Nodule at injection site as an adverse event following immunization: case definition and guidelines for data collection, analysis, and presentation


1. Preamble

To improve comparability of vaccine safety data the Brighton Collaboration Local Reactions Working Group has developed a case definition and guidelines for the clinical diagnosis of nodule at injection site, applicable in study settings with different availability of resources, in health care settings that differ by availability of and access to health care, and in different geographic regions.

The case definition and guidelines were developed through group consensus. They are grounded on both expert opinion and a review of the literature related to the assessment of nodules at injection site as an adverse event following immunization and to the diagnosis of nodule at injection site in humans. In general, published studies are scarce; most articles reviewed (MEDLINE 1966 to September 2002; search terms vaccination OR immunization, AND cold abscess OR sterile abscess, OR granuloma OR subcutaneous nodule OR antigen cyst) were case reports of relatively few subjects or mentioned formation of a nodule at the injection site briefly as part of a broader discussion of local reactions to immunization. A systematic review of the incidence and clinical symptoms of nodules at injection site was not found in the literature reviewed, and neither was a publication of a vaccine study aiming to define or to evaluate a definition of a nodule at injection site. Published clinical characteristics of nodules at injection site include firmness, tenderness or pain, and pruritus. Nodules at injection site have also been described as being asymptomatic. There have been several review papers about the role of aluminum salts in vaccines and the development of nodules at injection sites, especially when the vaccine is administered subcutaneously.

1.1. Rationale for decisions about case definition

The Working Group agreed that 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 on the basis of the current understanding of these reactions [12–34]. Onset and duration for these reactions can be overlapping and any cut-off can lead to decreased sensitivity and specificity of either event (i.e., false inclusion or exclusion based on such time considerations). Although a period of observation may be needed before a diagnosis of nodule at injection site can be made, it is expected that the inclusion and exclusion criteria listed in the definition will be met at the time of diagnosis.

The Working Group recognizes that a nodule at injection site may progress to a sterile abscess [1,10,35–37]; thus, an attempt was made to distinguish these entities by using the clinical and laboratory features of abscess at injection site at the time of diagnosis as exclusion criteria in the case definition of a nodule at injection site.

The Working Group concluded that the paucity of information on onset [5], duration [2,11,37], and size of nodules at injection site in the published literature precludes including this information in the case definition. Moreover, because the definition itself defines a clinical entity without inference of a causal relation to a given exposure, the time interval between immunization and onset of the event cannot be part of the definition itself, but should be assessed as described in the Guidelines. However, to enhance our current understanding of this reaction, the Working Group recommends that for all prospectively designed vaccine trials and surveillance studies, the protocols call for recording and reporting of onset (when it can be determined), date of first observation, and duration and size of nodules at injection (see Section 3).

While some of the clinical signs and symptoms listed in the definition and guidelines may be somewhat subjective and culturally influenced, it should be recognized that this is an unavoidable part of standard medical practice. If necessary in prospectively designed clinical trials, evaluation of inter-rater reliability may be done.

1.2. Granuloma as a subcategory of a nodule at injection site

A biopsy of a nodule at injection site is not routinely necessary or recommended. However, a granuloma at injection site represents a possible subcategory of nodules at injection site, which can present as persistent nodules many months post immunization [1,2,4,5]. To make the diagnosis of a granuloma at injection site, it is imperative to obtain histopathologic confirmation of granulomatous inflammation and granuloma. It was the consensus of the Working Group that the paucity of reports describing the histology of a granuloma at injection site [1–5,38–43] dictates the use of a standard textbook definition of granuloma. The histology is not only necessary to establish the diagnosis of a granuloma, but can also help to establish the etiology of different types of granulomata (e.g., immune-mediated, infectious or foreign-body) [1].

1.3. Temporal versus causal association with immunization

It is recognized by the Local Reactions Working Group and should be emphasized to parents, patients, health care providers, and all others concerned with immunization safety, that a nodule at injection site—or any other adverse event—which follows administration of an inactivated component or live vaccine may be temporally associated with, but is not necessarily the result of, administration of a vaccine. Any occurrence of nodules at injection site should be compared to a control group, ideally by placebo-controlled double-blinded and randomized comparisons.

1.4. Use of guidelines for data collection, analysis, and presentation

Many variables and uncertainties affect both the definition and the diagnosis of nodule at injection site. Therefore, the Brighton Collaboration Local Reactions Working Group has attempted to establish useful and practical guidelines directed at standardizing collection, analysis, and presentation of data on nodule at injection site in the setting of clinical trials, surveillance, and retrospective epidemiologic studies of vaccine safety. The guidelines are not intended to establish criteria for management of ill infants, children, or adults. As they represent a minimum standard, additional data may be collected, analyzed, and presented as deemed necessary by the investigators. This is particularly relevant for surveillance of nodules at injection site for new vaccines against chronic diseases (e.g., diabetes mellitus and rheumatoid arthritis) and therapeutic vaccines (e.g., tumor vaccines), as well as genetically-engineered vaccines, mucosal vaccines, or vaccines with slow-release delivery systems.

1.5. Periodic review

It is the recommendation of the Working Group that pre-licensure and postlicensure studies be specifically designed to investigate nodules at injection site as described in this document. Review and, when indicated, revision of the definition and guidelines is planned on a regular (every 3–5 years) or “as needed” basis.

2. Case definition for nodule at injection site as an adverse event following immunization

A nodule\(^3\) at injection site is defined\(^3\) by

- **Level 1 of diagnostic certainty**
  - The presence of a
    - ○ discrete or well-demarcated soft tissue mass or lump
      - **THAT IS**

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\(^3\) Sometimes referred to as a subcutaneous nodule, antigen cyst, or granuloma.

\(^3\) All criteria apply to the time of diagnosis.
surgical drainage, or by an imaging technique.

soft tissue collection of fluid determined clinically, by spontaneous or

3. Guidelines for data collection, analysis, and presentation of nodule at injection site as an adverse event following immunization

It was the consensus of the Brighton Collaboration Local Reactions Working Group to recommend the following guidelines to enable meaningful and standardized data collection, analysis, and presentation of information about nodules at injection site. However, implementation of all guidelines might not be possible in all settings. The availability of information may vary depending upon resources, geographic region, and whether the source of information is a prospectively designed clinical trial, a post-marketing surveillance region, and whether the source of information is a prospective or epidemiologic study, or an individual report of a nodule at injection site. These guidelines represent a minimum standard for the collection of data on nodules at injection site to allow for comparability of data. Additional information may be collected depending on the study question and setting. See Appendix A for a sample check list for data collection.

3.1. Data collection

These guidelines represent a minimum standard for the collection of data on nodules at injection site to allow for comparability of data. Additional information may be collected depending on the study question and setting. See Appendix A for a sample check list for data collection.

(1) Documentation of the pre-immunization health status of a vaccine recipient should be available to identify indicators for, or the absence of, a nodule at injection site. However, implementation of all guidelines might not be possible in all settings. The availability of information may vary depending upon resources, geographic region, and whether the source of information is a prospectively designed clinical trial, a post-marketing surveillance or epidemiologic study, or an individual report of a nodule at injection site. These guidelines represent a minimum standard for the collection of data on nodules at injection site to allow for comparability of data. Additional information may be collected depending on the study question and setting. See Appendix A for a sample check list for data collection.

(2) The size (i.e., diameter) of the nodule should be measured and recorded in cm.

(3) Frequency of measurement should be at least once per week and should be determined by clinical course.

(4) The duration of surveillance for nodule at injection site, when collected as a pre-specified adverse event in clinical trials, is to some extent arbitrary and depends on:

- biologic characteristics of the vaccine (e.g., live attenuated versus inactivated component vaccines);
- biologic characteristics of the vaccine-targeted disease;
- biologic characteristics of nodules at injection site including patterns identified in previous trials (e.g., early-phase trials).

Monitoring of a nodule at injection site still present on the last day of follow-up should be extended to recovery or until a final outcome is reached (see guideline 5).

(5) The outcome should be recorded, including the respective time course of the evolution of the lesion. Outcomes include:

- Spontaneous resolution.
- Status quo (i.e., no more change observed). Ideally lesions should be followed until resolved. After stabilization, the lesion should be followed a minimum of 3 months.
- Excision (not usually needed or recommended).
- Development of a sterile abscess.
- A description of any other outcome.

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

- Date of birth, sex, and ethnicity;
- Date and time of immunization;
- Time interval between birth and immunization for neonatal immunizations;
- Description of vaccine(s) (name of vaccine, manufacturer, lot number, dose [e.g., 0.25 ml and 0.5 ml], and dose number);
- Method and route of administration (e.g., intramuscular, intradermal, subcutaneous [deep or superficial, if known], and needle-free or other injection devices);
- Needle length and gauge;
- The anatomic sites (including left or right side) and exact location for each injection (e.g., vaccine A in proximal left lateral thigh, vaccine B in left deltoid) and of the nodule need to be stated and depicted as accurately as possible (see Appendix B with drawings for possible use);
- Detailed clinical description including characteristics of the nodule (e.g., fixed/movable, smooth/irregular, soft, diffuse swelling, tenderness, pruritus, and induration);
- Concurrent signs, symptoms, and diseases;
- Concurrently administered biologics and prescription and non-prescription medication (e.g., herbal or homeopathic medication) as well as medication with long half-life (e.g., immunoglobulins and blood transfusion);
- Person reporting, diagnosing and/or measuring the nodule at injection site (e.g., medical provider, parent/patient, other third-party reporters), including contact information;
- Method and location of measurement (e.g., device and anatomic site);
- Abscess formation;
- Erythema AND warmth.

- Level 2 of diagnostic certainty
- Not applicable.
- Level 3 of diagnostic certainty
- Not applicable.

3.1. Data collection

These guidelines represent a minimum standard for the collection of data on nodules at injection site to allow for comparability of data. Additional information may be collected depending on the study question and setting. See Appendix A for a sample check list for data collection.

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- biologic characteristics of the vaccine-targeted disease;
- biologic characteristics of nodules at injection site including patterns identified in previous trials (e.g., early-phase trials).

Monitoring of a nodule at injection site still present on the last day of follow-up should be extended to recovery or until a final outcome is reached (see guideline 5).

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- Development of a sterile abscess.
- A description of any other outcome.

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- Needle length and gauge;
- The anatomic sites (including left or right side) and exact location for each injection (e.g., vaccine A in proximal left lateral thigh, vaccine B in left deltoid) and of the nodule need to be stated and depicted as accurately as possible (see Appendix B with drawings for possible use);
- Detailed clinical description including characteristics of the nodule (e.g., fixed/movable, smooth/irregular, soft, diffuse swelling, tenderness, pruritus, and induration);
- Concurrent signs, symptoms, and diseases;
- Concurrently administered biologics and prescription and non-prescription medication (e.g., herbal or homeopathic medication) as well as medication with long half-life (e.g., immunoglobulins and blood transfusion);
- Person reporting, diagnosing and/or measuring the nodule at injection site (e.g., medical provider, parent/patient, other third-party reporters), including contact information;
- Method and location of measurement (e.g., device and anatomic site);
- Date/time of onset, first observation, diagnosis, end of an episode, and final outcome (see guideline 5);
- Immunization history (i.e., previous immunizations and any adverse events following immunization);
- Recurrence of the event or occurrence of similar event prior to immunization or in conjunction with previous immunization.

(7) If tissue is obtained from a biopsy or excision (not usually needed or recommended), it should be submitted to a qualified pathologist for microscopic examination, and pathological findings should be attached to the diary card.

(8) Methods of data collection, including the method of measurement (e.g., caliper and ruler) should be consistent within and between study groups, if applicable.

(9) For all cases at Level 1 of diagnostic certainty and for reported events with insufficient evidence, the criteria fulfilled to meet the case definition and other signs and symptoms indicative for nodule at injection site should be recorded.

(10) Follow-up of cases should attempt to verify and complete the information collected as outlined in guidelines 1–9.

3.2. Data analysis

These guidelines represent a minimum standard for the analysis of data on nodule at injection site to allow for comparability of data. Additional information may be analyzed depending on the study question and setting.

(11) Reported events should be classified into one of the following three categories. Events that meet the case definition should be classified as Level 1 of diagnostic evidence as specified in the case definition; Level 2 and Level 3 are not applicable for nodule at injection site. Events that do not meet Level 1 of diagnostic certainty of the case definition should be classified in the additional categories for analysis.

Event classification in three categories

Event meets case definition

(1) Level 1: as specified in the case definition for nodule at injection site.

Event does not meet case definition

Additional categories for analysis

(2) Reported nodule at injection site with insufficient evidence to meet the case definition.

(3) No, not a case of nodule at injection site.

(12) The interval between immunization and nodule at injection should be determined using the date of immunization and date/time of onset and/or first observation and/or diagnosis, whichever is available. Whatever dates are used, they should be used consistently within and across study groups. For a limited number of cases, the exact time course should be analyzed for each; for a large number of cases, data should be analyzed in predefined increments.

The number of subjects (n) with nodules newly present (date of onset or date of first observation or date of diagnosis) over the number of the study population (N) with nodules should be analyzed in pre-defined time intervals.

<table>
<thead>
<tr>
<th>Time interval</th>
<th>Number of subjects with nodules present at the specified time interval/number of study population with nodules (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–2 weeks</td>
<td>n/N ... (%)</td>
</tr>
<tr>
<td>2–4 weeks</td>
<td>n/N ... (%)</td>
</tr>
<tr>
<td>4–6 weeks</td>
<td>n/N ... (%)</td>
</tr>
<tr>
<td>6–8 weeks</td>
<td>n/N ... (%)</td>
</tr>
<tr>
<td>8–10 weeks</td>
<td>n/N ... (%)</td>
</tr>
<tr>
<td>10–12 weeks</td>
<td>n/N ... (%)</td>
</tr>
<tr>
<td>12–16 weeks</td>
<td>n/N ... (%)</td>
</tr>
<tr>
<td>16–20 weeks</td>
<td>n/N ... (%)</td>
</tr>
<tr>
<td>Etc.</td>
<td>n/N ... (%)</td>
</tr>
</tbody>
</table>

(13) The duration of the nodule at injection site should be analyzed in clinical trials, and whenever possible in surveillance systems as the date of onset, if known, or date of first observation to the date of final outcome (see guideline 5). Whatever start and ending dates are used, they should be used consistently within and across study groups. For a limited number of cases, the exact time course should be analyzed for each; for a large number of cases, the duration should be analyzed in predefined increments mentioned in guideline 12.

(14) If more than one measurement is taken and recorded, the largest diameter should be used as the basis for analysis.

(15) Nodule size should be analyzed in 0.5-cm increments as the number of subjects whose largest nodule size fell within the specified increment (n) over the Number of all subjects with nodule (N).

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6 The date and/or time of onset is defined as the time postimmunization, when the first sign or symptom indicative for nodule at injection site occurred. This may only be possible to determine in retrospect. The date and/or time of first observation of the first sign or symptom indicative for nodule at injection site can be used if date/time of onset is not known.

7 The date of diagnosis of an episode is the day the event met the case definition.

8 The end of an episode is defined as the time the event failed to meet the case definition.

9 If tissue is obtained from a biopsy or excision (not usually needed or recommended), it should be submitted to a qualified pathologist for microscopic examination, and pathological findings should be attached to the diary card.

10 Methods of data collection, including the method of measurement (e.g., caliper and ruler) should be consistent within and between study groups, if applicable.

11 For all cases at Level 1 of diagnostic certainty and for reported events with insufficient evidence, the criteria fulfilled to meet the case definition and other signs and symptoms indicative for nodule at injection site should be recorded.

12 Follow-up of cases should attempt to verify and complete the information collected as outlined in guidelines 1–9.

13 Event classification in three categories

Event meets case definition

(1) Level 1: as specified in the case definition for nodule at injection site.

Event does not meet case definition

Additional categories for analysis

(2) Reported nodule at injection site with insufficient evidence to meet the case definition.

(3) No, not a case of nodule at injection site.
(16) The complete pathology report should be appended to the adverse event report. The lesion should not be termed a granuloma unless it meets the standard cellular criteria for such a diagnosis.

(17) In clinical trials, data on nodules at injection site should be analyzed by study arm and dose.

(18) Results obtained in subjects receiving a vaccine under study ideally should be compared with those obtained from one or more control groups.

3.3. Data presentation

These guidelines represent a minimum standard for the presentation and publication of data on nodules at injection site to allow for comparability of data. Additional information collected and analyzed may be presented depending on the study question and setting. The guidelines are NOT guidelines for primary reporting of nodule at injection site to a surveillance system or study monitor. It is recommended to also refer to existing guidelines (e.g., CONSORT and MOOSE for presentation and publication of vaccine safety studies [44]).

(19) All reported events of nodules at injection site should be presented according to the categories listed in guideline 11.

(20) Data on nodules at injection site should be presented in accordance with data collection guidelines 1–9 and data analysis guidelines 11–18.

(21) Data should be presented with numerator and denominator \( (n/N) \) and not only in percentages.

Because in surveillance systems denominators 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 described (e.g., obtained from manufacturer, Ministry of Health and coverage/population based data).

(22) If the distribution of data is skewed and a median and range are the more appropriate statistical descriptor than a mean, the mean and standard deviation also should be provided to permit meta-analysis.

(23) Any publication of data on nodule at injection site should include a detailed description of the methods used for data collection and analysis. It is essential to specify

- the study design of clinical trials;
- the search strategy in surveillance databases;
- 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;
- comparator group(s), if used for analysis;
- whether the day of immunization was considered “day 1” or “day 0” in the analysis; and
- whether the date of onset and/or the date of first observation and/or the date of diagnosis was used for analysis.

(24) If a nodule at injection site develops into an abscess, each should be reported as an adverse event following immunization with their respective start and ending dates.

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

(26) The use of the Brighton Collaboration case definition for nodule at injection site should be mentioned in the abstract or method section of a publication, and this document referenced.

Acknowledgements

The authors are grateful for the support and helpful comments by the Brighton Collaboration Steering Committee and Reference Group, and medical editor Mary McCauley and medical illustrator Patty Chen, as well as the steering group of the European Research Programme For Improved Vaccine Safety Surveillance (EUSAFEVAC) Project.

Appendix A. Template of data collection checklist for the case definition and data collection guidelines of nodule at injection site

This checklist is derived from the criteria listed in the case definition and items from the guidelines for data collection. It is intended as a data collection template for use in study protocols and active follow up in surveillance systems. Additional information or a different format depending on the study question and setting may be required.
<table>
<thead>
<tr>
<th>Definition</th>
<th>Yes</th>
<th>No</th>
<th>Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) The lesion is firm</td>
<td></td>
<td></td>
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<tr>
<td>2) The lesion is a discrete or well-demarcated soft tissue mass</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>3) The lesion is at the injection site (depict on drawing attached)</td>
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<td></td>
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</tr>
<tr>
<td>4) At the time of diagnosis, note if an abscess is present</td>
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<tr>
<td>5) At the time of diagnosis, note if the lesion is erythematous</td>
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</tr>
<tr>
<td>6) At the time of diagnosis, note if the lesion is warm or hot to touch</td>
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</tr>
</tbody>
</table>

**Guidelines for Data Collection**

Document the presence of pre-immunization conditions (local or systemic) that may predispose to developing or affect the swelling at injection site

<table>
<thead>
<tr>
<th>Measurement of nodule</th>
<th>Dates of measurement (mm/dd/yyyy)</th>
<th>Size Ø cm</th>
<th>Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Dates of measurement (mm/dd/yyyy)</th>
<th>Size Ø cm</th>
<th>Unknown</th>
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<tbody>
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</table>

<table>
<thead>
<tr>
<th>Dates of measurement (mm/dd/yyyy)</th>
<th>Size Ø cm</th>
<th>Unknown</th>
</tr>
</thead>
<tbody>
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<td></td>
<td></td>
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</tbody>
</table>

Greatest size (Ø=diameter) measured Size Ø cm Unknown

<table>
<thead>
<tr>
<th>Duration of measurement</th>
<th>Yes</th>
<th>No</th>
<th>Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>days/weeks/months</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Until final outcome reached

<table>
<thead>
<tr>
<th>Outcome known?</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Spontaneous resolution?
- Yes
- No
- Unknown

### No more change over time (status quo)?
- Yes
- No
- Unknown

### – follow up for at least three months
- Yes
- No
- Unknown

### Excision? (if yes, please append pathologic report)
- Yes
- No
- Unknown

### Development of a sterile abscess?
- Yes
- No
- Unknown

### Other (please describe, use additional paper if necessary)

### Patient Demographics

<table>
<thead>
<tr>
<th>Date of birth</th>
<th>Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>mm/dd/yyyy</td>
<td></td>
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<table>
<thead>
<tr>
<th>Sex</th>
<th>M</th>
<th>F</th>
<th>Unknown</th>
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<td></td>
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</table>

<table>
<thead>
<tr>
<th>Ethnicity, please list</th>
<th></th>
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<tbody>
<tr>
<td></td>
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</tbody>
</table>

### Immunization and Vaccine details

<table>
<thead>
<tr>
<th>Date of immunization</th>
<th>Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>mm/dd/yyyy</td>
<td></td>
</tr>
</tbody>
</table>

For neonatal immunizations: time interval between birth and immunization

<table>
<thead>
<tr>
<th>hrs/days</th>
<th>Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</table>

#### Vaccine details

If >1 vaccine was given in the affected limb and the specific site of the injection in question (i.e., temporarily linked to the adverse event) cannot be identified, report all vaccines given in that limb.

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trade name</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Manufacturer</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lot number</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dose (µL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dose number</td>
<td></td>
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</tr>
</tbody>
</table>

### Administration details for each vaccine temporarily linked with the adverse event

Insert or circle response
<table>
<thead>
<tr>
<th>Device (list name of device and manufacturer)</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Route of Administration</td>
<td>Intradermal</td>
<td>Intradermal</td>
<td>Intradermal</td>
</tr>
<tr>
<td></td>
<td>Intramuscular</td>
<td>Intramuscular</td>
<td>Intramuscular</td>
</tr>
<tr>
<td></td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>Needle length</td>
<td>cm</td>
<td>cm</td>
<td>cm</td>
</tr>
<tr>
<td></td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>Needle gauge</td>
<td>g</td>
<td>g</td>
<td>g</td>
</tr>
<tr>
<td></td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

Please depict anatomic site of nodule and anatomic site(s) of injections on the drawing attached in Appendix II in the case definition and guideline document or list here.

<table>
<thead>
<tr>
<th>Clinical description and characteristics of nodule</th>
<th>Insert or circle response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nodule site tender?</td>
<td>Yes</td>
</tr>
<tr>
<td>Nodule site pruritic?</td>
<td>Yes</td>
</tr>
<tr>
<td>Additional swelling around nodule?</td>
<td>Yes</td>
</tr>
<tr>
<td>Characteristics of the nodule</td>
<td>movable</td>
</tr>
<tr>
<td></td>
<td>Unknown</td>
</tr>
</tbody>
</table>

List concurrent signs and symptoms

Other than vaccines listed above, list concurrently administered -- by any route -- biologics and medications
<table>
<thead>
<tr>
<th>Person reporting / diagnosing / measuring nodule (check each)</th>
<th>Report</th>
<th>Diagnose</th>
<th>Measure</th>
<th>Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physician</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nurse (licensed)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parent, guardian</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>List method of measurement</td>
<td>______</td>
<td></td>
<td></td>
<td>Unknown</td>
</tr>
<tr>
<td>Dates</td>
<td>Unknown</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Date of onset (mm/dd/yy)</td>
<td>_____ /____ /_____</td>
<td>Unknown</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Date of first observation (mm/dd/yy)</td>
<td>_____ /____ /_____</td>
<td>Unknown</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Date of diagnosis (mm/dd/yy)</td>
<td>_____ /____ /_____</td>
<td>Unknown</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Date of end of episode (mm/dd/yy)</td>
<td>_____ /____ /_____</td>
<td>Unknown</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Date of final outcome (mm/dd/yy)</td>
<td>_____ /____ /_____</td>
<td>Unknown</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immunization history (attach immunization record, or be exact on information on vaccines, e.g., if combination vaccines, list all components)</td>
<td>Unknown</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrence of event: History of previous nodule at injection site in this patient?</td>
<td>Yes</td>
<td>No</td>
<td>Unknown</td>
<td></td>
</tr>
<tr>
<td>If yes – after which vaccine(s)?</td>
<td>Unknown</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Miscellaneous: Please add any other comments or a clinical narrative if you think it will add to the understanding of the clinical course or pathophysiology of this adverse event. Copy of medical record relating to the event may be attached. Remove anything that might identify the patient (name, address, phone number, etc.)</td>
<td>Unknown</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2 Provide contact information on reporting source, if possible.
Appendix B

B.1. Drawing of front and back of adult to mark injection site(s) with respective vaccines and site of nodule at injection site

B.2. Drawings of left and right side of adult to mark injection site(s) with respective vaccines and site of nodule at injection site

B.3. Drawings of front and back of Infant to mark injection site(s) with respective vaccines and site of nodule at injection site

B.4. Drawings of left and right side of Infant to mark injection site(s) with respective vaccines and site of nodule at injection site
References


11 The complete literature search is available from the Brighton Collaboration Secretariat: secretariat@brightoncollaboration.org.