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

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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 nodule 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 [1], tenderness or pain [1–5], and pruritus [2,6]. Nodules at injection site have also been described as being asymptomatic [1,2,7]. There have been several review papers about the role of aluminum salts in vaccines and the development of nodules at injection sites [8–10], especially when the vaccine is administered subcutaneously [11].

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

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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 prelicensure 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[2] 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*

[2] Sometimes referred to as a subcutaneous nodule, antigen cyst, or granuloma.

[3] All criteria apply to the time of diagnosis.

- firm *AND*
- is at the injection site[4]

There may be additional less discrete, softer swelling surrounding the nodule at the injection site, especially early in its development. There may also be tenderness and pruritus.

In the *absence* of

- abscess formation[5] *AND*
- erythema *AND*
- warmth.

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

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 or epidemiologic study, or an individual report of a nodule at injection site.

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.
(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; and
   - 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 reporter), including contact information;
   - Method and location of measurement (e.g., device and anatomic site);

[4] In subcutaneous tissue, fat, fascia, or muscle.
[5] See Brighton case definition for abscess at injection site: localized soft tissue collection of fluid determined clinically, by spontaneous or surgical drainage, or by an imaging technique.

- Date/time of onset,[6] first observation,[6] diagnosis,[7] end of an episode,[8] 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.[9]

(3) No, not a case of nodule at injection site.[10]

(12) *The interval between immunization and nodule at injection* should be determined using the date of immunization and date/time of onset[6] and/or first observation[6] and/or diagnosis,[7] 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.

Time interval	Number of subjects with nodules present at the specified time interval/number of study population with nodules (%)
0–<2 weeks	*n*/*N* ___ (%)
2–<4 weeks	*n*/*N* ___ (%)
4–<6 weeks	*n*/*N* ___ (%)
6–<8 weeks	*n*/*N* ___ (%)
8–<10 weeks	*n*/*N* ___ (%)
10–<12 weeks	*n*/*N* ___ (%)
12–<16 weeks	*n*/*N* ___ (%)
16–<20 weeks	*n*/*N* ___ (%)
Etc.	*n*/*N* ___ (%)

(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,[6] if known, or date of first observation[6] 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*).

[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 the evidence available for an event is insufficient because information (i.e., inclusion and/or exclusion criteria) is missing. Such an event should be classified as "reported event of nodule at injection site, with *insufficient evidence* to meet the case definition."

[10] An event does not meet the case definition if an exclusion criterion is met or if investigation reveals a negative finding of a necessary criterion. Such an event should be rejected and classified as "No, *not a case* of nodule at injection site."

Size increments	Number of subjects with nodule within specified increments/number of study population with nodules (%)
>0–<0.5 cm	*n*/*N* ___ (%)
0.5–<1.0 cm	*n*/*N* ___ (%)
1.0–<1.5 cm	*n*/*N* ___ (%)
1.5–<2.0 cm	*n*/*N* ___ (%)
Etc.	

(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[6] and/or the date of first observation[6] and/or the date of diagnosis[7] 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.

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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.

Definition	Yes	No	Unknown
1) The lesion is firm			
2) The lesion is a discrete or well demarcated soft tissue mass			
3) The lesion is at the injection site (depict on drawing attached)			
4) At the time of diagnosis, note if an abscess is present			
5) At the time of diagnosis, note if the lesion is erythematous			
6) At the time of diagnosis, note if the lesion is warm or hot to touch			

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	_____ _____ _____ _____	Unknown
Measurement of nodule		
Dates of measurement _____/_____/_____ (mm / dd / yyyy)	Size Ø _____ cm	Unknown
Dates of measurement _____/_____/_____ (mm / dd / yyyy)	Size Ø _____ cm	Unknown
Dates of measurement _____/_____/_____ (mm / dd / yyyy)	Size Ø _____ cm	Unknown
Greatest size (Ø=diameter) measured	Size Ø _____ cm	Unknown
Duration of measurement - Until final outcome reached	_____ days/weeks/months Yes no	Unknown
Outcome		
Outcome known?	Yes No	
If outcome known:		

Spontaneous resolution?	Yes No	Unknown
No more change over time (status quo)? – follow up for at least three months	Yes No Yes No	Unknown
Excision? (if yes, please append pathologic report)	Yes No	Unknown
Development of a sterile abscess? (if yes, please report as separate event)	Yes No	Unknown
Other (please describe, use additional paper if necessary)		

Patient Demographics		
Date of birth	_____/_____/_____ (mm / dd / yyyy)	Unknown
Sex M	F	Unknown
Ethnicity, please list		
Immunization and Vaccine details		
Date of immunization	_____/_____/_____ (mm / dd / yyyy)	Unknown
For neonatal immunizations: time interval between birth and immunization	_____ hrs / days	Unknown

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.

Vaccine	1	2	3	4
Trade name				
Manufacturer				
Lot number				
Dose (mL)				
Dose number				
Administration details for each vaccine temporarily linked with the adverse event	**Insert or circle response**			

Device (list name of device and manufacturer)	_____ _____	_____ _____	_____ _____	_____ _____
Route of Administration	Intradermal Intramuscular Unknown	Intradermal Intramuscular Unknown	Intradermal Intramuscular Unknown	Intradermal Intramuscular Unknown
Needle length	____ cm Unknown	____ cm Unknown	_____cm Unknown	____cm Unknown
Needle gauge	_____ g Unknown	_____ g Unknown	_____ g Unknown	_____ g Unknown

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.

Clinical description and characteristics of nodule	**Insert or circle response**	
Nodule site tender?	Yes No	Unknown
Nodule site pruritic?	Yes No	Unknown
Additional swelling around nodule?	Yes No	Unknown
Characteristics of the nodule	movable fixed smooth irregular	Unknown

List concurrent signs and symptoms

Other than vaccines listed above, list concurrently administered -- by any route -- biologics and medications

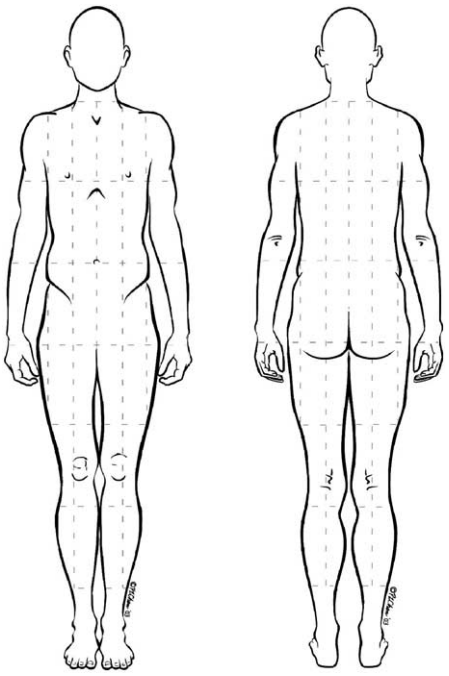
Person reporting[1] / diagnosing / measuring nodule (check each)		Report	Diagnose	Measure	Unknown
	Physician				
	Nurse (licensed)				
	Parent, guardian				
	Patient				
	Other				
List method of measurement		_____			Unknown
Dates					
Date of onset (mm/dd/yy)		_____/_____/_____			Unknown
Date of first observation (mm/dd/yy)		_____/_____/_____			Unknown
Date of diagnosis (mm/dd/yy)		_____/_____/_____			Unknown
Date of end of episode (mm/dd/yy)		_____/_____/_____			Unknown
Date of final outcome (mm/dd/yy)		_____/_____/_____			Unknown
Immunization history (attach immunization record, or be exact on information on vaccines, e.g., if combination vaccines, list all components)					
Recurrence of event: History of previous nodule at injection site in this patient?		Yes No			Unknown
If yes – after which vaccine(s)?					Unknown

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.)

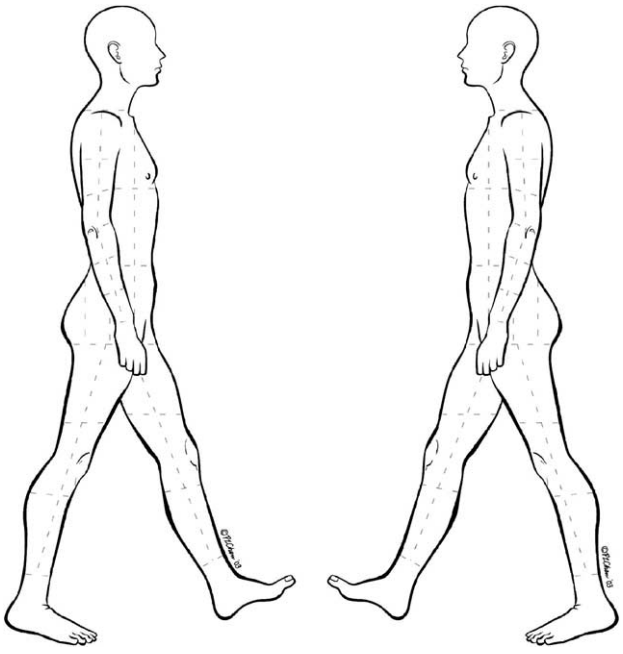
[1] Provide contact information on reporting source, if possible.

Appendix B

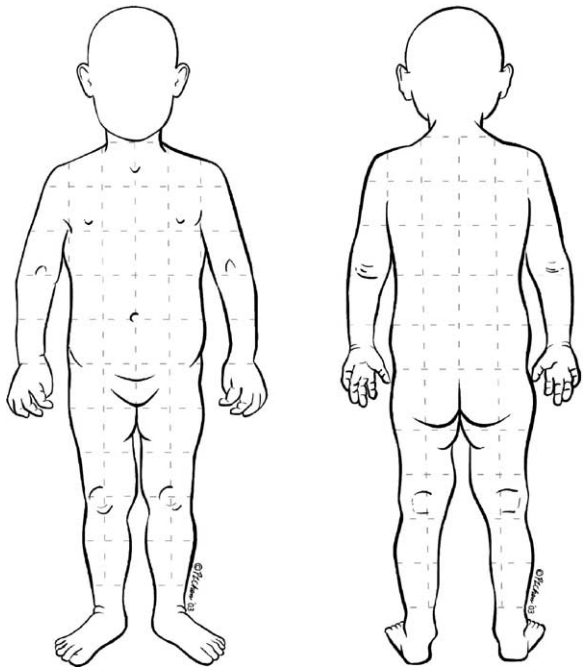
B.1. Drawing of front and back of adult to mark injection site(s) with respective vaccines and site of nodule at injection site



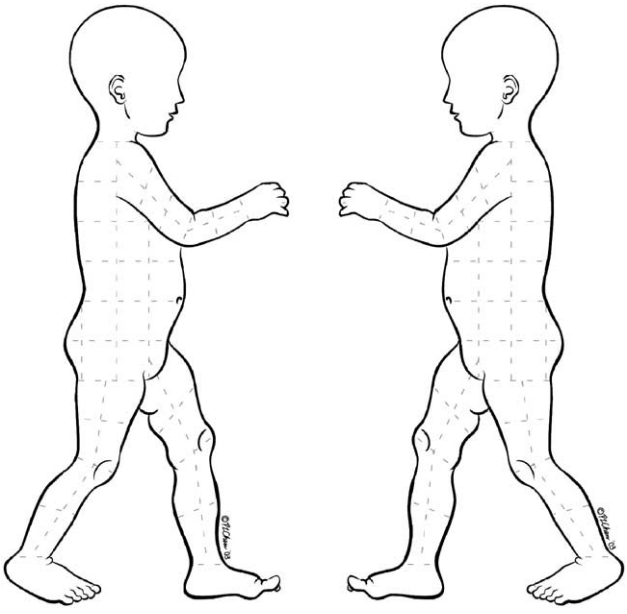
B.2. Drawings of left and right side of adult to mark injection site(s) with respective vaccines and site of nodule at injection site



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



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