Diarrhea: Case definition and guidelines for collection, analysis, and presentation of immunization safety data


The Brighton Collaboration Diarrhea Working Group

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1. Preamble

1.1. Need for developing a case definition and guidelines for diarrhea as an adverse event following immunization [AEFI]

Diarrhea, also spelled diarrhoea, is a common medical condition that is characterized by increased frequency of bowel movements and increased liquidity of stool [1,2]. Although acute diarrhea is typically self-limiting, it can be severe and can lead to profound dehydration, which can lead to abnormal low blood volume, low blood pressure, and damage to the kidneys, heart, liver, brain and other organs. Acute diarrhea remains a major cause of infant mortality around the world. Over 2 million deaths are attributed to acute diarrhea each year worldwide, most of them in the developing world. [3–5]. Children and the elderly are particularly prone to dehydration secondary to diarrhea.

Diarrhea has been defined over time by various scientific groups and health organizations in different ways, such as: “the passage of loose unformed stools” [6] or “three looser-than-normal stools in a 24-h period” [7,8] with emphasis on the consistency of stools rather than the number [9]. In epidemiological studies, diarrhea is usually defined as the passage of three or more loose or watery stools in a 24-h period, a loose stool being one that takes the shape of a stool container [8–16].

Diarrhea is also a commonly reported AEFI in both passive surveillance systems and clinical trials, for both oral and non-oral vaccines [14,17–25]. The lack of a commonly accepted, standardized definition for diarrhea as an AEFI hinders comparability and uniform reporting of diarrhea across various study settings or surveillance systems.

There are currently two vaccines (Rotarix and Rotatex) licensed and recommended for use against rotavirus gastroenteritis in the U.S. population [92–95]. Additionally, recent advances in biotechnology have provided the impetus for developing new vaccines against several infectious diarrheal agents; examples include vaccine candidates against Vibrio cholerae, enterotoxigenic Escherichia coli (ETEC), rotavirus, and Shigella species [26–29]. A standardized definition of diarrhea is key to a better understanding and prevention of diarrheal disease since it is frequently reported and evaluated as an endpoint in vaccine clinical trials [12].

Sections 2 and 3 of this paper provide the case definition and guidelines for data collection, analysis, and presentation that the Brighton Collaboration Diarrhea Working Group (hereafter referred to as the Working Group) has developed for the standardized collection and assessment of information about diarrhea as an AEFI. Widespread use of this definition with its guidelines will improve data comparability and allow for a better understanding of diarrhea as an AEFI. The case definition could be used to inform discussions between regulatory agencies and industry regarding diarrhea as an AEFI. This case definition can also be used in the assessment of diarrhea as an adverse event in efficacy and effectiveness studies. The case definition and guidelines are intended to be applicable in diverse geographic, administrative, and cultural settings, regardless of differences in the availability of healthcare resources.

1.2. Methods for the development of the case definition and guidelines for diarrhea as an AEFI

Following the process described previously [30], a Brighton Collaboration Working Group was formed in August 2007, initially with 49 members having public health, regulatory, clinical, academic, or industry backgrounds. In September 2007, the Working Group began to develop the current definition of “diarrhea”, together with guidelines for collection, analysis, and presentation of vaccine safety data related to diarrhea as AEFI.

To guide the decision-making for the case definition and guidelines, a literature search was conducted using English and non-English citations of diarrhea in the context of immunization published between 1966 to April 2007. The terms used within Medline, the Cochrane library, and Embase included: diarrhea/diarrhoea, vaccines/complications, vaccines/contraindications, vaccines/toxicity, immunization/vaccines/adverse effects, side effects/immunization/ complications, immunization/toxicity, case definitions/immunization/contraindications, and humans. The search resulted in the identification of about 800 references including review articles. Of these references, 26 abstracts were non-English. An additional search from the articles reviewed yielded an additional 150 articles that were also reviewed. Relevant citations from the articles above were included in this paper. Our in-depth literature review was limited to English language articles due to practicability; the Working Group recognizes this as a limitation however, since the working group and review committee consist of professionals from different language backgrounds, the bias introduced by English-only reviewing could be reduced to the minimum.

Additionally, the Working Group queried the more than 1200 scientists enrolled in the Brighton Collaboration e-mail list about use or development of any standardized definition of diarrhea. Responses were received from different groups involved with pre- and post-marketing surveillance or vaccine safety clinical trials, including regulatory agencies, universities, and vaccine manufacturers; however, they did not yield a standardized definition of diarrhea.

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

It was the consensus of the working group to define diarrhea as an adverse event from an epidemiological or clinical stand point for use in both clinical trials and post marketing surveillance. The Working Group agreed to adapt the simple World Health Organization (WHO) [9] definition of diarrhea with modification into two levels of diagnostic certainty (Section 2). The variables listed in Appendix A were then developed to better characterize diarrhea as an AEFI.

The Working Group recognizes several potential reporters of diarrhea, including parents or guardians of young children, self-reports in adults, and study-site clinical personnel. It was, however, considered that mothers were the best reporters of diarrhea in young children [83].

1.3.1. Time frames

The Working Group agreed on using a 24-h period as the time frame for capturing the number and consistency of stools to define diarrhea instead of other time periods used in the literature [11,31–35]. The 24-h period has been used in the WHO definition criteria and is currently being used in many countries, as this definition has proven to be easily applicable in various global settings. For example, in community studies in Guinea-Bissau, it has been demonstrated that mothers of younger children can report diarrhea according to this definition with high validity [36]. The Working Group agreed on a 24-h period for defining the onset of diarrhea acknowledging that, in some cases, exact times may not be possible to obtain. The time of onset of diarrhea would be best perceived by the parent, caregiver or guardian (or self in adults).

The Working Group further agreed to refrain from suggesting a follow-up time frame for surveillance for diarrhea following immunization. The duration for surveillance depends on a range of variables (see guideline 34) and does not further define diarrhea as a clinical entity. Instead, this allows defining diarrhea without...
assuming causality, based on the timing of onset post immunization alone.

1.3.2. Dehydration

The Working Group agreed that, although dehydration does not define diarrhea, it represents a critical variable in describing the severity of diarrhea and can be assessed in developed and developing country settings. The working group adapted, with slight modification, the WHO [9] criteria for the assessment of dehydration, which is based on a variety of signs and symptoms as well as fluid deficit estimates, as outlined in Appendix A.

1.3.3. Grading severity of diarrhea

Several scoring scales have been used inconsistently in studies to grade the severity of diarrhea [37–43]. Should an investigator decide to grade severity of diarrhea, the Working Group recommends the use of 3 grades for severity of diarrhea, based on symptoms: grade 1 or mild, grade 2 or moderate and grade 3 or severe, developed by this Working Group in guideline 28 with details in Appendix A. The Working Group acknowledges that many cases of diarrhea in clinical studies will fall into the mild or moderate categories. One key secondary outcome is dehydration, for which grading is also included based on a modification of the WHO [9] criteria outlined in Appendix A.

The Working Group refrained from developing a composite severity scoring scale incorporating additional information describing diarrhea, as this could add complexity in weighting scores across various variables. Instead, the Working Group decided to develop a list of variables (Appendix A) considered relevant to describing diarrhea and makes reference to the Vesikari numerical scale [44] (Appendix C) as applicable. It should be noted that the list of variables developed by this Working Group has not yet been used or validated in studies; furthermore, the Vesikari scale has been shown to be useful and robust in studies involving children, [96] but it has not been used in adults.

1.3.4. Stool consistency

The Working Group recommends the use of a 5-point visual stool consistency scale: 1 = hard stool, 2 = soft stool, 3 = runny stool and/or takes the shape of the container, 4 = brown liquid stool, 5 = “rice water” stool [45,91]. This is a different scale from the grading of severity (mild, moderate to severe) described earlier; see Guideline 31 and a demonstration at: http://www.youtube.com/watch?v=I8KMwWR2ZDk (last accessed December 2009).

1.3.5. Age cut-off

It was debated whether the definition should include different age categories. Age-related differences in nutrition and behaviors vary greatly across the globe, and are known to affect bowel habits, especially in infants, whose bowel habits are affected by breastfeeding and weaning practices. However, it was agreed to not include age as part of the definition, because age categorization itself cannot describe the individual patient’s habits that may influence bowel movement. For the sake of simplicity of the definition, which is intended to be applicable in a variety of settings (e.g. developed and developing countries, clinical trials and passive surveillance systems) age categorization was also not included. Instead, the Working Group proposes to consider age as a key variable in further describing diarrhea. Suggested age categorizations are 0–5 years and >5 years [15,18,46–54], with preference given to listing the actual age (see Appendix A).

1.3.6. Diarrhea and gastroenteritis

Diarrhea has often been used interchangeably with gastroenteritis [55,39]. However, while diarrhea is frequently part of gastroenteritis, gastroenteritis is a broader disease entity encompassing additional gastrointestinal symptoms [37,38,40,39,56,57]. Gastroenteritis is an acute inflammation of the lining of the stomach and intestines caused by a multitude of viruses, bacteria, parasites, toxins and chemicals; its signs and symptoms can include anorexia, nausea, vomiting, diarrhea, abdominal pain, weakness, and fever (see: http://www.nlm.nih.gov/medlineplus/gastroenteritis.html).

1.3.7. Duration of diarrhea

Diarrhea has been further categorized into acute, persistent, and chronic, based on the duration of diarrhea. The Working Group adopted the following frequently used categories: acute diarrhea = an episode that lasts <14 days [58]; persistent diarrhea = an episode of diarrhea that lasts >14 days to <28 days [59,60] and chronic diarrhea = an episode of diarrhea that lasts >28 days [58,61,62]. See Data Analysis Guideline 39 in Section 3 of this document.

1.3.8. Conditions causing diarrhea

The Working Group recommends collecting information on underlying causes of diarrhea and considering separate analysis of those persons with and without known underlying causes: Examples of such conditions are listed in Appendix D.

Relevant past medical conditions that may affect the evaluation of diarrhea as a AEFI, including recent hospitalizations, diseases, or travel, have been listed in guidelines 9 and 10 and Appendices B and D.

1.4. Structure of the case definition and guidelines

The case definition is structured in two levels of diagnostic certainty [30]. It should be stressed that, although potentially applicable in a clinical setting, the level of diagnostic certainty is primarily intended for epidemiologic purposes and not as a criterion for treatment. Similar to other Brighton Collaboration definitions, the definition itself defines a clinical entity without inference of a causal relation to a given exposure.

The guidelines are structured according to the steps of conducting a study, i.e. data collection, analysis, and presentation. The guideline section includes the information necessary to assess diarrhea as an AEFI.

Finally, similar to all Brighton Collaboration case definitions and guidelines, a review of the definition and its guidelines is planned on a regular basis (i.e. every 3–5 years or more often, if needed).

2. Case definition

2.1. Level 1 of diagnostic certainty

Diarrhea is defined as:

- An increase by 3 or more bowel movements (above normal or baseline) occurring within a 24-h period

AND

1 This definition does not attempt to establish a causal link between immunization and diarrhea. Assessing causality requires a range of complex factors that are independent from establishing the presence of diarrhea as a clinical entity.
2 Any 24-h period e.g., Wednesday 6:00 hours to next day Thursday at 6:00 hours.
3 Normal bowel habits are the baseline bowel habits of that person and may vary depending on age, type of feeding (in infants) and dietary factors.
• A runny or liquid consistency of these stools.4,5,6

2.2. Level 2 of diagnostic certainty

Diarrhea is defined as:

• An increase in frequency of bowel movements (above normal or baseline).3,7

AND

• A runny or liquid consistency of these stools.4,5,6

3. Guidelines for data collection, analysis, and presentation

It was the consensus of the Working Group to recommend the following guidelines to enable meaningful and standardized data collection, analysis, and presentation of data about diarrhea. 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 diarrhea. Also, as explained in more detail in an overview paper for all Brighton Collaboration case definitions and guidelines [30], these guidelines are not 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 on diarrhea cases to allow for comparability of data, and are recommended as a supplement to data collected for the specific study question and setting. These guidelines are not intended to replace local legal reporting requirements, but rather to serve as a guide towards harmonization of vaccine safety reporting of diarrhea as an AEFI 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 in Section 2, which are not repeated in this section.

Guidelines 2, 4, 5, 13, 22–23, 27–33 below have been developed to address data elements for the collection of adverse event information as specified in general drug safety guidelines by the International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use [68], and the form for reporting of drug adverse events by the Council for International Organizations of Medical Sciences (CIOMS) [69]. These data elements include an identifiable reporter and patient, one or more prior immunizations, and a detailed description of diarrhea as an AEFI.

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 reporting8 and/or assessing or diagnosing diarrhea, in accordance with country specific data protection law.
(3) Relationship to the patient (e.g., immunizer [clinician, nurse], investigator, other).

3.1.2. Vaccine

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

3.1.2.1. Demographics.

(4) Case/study participant identifiers (e.g., first name initial followed by last name initial), or code (in clinical trial), or as otherwise specified in country-specific data protection laws.
(5) Date of birth (specify calendar used if not the commonly used Julian calendar)9, age, sex, race/ethnicity (if appropriate).
(6) For infants (<12 months of age): Gestational age, birth weight, weight at the time of assessment, and length, as applicable.
(7) Nutritional status: height (or length for infants), weight or Body Mass Index (BMI).
(8) Location of subject within study area including country, if a multi-country study, as appropriate.

3.1.2.2. Clinical and immunization history.

(9) Medical history of recent (1 month prior to current episode) conditions including examples listed in Appendix D.
(10) Medical history of chronic conditions including examples listed in Appendix D.
(11) Any medication history prior to, during, and after vaccination, including prescription and non-prescription medication (e.g., herbal or homeopathic medications) as well as medication with long half-life or long-term effect (e.g., immunoglobulins, blood transfusions, immunosuppressants) that could affect the evaluation of diarrhea, but excluding treatment given for diarrhea.
(12) History of change in feeding habits (e.g. in infants, change from breast feeding to use of formula) within the past month or other dietary change as appropriate.
(13) Immunization history, including exact dates of administration and vaccines given including their number in series; indicate if the history for previous immunizations and AEFI (including occurrence of diarrhea after previous immunizations) is documented or verbal.

3.1.3. Details of recent immunization

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

(14) Date and time of immunization, specify if a 12 or 24-h clock was used. The 24-h clock is preferred, as it avoids potential confusion about a.m. and p.m. times.
(15) Description of vaccine(s): trade name and generic name of vaccine, lot number, expiration date, manufacturer, dose, multi- or mono-dose vial, pre-filled syringe, volume (e.g., 0.5 mL) and number of dose (if part of a series of immunizations against the same disease), diluent lot number (if used), adjuvants, preservatives, buffer preparation (for some oral vaccines), expiration date, preparation of vaccine, e.g., for multidose vials of lyophilized vaccines, whether reconstituted vaccine was used within the recommended period and condition.
(16) Detailed description of combination vaccines: if used, indicate both trade name and generic names if present. Specify the

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4 Diarrhea may have blood or mucus in the stools and can occur with or without dehydration.
5 Grading the severity of diarrhea is further described in Appendix A.
6 For example, to meet the case definition, a person who normally has three bowel movements per day would need to have an increase to 6 bowel movements per day that are looser than normal.
7 Diarrhea is described without specification of numbers for frequency or time
8 If the reporting center is different from the vaccinating center, appropriate and timely communication of the adverse event should occur.
9 The Julian Calendar is the common calendar widely used. The average length of a year in the Julian calendar is 365.25 days (one additional ‘leap’ day being added every four years). http://www.hermetic.ch/cal_stud/cal_art.html#Julian_Calendar.
antigen components if the vaccine was a combination vaccine (single shot).

(17) Anatomical sites\textsuperscript{10} (including left or right side) of all immunizations (e.g., vaccine A in proximal left lateral thigh, vaccine B in left deltoid, vaccine C oral) and needle length and gauge [77].

(18) Storage conditions of the vaccine: vaccines should be stored at temperatures according to the manufacturer’s recommendations. If possible, temperature logs, type of refrigerator, power outages, and vaccine storage conditions should be reviewed and noted, especially in prospective studies [70–72].

(19) Type of professional who immunized the subject (e.g., physician, nurse, other health care provider).

(20) Route and method of administration (e.g., oral, intranasal, intramuscular, intradermal, subcutaneous, or needle-free or other injection devices). Include type and size of needle, if used.

3.1.4. The adverse event

For all cases and/or all study participants, as appropriate, the following information including a detailed clinical description of diarrhea should be recorded.

(21) Criteria fulfilled to meet a case definition and other signs or symptoms indicative of diarrhea.

(22) Detailed clinical description\textsuperscript{11} of the event.

(23) Date and time of: onset,\textsuperscript{11} diagnosis,\textsuperscript{12} end of an episode,\textsuperscript{13} and final outcome\textsuperscript{14}; see Guideline 33 on outcome below and whether hospitalization was required.

(24) Concurrent signs, symptoms, and diseases other than diarrhea. These include both systemic symptoms (such as fever, lethargy or other gastrointestinal symptoms, including vomiting, nausea, and tenesmus) and signs of dehydration status and/or nutritional status. See Appendix A “Variables Describing Diarrhea Episodes”.

(25) Values and units of routinely measured parameters, e.g., number of stools/day, number of vomiting episodes/day, number of seizures, temperature (°C), weight (in kg or ounces), height/length (in cm, or feet, or inches, etc.). See Appendix A, in particular for parameters indicating the severity of the event.

(26) Method of measurement (e.g., in fever, the type of thermometer, body site [oral or other specific route], height-length if in infants, type of device used (e.g., infantometer, baby measuring rod with calipers, infant measuring mats); for weight, the type of scale used (e.g., digital floor scale, crane hanging type, chair scale, or manual stand-up scale). See Appendix A for additional variables.

(27) The severity of diarrhea can be described by the severity of diarrhea symptoms themselves and/or by dehydration status based on modified WHO criteria.

(a) Severity of diarrhea can be assessed using Grade 1 or mild, Grade 2 or moderate and Grade 3 or severe based on symptoms described in Appendix A.

(b) Dehydration is a secondary outcome that can be described using the modified WHO [9] dehydration criteria listed in Appendix A. Dehydration is categorized into three levels of intensity: (1) no signs of dehydration (mild), (2) moderate dehydration and (3) severe dehydration; outlined in Appendix A.

(28) Results of laboratory examinations such as stool microscopy and culture, and/or relevant pathological findings and diagnoses.

(29) Treatment given for the diarrhea: intravenous (I.V.) fluids, oral rehydration therapy, or medication (e.g., antimicrobial agents, anti-diarrheal agents, and others for symptomatic relief like analgesics and or atropine like substances).

(30) Describe the stool consistency using a visual stool consistency scale. A 5-point scale is recommended: 1 = firm stool, 2 = soft stool, 3 = runny stool and/or takes the shape of the stool container, 4 = brown liquid stool, 5 = “rice water” stool, especially applicable in prospective studies\textsuperscript{15} [45,91].

(31) Recurrence of diarrhea after resolution of initial reaction\textsuperscript{16} e.g., as a biphasic illness.

(32) Record the frequency of diarrhea as number of stools/day, patterns or re-occurrence, or if intermittent diarrhea occurs, include dates whenever possible.

(33) The outcome\textsuperscript{15} at last follow-up, as well as the timing relative to immunization and the time course of the evolution of the diarrhea (including date of final outcome or observation). The following terms can be used:

- Resolved without treatment;
- Resolved with treatment (e.g., intravenous fluids, antimicrobial agents);
- Diarrhea still present;
- Sequelae, please specify;
- Death;
- Outcome unknown/not reported;
- Description of any other outcome: please specify.

If the diarrhea has not resolved at the time of reporting or the end of a pre-defined study period, follow-up may be done as clinically necessary and additional reporting should be encouraged in order to describe progress until the final outcome is reached.

3.1.5. Miscellaneous/general recommendations

(34) The duration of surveillance for diarrhea is to some extent arbitrary, should be predefined, and depends on:

- Biologic characteristics of the vaccine, e.g., live attenuated versus inactivated component vaccines.
- Composition of the vaccine (including adjuvant, if present).
- Biologic characteristics of the vaccine-targeted disease.
- Biologic characteristics of the diarrhea including patterns identified in previous trials (e.g., early-phase trials); and
- Biologic characteristics of the vaccinee (e.g., nutrition, underlying disease like immunodepressing illness and any pre-existing gastro-intestinal condition).

(35) Methods of data collection should be consistent within and between study groups, if applicable.

Reports of diarrhea should be collected/included in the database regardless of the time elapsed between immunizations and the adverse event. If not feasible, the study period

\textsuperscript{10} See the case definition of the overall local reaction document that has specific medical illustrations as a guide to record local reactions if they exist [77].

\textsuperscript{11} The date and/or time of onset is defined as the time post immunization, when the first sign or symptom indicative for diarrhea is observed. This may only be possible to determine in retrospect.

\textsuperscript{12} The date of diagnosis of an episode is the day the event met the case definition.

\textsuperscript{13} The end of an episode is defined as the time the event no longer meets the case definition.

\textsuperscript{14} Diarrhea not resolved at the time of reporting or evaluation may be followed up as clinically necessary and additional reporting should be encouraged in order to describe progress until the final outcome. “Persistence of diarrhea” refers to diarrhea continuing to meet the case definition at the last time of follow-up. “Sequelae” are long term clinical consequences resulting from the event.

\textsuperscript{15} See the 5-point grading of diarrhea of Sack et al [45,91]. A visual demonstration is available at: http://www.youtube.com/watch?v=48KmdWRRZDK; this demonstration was developed by the Working Group and posted on YouTube for ease of access of the information globally.

\textsuperscript{16} For recurrence of diarrhea, there need to have been at least two intervening diarrhea-free days [84].
during which safety data are being collected and/or included in the database should be clearly defined.

(36) Follow-up of reported events should attempt to verify and complete the collection of information as outlined in the data collection guidelines 1 through 33.

3.2. Data analysis

The following guidelines represent a desirable standard for analysis of data on diarrhea to allow for comparability of data, and are recommended as an addition to data analyzed for the specific study question and setting.

(37) Reported events should be classified into one of the following four categories. When events meet the case definition, it should be classified according to the two levels of diagnostic certainty as specified in the case definition. Events that do not meet the case definition of diarrhea should be classified according to the additional two categories for analysis.

3.2.1. Event classification in four categories

3.2.1.1. Event meets case definition. Main categories

(1) Level 1: as specified in the case definition for diarrhea.
(2) Level 2: as specified in the case definition for diarrhea.

3.2.1.2. Event does not meet case definition. Additional categories

(3) Insufficient evidence for diarrhea.17
(4) Not a case of diarrhea.18

(38) The interval between immunization and diarrhea could be defined as the date/time of immunizations to the date/time of onset11 or diagnosis12, whichever is available and most appropriate in the given study setting. Whatever dates are used, they should be used consistently within and across study subjects and described. The Working Group recommends the use of date/time of onset.

The time interval could be analyzed in the following increments where n = the number of subjects with diarrhea newly present at, and N = the number of all subjects with diarrhea in the study population or all study subjects (specify which was used).

- ≤ 24 h: n/N (− (%))
- 25 to ≤ 48 h: n/N (− (%))
- 49 to ≤ 72 h: n/N (− (%))
- 73 h to ≤ 7 days: n/N (− (%))
- > 7 days to ≤ 14 days: n/N (− (%))
- > 14 days to ≤ 28 days: n/N (− (%))
- > 28 days: n/N (− (%))

(39) The duration of diarrhea, if applicable, could be analyzed as the interval between date/time of onset11 or diagnosis12 and the end of episode13 or final outcome14. Whatever start and ending dates are used, they should be used consistently within and across subjects and described. The duration could be analyzed in predefined time increments listed in guideline 38.

If detailed analysis is not available (e.g., in surveillance systems), at a minimum the proportion (n/N) of subjects with acute diarrhea (i.e., episode lasts < 14 days [58]); persistent diarrhea (i.e., episode of diarrhea that lasts > 14 days to ≤ 28 days [59,60]); and chronic diarrhea (i.e., episode of diarrhea that lasts > 28 days [58,61,62]) should be analyzed.

(40) If the diarrhea occurs intermittently, the event corresponding to the greatest magnitude, (e.g., the number of stools/day) could be used as the basis for analysis. Also the frequency and pattern of re-occurrence (i.e., periodicity) can be analyzed.

(41) If more than one measurement of a particular parameter is obtained and recorded, the value corresponding to the greatest magnitude of the adverse event should be used as the basis for categorization (e.g., highest body temperature). Analysis may also include other characteristics or qualitative patterns of criteria defining the event (e.g., periodicity, frequency, and fewer-days).

(42) Data on diarrhea in subjects receiving a vaccine should be compared with those obtained from appropriately selected and documented comparison group(s), and should be analyzed by study arm and dose, where possible, e.g., in prospective clinical trials.

3.3. Data presentation

These guidelines represent a desirable standard for presentation or publication of data on diarrhea in order to allow 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., statement of Consolidated Standards of Reporting Trials [CONSORT], of Improving the Quality of Reports of Meta-analyses of Randomized Controlled Trials [QUORUM], and of Meta-analysis Of Observational Studies in Epidemiology [MOOSE], respectively) [74–76].

(43) All reported events on diarrhea should be presented according to the categories listed in guideline 37.
(44) Data on diarrhea should be presented in accordance with data collection guidelines 1–36 and data analysis guidelines 37–42.
(45) Data should be presented with numerator and denominator (n/N) and not only in percentages, where possible. Although in immunization safety 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 doses distributed, as appropriate). Describe the numerator and denominator used in detail including any limitations.
(46) The distribution of data (as numerator and denominator data) should be presented in the predefined time increments as listed in the analysis guideline 38. If the number of cases is small, the exact time course could be presented for each case.
(47) The incidence and prevalence of events meeting the case definition should be presented and clearly identified as such.19
(48) If the distribution of data is skewed, the median and range are more appropriate statistical descriptors than a mean.
(49) Any publication of data on diarrhea as an AEFI should include a detailed description of the methods used for data collection and analysis. It is essential to specify:
  • The study design;
  • For surveillance systems

17 If information about necessary criteria to classify an event as Level 1 or 2 is missing, the case should be classified as category 3, capturing reported event of diarrhea with insufficient evidence to meet the case definition.
18 If criteria necessary to classify an event as Level 1 or 2 are known to be absent, the event should be classified as category 4 capturing reported events which are not diarrhea.
19 For example, total of 10 cases of diarrhea in 2000 study participants or 1 case per million during 5 days; use as appropriate.
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Appendix A. Table of variables describing diarrheal episodes

<table>
<thead>
<tr>
<th>Variable</th>
<th>Type of variable</th>
<th>Categorization or score suggested</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Age</td>
<td>Numerical</td>
<td>Suitable categorization of age 0-5 years, and 5 years and above, with preference for listing actual age if known [15,18,46-54]</td>
</tr>
</tbody>
</table>

Diarrhea/stool/nausea or vomiting associated characteristics

2. The WG recommends grading severity of diarrhea based on severity of symptoms (2a) and/or dehydration using modified WHO criteria (2b)

Table 2a: Severity based on symptoms of diarrhea

<table>
<thead>
<tr>
<th>Grade 1 or mild</th>
<th>Grade 2 or moderate</th>
<th>Grade 3 or severe</th>
</tr>
</thead>
</table>
| An increase by 3 bowel movements (above normal or baseline) that are looser than normal per day, or
| An increase by 4-6 bowel movements (above normal or baseline) that are looser than normal per day, or an increase of 3-6 bowel movements per day (above normal or baseline) that are looser than normal, with some interference with ADLS |
| An increase by 7 or more bowel movements per day (above normal or baseline) that are looser than normal, or an increase by 3 or more bowel movements per day (above normal or baseline) that are looser than normal, with incapacitating symptoms or interference with ADLS (or loose stools with visible red or tarry black blood in stool) |

1 Limitations in a person’s ability to engage in work, school, play, or other activities for health reasons.

2 This is visible blood in stool in the absence of hemorrhoids.

3 Any 24-h period, e.g. Wednesday 6:00 h to next day Thursday at 6:00 h.

Common sources of blood or redness in stools include: maternal breast fissures in breastfed infants; a diet with reddish foods or beverages, such as gelatin, when given to people with diarrhea.

NB. The grading is based on experience by Working Group members and communication with other investigators.

Table 2b: Assessment of patients with diarrhea for dehydration and fluid deficit using the modified WHO criteria [9]

<table>
<thead>
<tr>
<th>No signs of dehydration</th>
<th>Some dehydration</th>
<th>Severe dehydration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient has diarrhea but shows no symptoms of dehydration</td>
<td>Patient has diarrhea and shows the following signs and symptoms of dehydration</td>
<td></td>
</tr>
<tr>
<td>Well, alert</td>
<td>Restless, irritable</td>
<td>Patient has diarrhea and shows the following signs and symptoms of dehydration</td>
</tr>
<tr>
<td>Normal eyes</td>
<td>Eyes are sunken</td>
<td>Eyes are deeply sunken</td>
</tr>
<tr>
<td>Normal pulse</td>
<td>Lowered radial pulse volume</td>
<td>Thready, rapid or absent radial pulse</td>
</tr>
<tr>
<td>Drinks normally, not thirsty</td>
<td>Thirsty, drinks eagerly</td>
<td>Drinks poorly, or unable to drink</td>
</tr>
<tr>
<td>Skin pinch goes back quickly</td>
<td>Skin pinch goes back slowly</td>
<td>Skin pinch goes back very slowly</td>
</tr>
<tr>
<td>Fluid deficit of &lt;5% of body weight, or &lt;50 ml/kg body weight</td>
<td>Fluid deficit of 5-10% of body weight, or 50-100 ml/kg body weight</td>
<td></td>
</tr>
<tr>
<td>Fluid deficit of &gt;10% of body weight, or &gt;100 ml/kg body weight</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

20 Use of this document should be referenced by referring to the link on the Brighton Collaboration website https://brightoncollaboration.org/public/resources/case-definitions.html.
<table>
<thead>
<tr>
<th>Variable</th>
<th>Measurement unit or scale (if appropriate)</th>
<th>Categorization or score suggested</th>
</tr>
</thead>
<tbody>
<tr>
<td>3. Visual stool consistency scale</td>
<td>The working group recommends (as applicable given the study setting) the use of a 1–5 point visual stool scale [45]. See visual demonstration at: <a href="http://www.youtube.com/watch?v=I8KMwWRZDk">http://www.youtube.com/watch?v=I8KMwWRZDk</a>)</td>
<td>1–5 levels</td>
</tr>
<tr>
<td>4. Duration of diarrhea</td>
<td>Hours, days etc.</td>
<td>See Vesikari in Appendix C</td>
</tr>
</tbody>
</table>

The Vesikari numerical scoring scale should be used cautiously: While it has been found to be very useful in studies of infants with rotavirus diarrhea, with most use in active surveillance, its use has not been validated in passive surveillance and adult diarrhea studies.

5. Maximum number of diarrhea stool/24h
6. Duration of vomiting
7. Max number vomiting episodes/24h
8. Nausea

<table>
<thead>
<tr>
<th>Variable</th>
<th>Measurement unit or scale (if appropriate)</th>
<th>Categorization or score suggested</th>
</tr>
</thead>
<tbody>
<tr>
<td>5. Maximum number of diarrhea stool/24h</td>
<td>Numerical</td>
<td>See Appendix C</td>
</tr>
<tr>
<td>6. Duration of vomiting</td>
<td>Hours, days</td>
<td>See Appendix C</td>
</tr>
<tr>
<td>7. Max number vomiting episodes/24h</td>
<td>No of episodes</td>
<td>See Appendix C</td>
</tr>
<tr>
<td>8. Nausea</td>
<td>Yes/no</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Variable</th>
<th>Measurement unit or scale (if appropriate)</th>
<th>Categorization or score suggested</th>
</tr>
</thead>
<tbody>
<tr>
<td>9. Stool examination</td>
<td>[microscopy, culture or other test to identify pathogen]</td>
<td>Describe causative pathogen depending on study and availability of laboratory capacity</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10. Presence of mucus in stool</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

N.B. The bacteriology of mucus was considered non-specific to etiologic pathogens

11. Presence of gross blood in stool
12. Laboratory evidence of blood in stool

<table>
<thead>
<tr>
<th>Variable</th>
<th>Measurement unit or scale (if appropriate)</th>
<th>Categorization or score suggested</th>
</tr>
</thead>
<tbody>
<tr>
<td>11. Presence of gross blood in stool</td>
<td>Yes/no</td>
<td></td>
</tr>
<tr>
<td>12. Laboratory evidence of blood in stool</td>
<td>Yes/no</td>
<td></td>
</tr>
</tbody>
</table>

13. Fever
Continuous variable

Fever is defined as the endogenous elevation of at least one measured body temperature of 38°C [78] N.B. The value of 38°C is accepted as reflecting an abnormal elevation of temperature, irrespective of device, anatomic site, age or environmental conditions.

14. Presence of rectal prolapse
Yes/no

15. Tenesmus
Yes/no

16. Convulsions/seizures
Total number of episodes

Yes/no and number of seizures. Witnessed or history of sudden loss of consciousness AND generalized, tonic, clonic, tonic-clonic, or atonic, motor manifestations [79] Presence of crying which is continuous AND unaltered for ≥3 h or likely to be unaltered for ≥3 h AND likely to be continuous in infants and children [80] Yes/no: the invagination of one segment of intestine into a segment of distal intestine: demonstration of the invagination using surgical, radiological, autopsy or clinical criteria with major or minor criteria depending on setting [81] Yes/no

17. Attacks of persistent crying

18. Presence of intussusception

Yes/no: the invagination of one segment of intestine into a segment of distal intestine: demonstration of the invagination using surgical, radiological, autopsy or clinical criteria with major or minor criteria depending on setting [81] Yes/no

19. Cramping

N.B. Not easily ascertained in the very young and their description of cramping could be different such as “my tummy hurts”
Appendix B. Data collection checklist

This checklist is derived from the criteria listed in the case definition and guidelines for data collection. It is intended as a data collection template for use in study protocols and for active follow up in surveillance systems. Additional information or a different format depending on the study question and setting may be required.

### A. Source of information/reported by

<table>
<thead>
<tr>
<th>Assessing</th>
<th>Reporting</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Medical provider including professional status</td>
<td></td>
</tr>
<tr>
<td>b. Parent/Self</td>
<td></td>
</tr>
<tr>
<td>c. Other (Describe)</td>
<td></td>
</tr>
</tbody>
</table>

### B. Vaccinee/Control Subject

1. Demographics

   a. Patient’s initials (first name initial followed by last name initial) or code or as specified in country-specific data protection laws or study protocol.

   b. Date of birth\(^1\) 

   \[
   \begin{array}{c}
   \text{____/____/____} \\
   \text{(mm / dd / yyyy)} \text{\(^a\)} \\
   \text{Unknown}
   \end{array}
   \]

   \(^a\) All dates, specify type of calendar used, the common Julian calendar is preferred

   c. Age

   \[
   \begin{array}{c}
   \text{----- years-----months} \\
   \text{Unknown}
   \end{array}
   \]

   b. Sex

   If female, pregnancy status

   \[
   \begin{array}{c}
   \text{M [ ]} \\
   \text{F [ ]} \\
   \text{Non-pregnant [ ]} \\
   \text{Pregnant [ ]} \\
   \text{Unknown [ ]}
   \end{array}
   \]

   e. Race/Ethnicity (if appropriate)

   \[
   \begin{array}{c}
   \text{Unknown [ ]}
   \end{array}
   \]
### f. Infants (<12 months of age)

<table>
<thead>
<tr>
<th>Gestational age --------Years</th>
<th>Unknown [ ]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight ---------------</td>
<td>Unknown [ ]</td>
</tr>
<tr>
<td>---------kg/or --------ounces</td>
<td>Unknown [ ]</td>
</tr>
<tr>
<td>Weight at assessment -------kg/or--------ounces</td>
<td>Unknown [ ]</td>
</tr>
<tr>
<td>Length of infant --------cm/ or -------inches</td>
<td>Unknown [ ]</td>
</tr>
</tbody>
</table>

### g. Nutritional status

| Weight ---------kg/or --------ounces | Unknown [ ] |
| Height -------cm /m/ or -------inches | Unknown [ ] |
| Compound index [BMI] | Unknown [ ] |

### 2. Clinical / immunization history

a. Relevant past medical conditions including hospitalizations, underlying disease, immunological disorders, recent travel or Kindergarten/Day care attendance that may affect the evaluation of diarrhea as an AEFI?

Such diseases or disorders include:

- Gastrointestinal infections [GI] or infestations
- Non-GI infections such as meningitis, bacterial sepsis:
- Food allergy; intoxications such as drugs, toxins, insecticides
- Systemic illnesses e.g., malaria in endemic areas
- Chronic ear infections
- Immuno-deficiency e.g HIV infection
- Any pre-immunization signs and symptoms that might affect the evaluation of diarrhea

<table>
<thead>
<tr>
<th>Yes [ ]</th>
<th>No [ ]</th>
<th>Unknown</th>
</tr>
</thead>
</table>

NB. Additional conditions are listed in Appendix D of this
If YES, please describe condition

b. Any medication prior to, during, and after vaccination including prescription and non-prescription medication, especially antibiotics or treatment as well as medication and treatment with long half-life (e.g., immunoglobulins, blood transfusion, immunosuppressants) but excluding any treatment given for adverse event.

<table>
<thead>
<tr>
<th></th>
<th>Yes [ ]</th>
<th>No [ ]</th>
<th>Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

If YES, please specify (including the dates/and or times of their administration if available)

c. History of recent (past 1 month) change in feeding habits: e.g., in infants, change from breast feeding to use of formula-include.

<table>
<thead>
<tr>
<th></th>
<th>Yes [ ]</th>
<th>No [ ]</th>
<th>Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

If yes, mention the possible change dates if known and list the foods currently taken.

d. Immunization history: indicate if history is:

<table>
<thead>
<tr>
<th></th>
<th>verbal [ ]</th>
<th>documented [ ]</th>
<th>Unknown [ ]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

If documented, attach immunization record, be exact on information on vaccines, [e.g., if combination vaccines, list all components and dates of administration].

e. Recurrence of event: Is there a history of previous episodes of diarrhea following previous immunization(s) including recurrence of diarrhea after the current immunization(s)?

<table>
<thead>
<tr>
<th></th>
<th>Yes [ ]</th>
<th>No [ ]</th>
<th>Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

If yes, please list the vaccine(s) involved and a description of diarrhea, number in series,
C. Details of the immunization

1. Timing

<table>
<thead>
<tr>
<th>a. Date of immunization</th>
<th>_______ / _______ / _______ (mm / dd / yyyy)</th>
<th>Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>b. Time of immunization</td>
<td>_______ am / pm (check which)</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

Specify if 12 or 24 hour clock was used. The 24 hour clock is preferred since it eliminates the am and pm differences.

2. Vaccine details

If >1 vaccine was given

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Trade name</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>b. Manufacturer</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>c. Lot number and expiration date</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>d. Diluents, their lot number and expiration date [if used]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>e. Vaccine presentation</td>
<td>Single dose vial [ ]</td>
<td>Single dose vial [ ]</td>
<td>Single dose vial [ ]</td>
<td>Single dose vial [ ]</td>
</tr>
<tr>
<td></td>
<td>Multidose-vial [ ]</td>
<td>Multidose-vial [ ]</td>
<td>Multidose-vial [ ]</td>
<td>Multidose-vial [ ]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Liquid [ ]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lyophilized [ ]</td>
<td>Unknown</td>
<td></td>
</tr>
<tr>
<td>f. Vaccine reconstitution</td>
<td>Used within 6 hours</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------------------</td>
<td>---------------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Yes [ ]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No [ ]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Unknown [ ]</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

If other presentation, specify

<table>
<thead>
<tr>
<th>g. Volume (mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>h. Dose number</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
</tbody>
</table>

i. If combined vaccine, specify:
   - antigen components
   - was vaccine was administered as separate injection sites concomitantly? Yes[ ] No [ ]

<table>
<thead>
<tr>
<th>j. Route of administration</th>
<th>Oral [ ]</th>
<th>Injectable [ ]</th>
<th>Oral [ ]</th>
<th>Injectable [ ]</th>
<th>Oral [ ]</th>
<th>Injectable [ ]</th>
<th>Oral [ ]</th>
<th>Injectable [ ]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site:</td>
<td>Deltoid [ ]</td>
<td>Buttock [ ]</td>
<td>Deltoid [ ]</td>
<td>Buttock [ ]</td>
<td>Deltoid [ ]</td>
<td>Buttock [ ]</td>
<td>Deltoid [ ]</td>
<td>Buttock [ ]</td>
</tr>
<tr>
<td>Other route of administration (specify)</td>
<td>Unknown [ ]</td>
<td></td>
<td>Unknown [ ]</td>
<td></td>
<td>Unknown [ ]</td>
<td></td>
<td>Unknown [ ]</td>
<td></td>
</tr>
</tbody>
</table>

Unknown [ ]
### k. Person who immunized the subject

<table>
<thead>
<tr>
<th>Nurse [ ]</th>
<th>Other health care provider (specify)</th>
<th>Nurse [ ]</th>
<th>Other health care provider (specify)</th>
<th>Nurse [ ]</th>
<th>Other health care provider (specify)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unknown [ ]</td>
<td></td>
<td>Unknown [ ]</td>
<td></td>
<td>Unknown [ ]</td>
<td></td>
</tr>
</tbody>
</table>

### D. The adverse event

#### Diarrhea/stool-nausea or vomiting associated characteristics

<table>
<thead>
<tr>
<th>1. Presence of frequent bowel movement?</th>
<th>Yes</th>
<th>No</th>
<th>Insufficient evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Are the stools looser than normal (runny or liquid)?</td>
<td>Yes</td>
<td>No</td>
<td></td>
</tr>
</tbody>
</table>

If yes, to 1 and 2 above, continue to sub-sections below. Answer as appropriate.

<table>
<thead>
<tr>
<th>3. Maximum number of stools per day?</th>
<th>----- [Number]</th>
<th>Unknown</th>
</tr>
</thead>
</table>

| 4. Please check the following if present. |

- **a. Describe severity of diarrhea based on symptoms**
  
  Use the 1-3 grading scale described in Appendix A.

- **b. Is there dehydration?**
  
  Describe the severity of dehydration using the modified WHO criteria described in Appendix A.

- **c. Is stool consistency described?**
  
  If yes, describe consistency using a visual stool consistency scale. A 5-point scale is recommended:

  1 = firm stool, 2 = soft stool, 3 = runny stool and/or takes the shape of the stool container, 4 = brown liquid stool, 5 = “rice water” stool, especially applicable in prospective studies

  See this visual 5 point scale demonstrated at: [http://www.youtube.com/watch?v=I8KMwWR2ZDk](http://www.youtube.com/watch?v=I8KMwWR2ZDk)

- **d. Duration of diarrhea**
  
  ----- Hours
  
  ----- Days
  
  Unknown
<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
<th>Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>e. Presence of vomiting?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>If yes, maximum number of vomiting episodes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>-----[Number] per day/or hour</td>
<td></td>
<td>Unknown</td>
</tr>
<tr>
<td>f. Duration of vomiting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>-----Hours</td>
<td></td>
<td>Unknown</td>
</tr>
<tr>
<td>g. Presence of nausea?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>h. Was stool examination done?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>If yes, list any relevant results and pathogen obtained including lab evidence of blood in stool</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>i. Presence of mucus in stool?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>j. Presence of gross blood in the stool?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>k. Presence of abdominal cramping?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>l. Presence of fever?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>If yes, record highest temperature</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>---- C</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>---- F</td>
<td></td>
<td></td>
</tr>
<tr>
<td>m. Presence of rectal prolapse?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n. Presence of intussusception?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>o. Presence of tenesmus?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p. Presence of attacks of persistent crying in infants?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>q. Presence of seizures?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>r. Other description (specify)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Refer to the specific Brighton document for a more comprehensive description of the adverse event. Specific documents can be downloaded freely at:
https://brightoncollaboration.org/public/resources/case-definitions.html

5. Timing of diarrhea

<table>
<thead>
<tr>
<th>Question</th>
<th>Date</th>
<th>Time (check am or pm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Onset of diarrhea:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em><strong><strong>/____/</strong></strong></em> (mm/dd/yyyy)</td>
<td>_____ am/pm</td>
</tr>
</tbody>
</table>
b. 1st Observation:   ___/___/___ (mm/dd/yyyy)   _____ am/pm   Unknown

c. Diagnosis   ___/___/___ (mm/dd/yyyy)   _____ am/pm   Unknown

6. Other than the diarrhea, did the patient have any concurrent sign(s), symptom(s), and/or disease(s) different from those listed in question B.2?
   Yes   No   Unknown

   If yes, please list

*Please review guideline 38 on suggested time intervals in section 3 of this document.

7 Outcome at last follow-up

a. Date of outcome at last follow-up   ___/___/___ (mm/dd/yyyy)   Unknown

b. What was the outcome at final follow-up?
   Yes   No   Unknown

   Resolved without treatment
   Resolved with treatment
   Diarrhea still present
   Death

   Sequelae, please specify-------------

   Outcome unknown [ ]

   Any other outcome, (specify)

8. Outcome at last follow-up

E. 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

Contact the Brighton Collaboration secretariat for comments about this checklist at: secretariat@brightoncollaboration.org

Appendix C. Table showing the Vesikari Numerical Scoring Scale for Evaluation of Gastroenteritis in Children: [44,97].

<table>
<thead>
<tr>
<th>Symptom information</th>
<th>Point value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of diarrhea (days)</td>
<td></td>
</tr>
<tr>
<td>1–4</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
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<tr>
<td>≥6</td>
<td>3</td>
</tr>
<tr>
<td>Maximum number of diarrhea episodes per 24 h</td>
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<tr>
<td>1–3</td>
<td>1</td>
</tr>
<tr>
<td>4–5</td>
<td>2</td>
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<tr>
<td>≥6</td>
<td>3</td>
</tr>
<tr>
<td>Duration of vomiting (days)</td>
<td></td>
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<tr>
<td>1</td>
<td>1</td>
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<tr>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>≥3</td>
<td>3</td>
</tr>
<tr>
<td>Maximum number of vomiting episodes per 24 h</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>2–4</td>
<td>2</td>
</tr>
<tr>
<td>≥5</td>
<td>3</td>
</tr>
<tr>
<td>Temperature (°C)</td>
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</tr>
<tr>
<td>&lt;37.0</td>
<td>0</td>
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<tr>
<td>37.1–38.4</td>
<td>1</td>
</tr>
<tr>
<td>38.5–38.9</td>
<td>2</td>
</tr>
<tr>
<td>≥39</td>
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</table>

Appendix D. Conditions causing diarrhea

Below are examples of conditions that cause diarrhea.

Physiological process:

• Babies only fed on breast milk often pass “pasty” loose stools [9,15,16].
• Fecal incontinence [assessed as being unable to retain a standard volume of saline in rectum without leakage [66]].

Non-infectious conditions:

• Drug-induced [e.g., antibiotic-associated, laxatives, antacids that contain magnesium, opiate withdrawal, and abuse of diarrheal agents] [85,86].
• Food allergies or intolerance and malabsorption [e.g., lactose intolerance, soy protein allergy, multiple food allergies] [67].
• Insecticide toxicity e.g., organophosphate poisoning [89].
• Disorders of digestive/absorptive processes [e.g., sucrase-isomaltase deficiency, late-onset (adult-type) hypocalcitasia], resulting in lactose intolerance.
• Chemotherapy or radiation-induced enteritis [87].
• Malnutrition [e.g., Kwashiorkor] [9,90].
• Pancreatic insufficiency [e.g., Cystic Fibrosis, Schwachman-Diamond’s syndrome].
• Enzyme deficiencies [e.g., enterokinase, trypsinogen, congenital lipase deficiencies].
• Immune deficiencies [e.g., hypogammaglobulinemia, IgA deficiency, HIV/AIDS, defects in cellular immunity].
• Irritable bowel syndrome.
• Metabolic disorders; hyperthyroidism, Addison’s Disease, abetalipoproteinemia [e.g., Wolman’s Disease]; familial chylomicronemia [Congenital Alkalosis with Diarrhea].
• Inflammatory bowel disease [e.g., Crohn’s Disease and ulcerative colitis; celiac disease].
• Hormonal tumors [e.g., ganglio-neuromas, neuroblastomas].
• Gastrointestinal surgery [e.g. bariatic surgery for weight, post gastrectomy] [88].
• Surgical conditions [e.g., acute appendicitis, intussusception].
• Anatomic abnormalities [e.g., Hirschsprung’s Disease, malrotation, partial obstruction-stenosis, blind loop syndrome, enteric fistula, and short bowel syndrome].
• Vitamin deficiencies [e.g. Niacin and Folate] or toxicities [e.g., Vitamin C, Niacin, B3] [88].

Infectious conditions:
Infectious agents are by far the most common cause for sporadic or endemic episodes of acute diarrhea. These can be categorized into enteric infections (including food poisoning) and extra intestinal infections.

• Travelers’ diarrhea [64,65].
• Various microbial agents cause diarrhea including [82,84]
  • Viruses [e.g., adenovirus, HIV, norovirus, rotavirus].
  • Bacteria [e.g., Campylobacter jejuni, C. difficile, E. coli, salmonella, shigella, Vibrio cholerae].
  • Parasites [e.g., amoeba, cryptosporidium, C. lamblia, malaria].

Clinical history
Conditions causing diarrhea can also be categorized into more recent or chronic conditions listed below:

Medical history: Examples of recent conditions include:
• Gastro-intestinal infection/infections [e.g., viral, bacterial, parasitic].
• Non-gastrointestinal infections such as meningitis, bacterial sep-ticemia, pneumonia.
• Food allergy; intoxications (such as drugs, toxins, insecticides).
• Travel history.
• Kindergarten attendance; household contacts, community outbreaks; and
• Any pre-immunization signs and symptoms that might affect the evaluation of diarrhea.

Medical history: Examples of chronic conditions include:
• Chronic ear infections.
• Immune deficiency, e.g., HIV infection.
• Any pre-immunization signs and symptoms that might affect the evaluation of diarrhea.

References


[42] Division Of Microbiology And Infectious Diseases (DMDI). NIAID. Pediatrich. toxicity table and division of aids table for grading the severity of adult and pediatric adverse events; December, 2004.


