

Fever as an adverse event following immunization: case definition and guidelines of data collection, analysis, and presentation

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1. Preamble

To improve comparability of vaccine safety data, the Brighton Collaboration *Fever* Working Group has developed a case definition and guidelines for fever following immunization, 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 definition and guidelines were developed through group consensus. They are grounded on both expert opinion and a review of more than four hundred articles related to the assessment of fever as an adverse event following immunization and to the diagnosis of fever in humans.

1.1. Background on fever and rationale for decisions about case definition

Fever is defined as an elevation of body temperature above the normal. It is usually caused by infection, but it can also be associated with a number of immunologic, neoplastic, hereditary, metabolic, and toxic conditions. Fever is endogenously generated and is distinguished from hyperthermia [1], which is a warming of the body caused by external environmental factors. Since temperature regulation occurs at the hypothalamic level, the temperature of blood bathing the thermoregulatory centers in the hypothalamus probably best reflects true core body temperature [2,3]. Temperatures recorded within the pulmonary artery and upper oesophagus have been considered acceptable surrogates [3–6]. While these sites are generally regarded the “physiologic gold standards” for measurement of human body temperature, they are accessible only under surgical or experimental conditions and are impractical for detecting fever in a clinical setting.

A universally acceptable clinical definition of fever (a “clinical gold standard”) is, however, more elusive [7]. This

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is largely because normal body temperature, the yardstick against which fever is defined, is not a single value, but rather a range of values that fluctuate from time to time and place to place in different individuals. These values also vary by anatomic site, with different norms for rectal, oral, axillary, temporal artery, tympanic membrane, umbilical, inguinal, or skin-mattress temperatures. While general trends are observed when temperatures at these sites are compared (e.g., oral temperatures tend to be lower than rectal and higher than axillary temperatures) the relationship between temperatures taken at these various sites has been found to be inconsistent. It is fundamental to an understanding of the recommendations given below that there are no reliable mathematical formulae that permit temperature recorded at one anatomic site to directly predict temperature at another site. Further, no anatomic site for measuring fever in a clinical setting has been shown to be consistently superior to another [5,8–37].

Both normal body temperature and fever are usually recognized clinically through symptoms or signs (e.g., skin warmth) and confirmed through thermometry. Establishing the significance or severity of the signs or symptoms of a presumed febrile illness is highly subjective and open to wide interpretation, particularly in young children, as is tactile determination of skin temperature [38]. Several studies have attempted to define the ability of caregivers to diagnose fever by palpation [39–46]. The results of their observations indicate that there are significant inaccuracies in attempting to define the presence or absence of fever by touch—errors of both over- and under-diagnosis.

Deciding whether thermometry accurately indicates the presence of fever requires consideration of numerous influences that are difficult or impossible to control. For example, body temperature in healthy infants, children, and adults is affected by level of activity [47,48], meals [27,48–50], time of day [9,47,48,51], and environmental conditions [52–54]. Among young infants, gestational age [55] and postnatal age [22,51,52,56] also affect temperature. Mouth-breathing during oral thermometry; failure to properly position a rectal, axillary, or aural thermometer; hurried measurements; and failure to properly standardize and maintain instruments have all been shown to adversely affect the accuracy and reproducibility of readings. Any complete description of elevated temperature in an individual must include, in addition to the anatomic site, where the temperature was measured, placement within that site [1,51,55,57–59], and the duration of measurement [17,60]. The device used to assess temperature should be specified: mercury-in-glass, electronic, infrared, or thermophototropic liquid crystal. Only measurements obtained with validated devices should be considered acceptable.

1.2. Temporal versus causal association with immunization

It is recognized by the *Fever Working Group* and should be emphasized to parents, patients, health care providers,

and all others concerned with immunization safety, that fever (or any other adverse event) that 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. Because of known high background rates particularly of fever [61,62], any occurrence of fever should be compared to a control group (ideally by placebo-controlled double-blinded and randomized comparisons) or against a background rate.

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.

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

Recognizing the many variables and uncertainties affecting both the definition and the determination of normal and elevated body temperature, the Brighton Collaboration *Fever Working Group* has attempted to establish useful and practical guidelines for standardizing the collection, analysis, and presentation of data on temperature measurement in the setting of prelicensure and postlicensure 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 fever as an adverse event 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.

1.4. Periodic review

It is the recommendation of the Brighton Collaboration *Fever Working Group*, that prelicensure and postlicensure studies be specifically designed to investigate fever as an adverse event following immunization as described in this document. Review and, when indicated, revision of the definition and guidelines is planned on a regular (i.e., every 3–5 years) or “as needed” basis.

2. Case definition of fever as an adverse event following immunization

• Level 1 of diagnostic certainty

Fever is defined as the endogenous elevation of at least one measured body temperature of $\geq 38^{\circ}\text{C}$.^{2,3}

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

3. Guidelines for data collection, analysis, and presentation of fever as an adverse event following immunization

It was the consensus of the Brighton Collaboration *Fever Working Group* to recommend the following guidelines to enable meaningful and standardized collection, analysis, and presentation of information about fever following immunization. However, implementation of all guidelines may 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 elevated temperature.

3.1. Data collection

These guidelines represent a minimum standard for the collection of data on fever to allow for comparability of data. Additional information may be collected depending on the study question and setting.

- (1) Documentation of the *pre-immunization health status*, including temperature measurement, of a vaccine recipient should be available to document the presence or absence of elevated body temperature.
- (2) *Tactile determinations* of fever are not acceptable forms of measurement unless confirmed by thermometry.
- (3) *Temperature measurement* in clinical trials should be performed whenever fever is suspected, but no less than once a day even in the absence of suspected fever. If fever is detected, temperature should be measured at least twice a day (in the morning and evening) or as clinically appropriate until two consecutive measurements are $< 38^{\circ}\text{C}$.
- (4) Any *device validated* to provide accurate and reproducible results is acceptable for measuring body temperature. Appropriate anatomic site(s), duration of measurement, and maintenance/standardization schedules should be specified for each such device and recorded on the diary card.

² The value of $\geq 38^{\circ}\text{C}$ is accepted as reflecting an abnormal elevation of temperature, irrespective of device, anatomic site, age, or environmental conditions.

³ While it is recognized that this value is to some extent *arbitrary*, it is based upon a conservative interpretation of definitions proposed and used by clinicians, investigators, and the public at large.

- (5) The *duration of surveillance* for fever, when collected as a prespecified adverse event in prelicensure and postlicensure clinical trials on a diary card, 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 fever including patterns identified in previous trials (e.g., early-phase trials).
 Monitoring of fever still present on the last day of follow-up should be extended to resolution.
- (6) For all cases and/or all study participants, as appropriate, the *following information should be recorded*.
 - Temperature.
 - The method of temperature measurement, i.e., route and device.
 - Date of birth, sex, ethnicity.
 - Date and time of immunization.
 - Description of vaccine(s) (i.e., name of vaccine, manufacturer, lot number, dose, and dose number).
 - Method and route of administration (e.g., intramuscular, intradermal, subcutaneous, oral, intranasal, and needle-free or other injection devices).
 - Needle length and gauge.
 - Anatomical site (including left or right side) of immunization (e.g., vaccine A in proximal left lateral thigh, vaccine B in left deltoid).
 - Detailed clinical description of the pattern of elevated temperature.
 - Concurrent signs, symptoms, and diseases.
 - Concurrently administered biologics and prescription and non-prescription medication, particularly antipyretics.
 - Laboratory examination and/or pathological findings and diagnoses.
 - Person reporting and/or measuring the temperature (e.g., medical provider, parent/patient, and other third party reporter), including contact information.
 - Date/time of diagnosis⁴ and end of episode.⁵
 - Immunization history (i.e., previous immunizations and any adverse events following immunization).
- (7) *Additional* desirable but not essential information to be collected includes:
 - placement of measuring device within or upon the anatomic site;
 - level of prior activity, relationship to a meal;
 - time of day, environmental conditions;
 - the duration of measurement;
 - gestational age and birth weight of infants (< 37 weeks gestation);

⁴ The *date and time of diagnosis* of an episode is the time the event met the case definition.

⁵ The *end of an episode* is defined as the time the event failed to meet the case definition (i.e., temperature measurement reached $< 38^{\circ}\text{C}$).

- time interval between birth and immunization for neonatal immunizations; and
 - presence or absence of concurrent local disease outbreaks.
- (8) The device, route, method, duration of measurement, and time of day should be *consistent within and between study groups*, if applicable.
- (9) *Follow-up of cases* should attempt to verify and complete the information collected as outlined in guidelines 1–7.

3.2. Data analysis

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

- (10) Reported events should be *classified* in one of the following two categories. Events that meet the case definition should be classified as Level 1 of diagnostic certainty as specified in the case definition; Level 2 and Level 3 are not applicable for fever. Events that do not meet the case definition should be classified in the additional category for analysis.

Event classification in two categories

Event meets case definition

- (1) Level 1: as specified in the case definition for fever

Event does not meet case definition

Additional category for analysis

- (2) Reported event of fever with insufficient evidence to meet the case definition

This applies if the evidence available for an event is insufficient because information is missing (e.g., only tactile temperature information, no actual measured temperature $\geq 38^\circ\text{C}$ with validated device provided).

- (11) Temperature measurement in clinical trials, and whenever possible in surveillance systems, should be analyzed in *defined time increments*. These may vary according to the biological activity of the vaccine under consideration. The *time interval between immunization and fever* should be determined by using the date of immunization and the date of diagnosis.

For example:

Number (<i>n/N</i> (%)) of subjects with fever
0 (time of immunization) to 24:00 h (Day 1)
00:01–24:00 h (Day 2)
Days 3–7
Days 8–14
Days 15–21
Days 22–28, etc.

- (12) The *duration of fever* should be analyzed as the *number of days* with one or more temperature readings of $\geq 38^\circ\text{C}$.
- (13) Temperature measurement should be analyzed in 0.5°C increments, and as the percentage of subjects whose *highest temperature* fell within that increment during a specified time span.

Temperature increments		Subjects (<i>n/N</i> (%)) within those increments
$^\circ\text{C}$	$^\circ\text{F}$	
<38.0	<100.4	<i>n/N</i>
38.0–38.4	100.4–101.1	<i>n/N</i>
38.5–38.9	101.3–102.0	<i>n/N</i>
39.0–39.4	102.2–102.9	<i>n/N</i>
39.5–39.9	103.1–103.8	<i>n/N</i>
40.0–40.4	104.0–104.7	<i>n/N</i>
40.5–40.9	104.9–105.6	<i>n/N</i>
>41.0	>105.8	<i>n/N</i>

If detailed analysis in increments is not possible, at a minimum the overall number of subjects with a temperature of $\geq 38.0^\circ\text{C}$ should be used as a basis for analysis of incidence and prevalence.

- (14) In clinical trials, measured temperature should be analyzed by *study arm and dose*.
- (15) 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 fever 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 fever to a surveillance system or study monitor. It is recommended also to refer to existing guidelines (e.g., CONSORT and MOOSE) for presentation and publication of vaccine safety studies [63].

- (16) All reported events of fever should be presented according to the *categories* listed in guideline 12.
- (17) Data on fever should be presented in accordance with *data collection guidelines 1–7* and *data analysis guidelines 10–15*.
- (18) *Terms* to describe fever (e.g., “low-grade,” “mild,” “moderate,” “high,” “severe,” or “significant”) are highly subjective and prone to wide interpretation, and therefore should be avoided.
- (19) Data should be presented with *numerator and denominator (*n/N*)* and not only in percentages.

Since in surveillance systems denominators are usually not readily available, attempts should be made to identify approximate denominators. The source of

denominator data should be reported and calculations of estimates described (e.g., obtained from manufacturer, Ministry of Health and coverage/population based data).

- (20) If the *distribution of data* is skewed and a median and range are more appropriate statistical descriptors than a mean, the mean and standard deviation also should be provided to facilitate meta-analysis. Modal values would provide a useful insight into the etiology of fever following immunization particularly for the analysis of fever with bimodal distribution.
- (21) Any publication of data on fever following immunization should include as detailed as possible a *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; and
 - whether the day of immunization was considered “day 1” or “day 0” in the analysis.
- (22) The *incidence and prevalence* of cases in the study population should be presented and clearly identified as such in the text.
- (23) The use of the Brighton Collaboration case definition for fever should be *mentioned in the abstract or methods section* of a publication, and this document referenced.

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⁶ The complete literature search is available from the Brighton Collaboration Secretariat: secretariat@brightoncollaboration.org.

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