbers).
(38) Terms to describe Acute Aseptic Arthritis such as "low-grade", "mild", "moderate", "high", "severe" or "significant" are highly subjective, prone to wide interpretation, and should be avoided, unless clearly defined.
(39) Data should be presented with numerator and denominator (n/N) (and not only in percentages), if available.

Although immunisation 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.).

(40) The incidence of cases in the study population should be presented and clearly identified as such in the text.
(41) 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.
(42) Any publication of data on Acute Aseptic Arthritis 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 Acute Aseptic Arthritis;
- 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 immunisation was considered "day one" or "day zero" in the analysis;
- Whether the date of onset and/or the date of first observation and/or the date of diagnosis was used for analysis; and
- Use of this case definition for Acute Aseptic Arthritis, in the abstract or methods section of a publication.[25]

[22] The highest possible level of classification should be recorded for each event.
[23] If the evidence available for an event is insufficient because information is missing, such an event should be categorised as "Reported Acute Aseptic Arthritis with insufficient evidence to meet the case definition".
[24] 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 Acute Aseptic Arthritis".
[25] Use of this document should preferably be referenced by referring to the respective link on the Brighton Collaboration website (http://www.brightoncollaboration.org).

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Disclaimer

The findings, opinions and assertions contained in this consensus document are those of the individual scientific professional members of the working group. They do not necessarily represent the official positions of each participant's organisation (e.g., government, university, or corporation).

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.vaccine.2017.08.087.

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