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Commentary

Acute wheeze in the pediatric population: Case definition & guidelines for data collection, analysis, and presentation of immunization safety data

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1. Preamble

1.1. Need for developing a case definition and guidelines for data collection, analysis, and presentation of wheeze as an adverse event following immunization

Wheeze is a common presenting symptom of respiratory disease in children [1]. It is a high pitched, whistling, adventitious breath sound lasting, indicating limitation of airflow [2]. Limitation of airflow in a compliant airway is accompanied by flutter of the walls at the site of flow limitation [3,4]. In the presence of airway narrowing, this flutter may include the airway walls and become large enough to generate sound, heard as wheezing [5]. The lung volume, the air flow rate, the mechanical properties of the airway wall and adjacent tissues that are set into oscillation determine the intensity, pitch, composition (monophonic or polyphonic notes), duration (long or short), and timing (inspiratory or expiratory, early or late) of this dynamic process [5,6]. Processes including mucosal swelling, mucus deposition in the airway, bronchoconstriction, and airway narrowing by foreign body or tumor may result in airflow limitation.

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Wheeze generated by the obstruction of larger airways has a constant acoustical character throughout the lung, but varies in loudness depending upon the distance from the site of obstruction. It is referred to as monophonic (or homophonous) wheezing. In contrast, in small airway obstruction, the degree of narrowing varies from place to place within the lung. As a result, the sounds generated also vary in acoustical character and are described as polyphonic (or heterophonous) wheezes [1,7].

Bronchiolitis, bronchitis, and asthma are common clinical conditions which may present with multiple respiratory signs and symptoms including wheeze. For clinical purposes wheeze has been used synonymously with some of these conditions, e.g. a first episode of wheezing in infants is commonly called bronchiolitis [8]. In turn, wheeze definitions vary and range from transient audible breath sounds with no associated respiratory symptoms to the presence of severe respiratory distress accompanying the breath sound. Rhonchi are similar to wheeze in that they are also musical sounds common in airway narrowing. However, they are low in pitch and not considered wheeze equivalents [9].

Wheeze may have multiple etiologies, including viral and allergic causes, particularly in infants and young children, and wheeze may reflect the immune response to immunization. Thus, it is an important clinical sign of a potential adverse respiratory event in pediatric drug and vaccine studies [10–13]. Reports of wheeze in children participating in live attenuated influenza vaccine trials have raised particular concern of adverse respiratory events associated with the trials [12,14–16]. A systematic review of definitions and severity gradings of wheeze as an adverse event in vaccine and drug randomized controlled trials (RCTs) enrolling children < 5 years old recently identified 51 eligible vaccine trials mainly conducted in high-income settings, 33 of which involved influenza vaccines [12]. Wheeze has also been used as a primary outcome of RCTs [17], highlighting the importance and challenge of objective wheeze assessment.

This systematic review included 26 trials that provided explicit definitions of wheeze. Only 28% of these studies described the severity of findings of respiratory distress, and only 7% reported severity of wheeze. Most wheeze descriptions (69%) were based on physical examination by a healthcare worker. However, wheeze definitions in 21 of 58 studies used combined caregiver and healthcare worker assessment. Use of the combined assessment appeared to have the highest sensitivity and specificity [12], but in the absence of a gold standard this finding is difficult to ascertain. Moreover, the systematic review was largely descriptive, with no meta-analysis performed on estimated risks of wheeze associated with the evaluated vaccines. Given the heterogeneity of case definitions, comparison of the risk and incidence of wheeze across studies and vaccines was problematic. Thus, the review highlighted the lack of a standardized case definition for wheeze as an adverse event following immunization (AEFI), particularly among children under the age of 5 years.

There is no uniformly accepted definition of wheeze as an AEFI. However, as described in the recent systematic review, there are a number of case definitions and severity grades that have been used to measure wheeze as an adverse event. This situation offers an opportunity to develop a case definition that improves data comparability across trials or surveillance systems, facilitates data interpretation and promotes the scientific understanding of the event and its potential relationship to vaccine administration.

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

Following the process described in the overview paper [18] as well as on the Brighton Collaboration Website [19], the Brighton Collaboration Wheeze Working Group was formed in 2015. It includes members with clinical, academic, public health and industry backgrounds.

To guide the decision-making for the case definition and guidelines, a literature search was performed using MEDLINE, EMBASE, Web of Science, Scopus, CINAHL, Cochrane Library databases and WHO Global Health Library, including MeSH terms related to wheeze (“Respiratory Sounds”[Majr]), children (“Child”[Mesh]), clinical trials (“Clinical Trials as Topic”[Mesh]), vaccines (“Vaccines”[Mesh]) e.g. (((“Respiratory Sounds”[Majr]) AND “Child” [Mesh]) AND “Clinical Trials as Topic”[Mesh]) AND “Vaccines” [Mesh] [12]. The search was conducted in October 2014, and included only English language publications and trials published after 1970. The search resulted in the identification of 1122 references after removal of duplicates. All abstracts were screened for possible reports of wheeze following immunization. Three hundred and thirty-one 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 58 articles, including information on the study type, the vaccine, the diagnostic criteria or case definition put forth, the time interval since time of immunization, and other symptoms [12].

Based on the literature search and identification of wheeze case definitions from multiple general medical, pediatric and infectious disease textbooks, an inventory comprising 20 relevant case definitions was developed and circulated to the working group members [1,2,5–7,9,12,20].

1.3. Rationale for selected decisions about the case definition of wheeze as an AEFI

1.3.1. The term wheeze

Wheeze may be used to refer to both a sign as well as a symptom. It can be reported by a patient or observed by a non-trained individual such as a parent or caregiver, or by a healthcare provider. For the purpose of this document we define “wheeze” as the sign heard and recorded by a professional and “wheezing” as the symptom reported by the patient or caregiver. This also reflects that “wheeze,” when assessed by a trained healthcare provider, in general has a higher specificity compared to “wheezing” as described by patient or caregiver [12,21–23].

Wheeze is an intrathoracic sound and a sign of airflow limitation, regardless of etiology. Wheeze is primarily an expiratory breath sound. Inspiratory wheeze may occur in addition to the expiratory component in severe airway obstruction. Silent chest may be the most severe form of airway narrowing since it denotes the lack of audible air entry and is never a normal finding. Thus, airflow limitation cannot be excluded in the absence of wheeze.

1.3.2. Differentiation from other similar and/or associated disorders

Primarily inspiratory noises tend to be extrathoracic and should be considered stridorous (e.g., croup). Acute and recurrent wheeze (e.g., as in bronchial asthma) should be differentiated from chronic or pre-existing wheeze (e.g., as in cystic fibrosis).

Wheeze may be associated with respiratory distress manifested as increased respiratory effort and/or dyspnea. However, wheeze may also be present in the absence of dyspnea. Furthermore, a patient with dyspnea may or may not have wheeze. Thus, dyspnea and wheeze may or may not co-occur as a result of a common cause – airflow limitation [20]. Dyspnea may also be both symptom (e.g., shortness of breath) and sign. Thus, it seems prudent to avoid the use of dyspnea in the case definition of wheeze. However, measurable characteristics and elements of dyspnea and wheeze can be specified and the co-occurrence of wheeze and dyspnea should be well documented, because, in the case of wheeze,

the degree of dyspnea is an expression of the severity of the airflow limitation.

1.3.3. Medical significance

The Working Group agrees that the medical significance of acute wheeze cannot be derived from any of its characteristics, including sound quality or loudness. The medical significance must be characterized by evaluating concomitant signs and symptoms of airway disease that indicate respiratory distress. The Working Group considered a standardized classification of wheeze severity and acknowledged that no internationally accepted standard classification system is available. The Working Group therefore considered existing grading scales of respiratory distress and respiratory illness [24–26] and proposes the grading as outlined in Guideline 34 below.

The Working Group recognizes that the clinical significance of mild wheezing illness is currently not established and the long-term impact and clinical meaning of an episode (mild, moderate, or severe) following vaccination is also currently not understood. The proposed severity grading may aid to further delineate different clinical presentations and help shed light on this question by harmonizing wheeze classification across vaccine safety studies.

1.3.4. Influence of treatment on fulfillment of the case definition

The Working Group decided to use "treatment response" as a part of the wheeze case definition (i.e., response to bronchodilators). This is because improvement or absence of physician-diagnosed wheeze following treatment with bronchodilators is suggestive of a known mechanism underlying this breath sound. This is deemed to increase the positive predictive value of the wheeze definition. In contrast, absence of clinical response to treatment does not exclude the presence of wheeze (e.g. as in bronchiolitis) for a variety of reasons including infant bronchial wall compliance, age-dependent beta 2-receptor sensitivity, dose, and route of administration. As treatment response is a useful but insufficient condition to define wheeze, an alternative pathway for classification at the same level of diagnostic certainty is provided where necessary.

1.3.5. Timing after immunization

We postulate that a definition designed to be a suitable tool for testing causal relationships requires ascertainment of the outcome (e.g. wheeze) independent from the exposure (e.g. immunizations). Therefore, to avoid selection bias, a restrictive time interval from immunization to onset of wheeze should not be an integral part of such a definition. Instead, where feasible, details of this interval should be assessed and reported as described in the data collection guidelines.

Furthermore, wheeze often occurs outside the controlled setting of a clinical trial or hospital. In some settings it may be impossible to obtain a clear timeline of the event, particularly in less developed or rural settings with limited access to healthcare. In order to avoid selecting against such cases, the Brighton Collaboration case definition avoids setting arbitrary time frames. However, based on previous studies, follow-up time periods of a minimum of 6 months are suggested in the guideline for data collection [27]. This minimal time frame may have to be increased in view of the specific characteristics of the vaccine used and the population investigated.

1.3.6. The meaning of acute onset in the context of wheeze

The term "acute onset" refers to an event that occurred unexpectedly and without warning, in a short space of time, leading to a marked change in a subject's previous condition. The temporal relation to immunization should be documented by determining the onset of wheeze after the exposure.

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

The grading of definition levels depends on 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. 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 One down to Level Three, while retaining an acceptable level of specificity at all levels. In this way it is hoped that all possible cases of confirmed wheeze can be captured.

The Working Group acknowledges that wheeze may be an expression of many different clinical conditions. A case definition of wheeze may be used for case identification (i.e., case finding) or case verification (i.e., data analysis). The standardized case definition presented in this document is intended for use at the time of data evaluation and analysis. If used for case identification, additional signs and symptoms may be considered and recorded to optimize detection sensitivity depending on the data source used.

1.4. Guidelines for data collection, analysis and presentation

The case definition of wheeze is accompanied by guidelines, which are structured according to the steps of conducting a clinical study (i.e. data collection, analysis and presentation). The case definition and the guidelines were developed to improve data comparability; they are not intended to guide or establish criteria for the clinical management of ill infants, children, or adults.

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.

2. Case definition of acute wheeze

Acute wheeze is the sudden onset of a high pitched, whistling, adventitious breath sound generated by turbulence of air in the intrathoracic airways due to airflow limitation.

For all levels of diagnostic certainty, acute wheeze is a clinical sign defined by

- Sudden onset[1]

AND

- Breath sound
- Audible on auscultation

AND

- Audible during expiration[2]

AND

- Characterized by the following criteria defining the level of diagnostic certainty:

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

[2] The sound is primarily expiratory. An inspiratory component is possible in severe forms. Stridor is a separate entity.

Level 1
- Classified as wheeze based on digital stethoscope [28–32] recording as compared with ref audio file
  OR
- Classified as wheeze by 2 health care providers with specific training[1,2]

Level 2a (one health care provider with specific training)
- Classified as wheeze by 1 health care provider with specific training[1,2]
  AND
- Immediate response to bronchodilator treatment[3,4]
  OR
- Infant diagnosed with acute bronchiolitis.

Level 2b (two health care providers)
- Classified as wheeze by two health care providers without specific training[5]
  AND
- Immediate response to bronchodilator treatment[3,4]
  OR
- Infant diagnosed with acute bronchiolitis.

Level 3 (pre-existing diagnosis)
- Classified as wheeze by 1 health care provider OR care taker (e.g. parent) without specific training
  AND
- Pre-existing physician diagnoses of a respiratory disease of which wheeze is a key symptom

[1] Pulmonologist or formal auscultation training based on standard wheeze training tool,
[2] e.g., Dr. Hans Pasterkamp. R.A.L.E. Lung Sounds 3.12 Professional Edition. Pix-Soft Inc. 1 June 2008. Winnipeg, Canada. 1 June 2008.
[3] Absence of wheeze following treatment or improvement of wheeze severity, as outlined in Guideline 19.
[4] Documented by heath care provider.
[5] Neither a pulmonologist nor someone with formal auscultation training based on standard wheeze training tool.

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

It was the consensus of the Brighton Collaboration Working Group for Wheeze to recommend the following guidelines to enable meaningful and standardized collection, analysis, and presentation of information about wheeze. 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, an epidemiological study, post-marketing surveillance or an individual case report of wheeze. Also, as previously explained in in the overview paper [18], 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 immunization to allow for comparability of data, and are recommended as an addition to data collected for the specific study question and setting. The guidelines are not intended to guide the primary reporting of wheeze 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 numbers 1–30 below have been developed to address data elements for the collection of AEFI information as specified in general drug safety guidelines by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use [33,34] and the form for reporting of drug adverse events by the Council for International Organizations of Medical Sciences [34]. These data elements include an identifiable reporter[A] and patient, one or more prior immunizations, and a detailed description of the adverse event, in this case, of wheeze following immunization. The additional guidelines have been developed as guidance for the collection of additional information to allow for a more comprehensive understanding of wheeze following immunization. For all information, documented source data (e.g. medical record) are preferable.

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

3.1.2. Vaccinee/control

3.1.2.1. Demographics. For all cases and/or all study participants, as appropriate, the following information should be recorded in accordance with country-specific data protection laws and ethic committee requirements:

(5) Case/study participant identifiers (e.g. code).
(6) Date of birth, age, and sex.
(7) For infants: Gestational age and birth weight.

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

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

3.1.3. Details of the immunization

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

[A] If the reporting center is different from the vaccinating center, appropriate and timely communication of the AEFI should occur.

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

3.1.4. The adverse event

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

(17) Clinical description of signs and symptoms of wheeze, specifically, if there was medical confirmation of the event (i.e. patient seen by healthcare provider).
(18) Date/time of onset,[B] first observation,[C] diagnosis,[D] end of episode[E] and final outcome[F]
(19) Concurrent signs and symptoms of respiratory distress including nasal flaring tachypnea, (increased respiratory rate (corrected for age)), prolonged expiration (e.g. I:E ratio > 1:3), lower chest wall indrawing, central cyanosis, pulse oximetry SPO2 < 92%, inability to breastfeed/drink/talk (as appropriate for age), and altered mental status.
(20) Measurement/testing
- Values and units of routinely measured parameters (e.g. vital signs including temperature, heart rate, respiratory rate, pulse oximetry (SaO_2)) – in particular those indicating the severity of the event;
- Method of measurement (e.g. type of thermometer, oral or other route, duration of measurement, etc.);

(21) Treatment given for wheeze, specifying type, dose and duration.
(22) Outcome[F] at last observation.
(23) Objective clinical evidence supporting classification of the event as "serious".[G]
(24) Exposures other than the immunization 24 h before and after immunization (e.g. food, environmental) considered potentially relevant to the reported event.

3.1.5. Miscellaneous/general

(25) The duration of surveillance for wheeze should be predefined. It is recommend to be at least 6 months and may be extended based on:
- Biologic characteristics of the vaccine e.g. live attenuated versus inactivated component vaccines;
- Clinical features/presentation of the vaccine-targeted disease;
- Biologic characteristics of wheeze, including patterns identified in previous trials (e.g. early-phase trials); and
- Underlying diseases/conditions of the vaccinee (e.g. nutrition, immune compromise).

(26) The duration of follow-up reported during the surveillance period should be predefined likewise. It should aim to continue to resolution of the event.
(27) Methods of data collection and documentation should be consistent within and between study groups, if applicable.
(28) Follow-up of cases should attempt to verify and complete the information collected as outlined in data collection guidelines 1 to 24.
(29) Investigators of patients with wheeze should provide guidance to reporters to optimise the quality and completeness of information provided.
(30) Reports of wheeze should be collected throughout the study period between immunization and the adverse event. Proposed time intervals are described below in the table in Point 32. 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 wheeze to allow for comparability of data, and are recommended as an addition to data analysed for the specific study question and setting.

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

Event classification in 5 categories[H]
Event meets case definition

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

Event does not meet case definition
Additional categories for analysis

(4) Reported *wheeze* with insufficient evidence to meet the case definition[I]
(5) Not a case of *wheeze*[J]

[B] The date and/or time of onset is defined as the time post immunization, when the first sign or symptom indicative for wheeze occurred. This may only be possible to determine in retrospect.
[C] The date and/or time of first observation is the first time the wheeze was assessed by a health care worker.
[D] The date of diagnosis of an episode is the day post immunization when the event met the case definition at any level.
[E] 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.
[F] E.g., recovery to pre-immunization health status, spontaneous resolution, therapeutic intervention, persistence of the event, sequelae, and death.
[G] 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.
[H] The highest possible level of classification should be recorded for each event.
[I] If the evidence available for an event is insufficient because information is missing, such an event should be categorised as "Reported wheeze with insufficient evidence to meet the case definition."
[J] An event does not meet the case definition if investigation reveals absence of a necessary criterion (necessary condition) for diagnosis. Such an event should be rejected and classified as "Not a case of wheeze".

(32) The interval between immunization and reported *wheeze* could be defined as the date/time of immunization to the date/time of onset (see Footnote B) of the first symptoms and/or signs consistent with the definition. If this is not available, the time of first observation (see Footnote C) or time of diagnosis (see Footnote D) can be used. If few cases are reported, the concrete time course could be analysed for each; for a large number of cases, data can be analysed in the following increments:

Subjects with *wheeze* by Interval to Presentation

Interval to Presentation	**Number**
< 60 min after immunization	_____
1 h to 24 h after immunization	_____
Daily increments thereafter through 7 days after immunization	_____
Days 8–31 after immunization	_____
>= 1 to 6 months after immunization	_____
>= 6 to 12 months after immunization	_____
TOTAL	_____

(33) The duration of a possible *wheeze* could be analysed as the interval between the date/time of onset (see Footnote B) (alternatively date/time of first observation (see Footnote C) or diagnosis (see Footnote D)) and the end of an episode (see Footnote E) (alternatively the date/time of the final outcome (see Footnote F)). Whichever start and ending are used, they should be used consistently within and across study groups.

(34) The severity of the wheeze should be classified according to the following grading system.

For severity grading, if more than one measurement of a particular variable is taken and recorded, the value corresponding to the greatest magnitude could be used as the basis for analysis (see Table 1).

(35) 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.

(36) Data on *wheeze* 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.

3.3. Data presentation

These guidelines represent a desirable standard for the presentation and publication of data on wheeze following immunization to allow for comparability of data, and are recommended as an addition to data presented for the specific study question and setting. Additionally, it is recommended to refer to existing general guidelines for the presentation and publication of randomized controlled trials, systematic reviews, and meta-analyses of observational studies in epidemiology (e.g. statements of Consolidated Standards of Reporting Trials (CONSORT) [35], of Improving the quality of reports of meta-analyses of randomized controlled trials (QUORUM) [36], and of meta-analysis Of Observational Studies in Epidemiology (MOOSE) [37], respectively).

Table 1
Wheeze severity grading system.

Grade I (mild)	Grade II (moderate)	Grade III (severe)
Wheeze only	Wheeze with respiratory distress	Wheeze with danger signs
Wheeze[1,2]	Wheeze AND • Prolonged expirium (i.e. I/E ration > 1:3) OR • Tachypnoea OR • Intercostal indrawing OR • Nasal flaring	Wheeze[3] AND • Oxygen saturation < 92% OR • Central Cyanosis OR • Confusion or drowsiness OR • Inability to speak or drink

[1] There may even be tachypnea without other signs of respiratory distress.
[2] There may be tachycardia without other signs of respiratory distress.
[3] OR silent chest on auscultation in a patient with history of wheeze.

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

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

(39) Terms to describe wheeze such as "low-grade", "mild", "moderate", "high", "severe" or "significant" are highly subjective, prone to wide interpretation, and should be avoided, unless clearly defined, such as by the severity grading system proposed above.

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

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

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

(43) Any publication of data on wheeze 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 *wheeze*;
- The trial profile, indicating participant flow during a study including drop-outs and withdrawals to indicate the size and nature of the respective groups under investigation;
- The type of surveillance (e.g. passive or active surveillance);
- The characteristics of the surveillance system (e.g. population served, mode of report solicitation);
- The search strategy in surveillance databases;
- Comparison group(s), if used for analysis;
- The instrument of data collection (e.g. standardized questionnaire, diary card, report form);
- Whether the day of immunization was considered "day one" or "day zero" in the analysis;
- Whether the date of onset (see Footnote B) and/or the date of first observation (see Fottnote C) and/or the date of diagnosis (see Footote D) was used for analysis; and

- Use of this case definition for wheeze, in the abstract or methods section of a publication.[K]

Conflict of interests

Louis J. Bont reports his institution received grants from Abbvie and MedImmune, and consultancy fees from Janssen, Gilead, Okairos, Mabxience, Alios, and AIT; Kathryn M. Edwards has been funded by the US Centers for Disease Control to assess wheezing after live attenuated influenza vaccines in children. She has also been funded by Novartis to conduct a vaccine study of Group B streptococcal vaccines in pregnant women, and her institution receives funding from Novartis for her participation in a DSMB for an influenza vaccine efficacy trial. Paul Turner is in receipt of a Clinician Scientist award funded by the Medical Research Council (MR/K010468/1) and has received research support from the Department of Health through the Policy Research Programme (National Vaccine Evaluation Consortium, 039/0031) and a NIHR comprehensive Biomedical Research Centre award to Imperial College London Healthcare NHS Trust. All other authors have no conflicts of interest to disclose.

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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. The authors alone are responsible for the views, findings and conclusions expressed in this publication. Specifically, this work does not necessarily represent the official position of the World Health Organization or any of the other organizations affiliated with the authors.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.vaccine.2017.01.083.

[K] 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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