



## **Diarrhea: Case Definition and Guidelines for 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 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 abnormally low blood volume, low blood pressure, and damage to the kidneys, heart, liver, brain, heart 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 world-wide, most of them in the developing world. (3,4,5). Children and the elderly are particularly prone to dehydration secondary to diarrhea. Diarrhea has been defined differently over time by various scientific groups and health organizations such as: “the passage of loose unformed stools” [6] or “three looser-than normal stools in a 24 hour period” (7, 8) with emphasis on the consistency of stools rather than the number (9). Diarrhea is usually defined in epidemiological studies as the passage of three or more loose or watery stools in a 24-hour 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 as well as clinical vaccine trials, for both oral and non-oral vaccines (14,17-25). The lack of a common definition for diarrhea as an AEFI hinders comparability and uniform reporting of diarrhea across various study settings or surveillance systems.

Recent advances in biotechnology have provided the impetus for developing new vaccines against several diarrheal agents; examples include vaccine candidates against cholera, enterotoxigenic *Escherichia coli* (ETEC), rotavirus, and *Shigella* (26-29). One concern is the proper definition of outcome events such as diarrhea in clinical trials (30).

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. The case definition and guidelines are intended to be applicable in diverse geographic, administrative, and cultural settings, regardless of differences in the availability of health care resources.

## **1.2 Methods for the Development of the Case Definition and Guidelines for Diarrhea as an AEFI**

Following the process described previously (31), a Brighton Collaboration Working Group was formed in August 2007 initially with 49 members with 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 data collection, analysis, and presentation of vaccine safety data.

To guide the decision-making for the case definition and guidelines, a literature search was conducted using English and non-English citations of local reactions in the context of immunization over the period from 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. 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 the English language articles due to practicability; the Working Group recognizes this as a limitation.

Additionally, the Working Group also 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 uniform 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 pathological 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 one level of diagnostic certainty (section 2). The variables listed in appendix A were then developed to better characterize diarrhea as an AEFI.

#### **1.3.1 Time frames**

The Working Group agreed on using a 24-hour 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, 32-36). The 24-hour 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 (37).

The Working Group further agreed to refrain from suggesting a follow-up time frame for the surveillance for diarrhea following immunization. The duration for surveillance depends on a range of variables (see guideline 31 in section 3) 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 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 guideline 25 and appendix A.

### **1.3.3 Grading severity of diarrhea**

Several scoring scales have been used inconsistently to grade the severity of diarrhea in studies (38-44). Should an investigator decide to grade severity of diarrhea, the Working Group recommends the use of the dehydration WHO (9) criteria in table 1 of guideline 25 using mild, moderate and severe as well as a 3-grade scale : Grade1=mild, Grade 2=moderate and Grade 3=severe based on symptoms of diarrhea (see table 2 in guideline 25 for details).

The Working Group refrained from developing a composite severity scoring scale for analyzing additional information describing diarrhea which 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 (45) as applicable, with a cautionary note that its use has not been validated in passive surveillance or adult studies (Appendix A).

### **1.3.4 Stool consistency**

The Working Group recommends the use of a 5-point visual stool consistency scale to further describe the type of diarrhea with: 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 (46). This is a different scale from the grading of severity (mild, moderate to severe) described earlier. See Guideline 28 and a demonstration at: <http://www.youtube.com/watch?v=I8KMwWR2ZDk>.

### **1.3.5 Age cut-off**

It was debated whether the definition should include different age categories, since differences in nutrition and behaviors by different age groups vary greatly nationally and internationally and are known to affect bowel habits, especially in infants due to differences in 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. Age categorization was also not included for the sake of simplicity of the definition that is intended to be applicable in a variety of settings i.e. developed and developing countries, clinical trials and passive surveillance systems. Instead, the Working Group proposes to consider age as a key variable in further describing diarrhea. The suggested age categorization is 0-5 years, and >5 years (15, 18, 47-55) with the preference given to listing the actual age (see appendix A).

### **1.3.6 Diarrhea and Gastroenteritis**

Diarrhea has often been used interchangeably with gastroenteritis (56, 57). However, while diarrhea is always part of gastroenteritis, gastroenteritis is a broader disease entity encompassing additional gastrointestinal symptoms (38, 39, 41, 57-59). 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, diarrhea, abdominal pain and 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  $\leq 14$  days (60); persistent diarrhea = an episode of diarrhea that lasts  $> 14$  days to  $\leq 28$  days (61, 62) and chronic diarrhea = an episode of diarrhea that lasts  $> 28$  days (60, 63, 64). See Data Analysis Guideline 36 in Section 3 of this document.

### **1.3.8 Conditions causing pathological diarrhea**

The Working Group recommends to collect information on underlying causes of diarrhea and to consider analyzing those with or without underlying known causes separately, including describing potential exacerbation of diarrhea after immunization. Non-infectious conditions causing diarrhea in children include: drug-induced [e.g., antibiotics], food intolerance and malabsorption (e.g., lactose), malnutrition, 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]; metabolic disorders; hyperthyroidism, Addison's Disease, abetalipoproteinemia [e.g., Wolman's Disease]; familial chloride diarrhea; Celiac Disease; hormonal tumors [e.g., ganglio-neuromas, neuroblastomas]; bariatric surgery for weight loss in adults, post gastrectomy, abuse of diarrheal agents in adolescent girls/adults with bulimia nervosa or anorexia nervosa; anatomic abnormalities (65) [e.g., Hirshsprung's Disease, malrotation, partial obstruction-stenosis, blind loop syndrome, enteric fistula, and short bowel syndrome].

Relevant past medical conditions including hospitalizations, underlying disease, immunological disorders, or recent travel (traveler's diarrhea ) (66,67) that may affect the evaluation of diarrhea as an AEFI have been listed under guideline 7 as well in Appendix B.

### **1.3.9 Conditions causing increased stool frequencies considered normal**

Many conditions that increase stool frequency but are examples of normal physiological processes include: babies who feed only on breast milk and who often pass loose "pasty" stools (9,15, 16); fecal incontinence [assessed as being unable to retain a standard volume of saline in rectum without leakage (68)]; osmotic diarrhea [as a result of too much water drawn into the bowels, for example in maldigestion (65)]; carbohydrate induced diarrhea due to poorly adsorbed dietary carbohydrates e.g., sorbitol or mannitol(69)]; motility-related diarrhea [hypermotility caused by the rapid movement of food through the intestine with lack of time for nutrients and water to be absorbed (65)]; or medication [for example, antibiotics that disturb the natural balance of gut bacteria (65)].

## **1.4 Case Definition Structure**

The case definition is structured in one level of diagnostic certainty (31). 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

### Level 1 of diagnostic certainty

Diarrhea is defined as the presence of

- 3 or more bowel movements or motions

THAT ARE

- looser than normal (liquid or semi-liquid consistency)<sup>1</sup>

AND ARE

- reported within a 24 hour time period<sup>2</sup> (9) from the onset of diarrhea

### Level 2 of diagnostic certainty

Not applicable

### Level 3 of diagnostic certainty

Not applicable

### Footnotes

<sup>1</sup> Diarrhea may have blood or mucus in the stools and can occur with or without dehydration.

<sup>2</sup> 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.

### **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 information 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 (31), 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 an addition to data collected for the specific study question and setting. These guidelines are not intended to replace local legal reporting requirements but to serve as a guide towards harmonization of vaccine safety reporting of diarrhea 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 these guidelines.

Guidelines 2, 4, 5, 10-17, 19-21, 23-25, 26, 28, and 29 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 (70), and the form for reporting of drug adverse events by the Council for International Organizations of Medical Sciences (CIOMS) (71). These data elements include an identifiable reporter and patient, one or more prior immunizations, and a detailed description of diarrhea an adverse event.

**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<sup>1</sup> and/or assessing or diagnosing, the AEFI, in accordance with country specific data protection law.
- 3) Relationship to the patient (e.g., immunizer [clinician, nurse], family member [indicate relationship], other).

**3.1.2 Vaccinee**

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 (first name initial followed by last name initial), or code, or as otherwise specified in country-specific data protection laws.
- 5) Date of birth (specify calendar used if not the commonly used Julian calendar)<sup>2</sup>, age, sex, ethnicity (if appropriate).
- 6) For infants (<12 months of age): Gestational age, birth weight, and weight at the time of assessment and length, as applicable.

**3.1.2.2 Clinical and immunization history**

- 7) Recent travel history, and medical history including hospitalizations, underlying diseases/disorders such as:
  - Gastro-intestinal infection/infestations, most commonly viral, bacterial, and parasitic;

- Non-gastrointestinal infections such as meningitis, bacterial sepsis;
  - Ear infections [e.g., otitis media];
  - Respiratory [e.g., pneumonia] or urinary tract infections;
  - Antibiotic-associated diarrhea;
  - Food allergy or intolerance, and other conditions outlined in section 1.3.8;
  - Any pre-immunization signs and symptoms that may affect the evaluation of diarrhea.
- 8) 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.
- 9) Nutritional history in infants: any recent dietary change in feeding habits of the infant such as a change from breast feeding to use of formula within the past month.
- 10) 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 the immunization**

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

- 11) Date and time of immunization, specify if a 12 or 24-hour clock was used. The 24-hour clock is preferred, as it avoids potential confusion about am and pm.

- 12) Description of vaccine(s): name of vaccine, lot number, expiration date, manufacturer, dose, multi- or mono-dose, pre-filled syringe, volume (e.g., 0.25 mL, 0.5 mL, etc) and number of dose (if part of a series of immunizations against the same disease), diluent lot number, and expiration date.
- 13) Detailed description on combination vaccines: if used, provide the trade name and generic names if present. Specify the antigen components and if the vaccine was a combined one (single shot) or was administered at separate injection sites concomitantly, as appropriate.
- 14) Anatomical sites<sup>3</sup> (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.
- 15) Storage conditions of the vaccine: vaccines should be stored at temperatures according to the manufacturer's recommendations. If possible, temperature logs, type of fridge, power outages, and vaccine storage conditions should be reviewed and noted, especially in prospective studies (72-74).
- 16) Type of professional who immunized the subject (e.g., physician, nurse, other health care provider).
- 17) Route and method of administration (e.g., oral, intranasal, intramuscular, intradermal, subcutaneous, needle-free such as transcutaneous patch [including type and size of needle] or other injection devices).

#### **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:

- 18) Criteria fulfilled to meet a case definition and other signs or symptoms indicative of diarrhea.
- 19) Detailed clinical description of the event.
- 20) Date and time of: onset<sup>4</sup>, first observation<sup>5</sup>, diagnosis<sup>6</sup>, end of an episode<sup>7</sup>, and final outcome<sup>8</sup>; see Guideline 30 on outcome below.
- 21) Recurrence of diarrhea after resolution of initial reaction e.g., as a biphasic illness.
- 22) Concurrent signs, symptoms, and diseases other than diarrhea. These include both systemic symptoms, such as fever, reduced activity or other gastrointestinal symptoms including vomiting, nausea, and tenesmus, and signs such as dehydration status and nutritional status. See Appendix A.
- 23) 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.
- 24) 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); in 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.
- 25) The severity of diarrhea can be described by the severity of dehydration and by the severity of diarrhea symptoms.
  - a) Dehydration can be described using the WHO dehydration criteria listed in the table below (without modification). The dehydration is categorized into three

levels of intensity: 1) no signs of dehydration (mild), 2) some dehydration (moderate) and 3) severe dehydration. (9) as outlined in Table 1 below. See appendix A for additional information on signs and symptoms;

b) Severity of diarrhea can also be based on symptoms are described in table 2 below.

**Table 1: Assessment of patients with diarrhea for dehydration and fluid deficit using the unmodified WHO criteria (9)**

<b>Mild</b>	<b>Moderate</b>	<b>Severe</b>
Patient has diarrhea but shows no signs of dehydration	Patient has diarrhea and shows the following signs of dehydration	Patient has diarrhea and shows the following signs of dehydration
Well, alert	Restless, irritable	Lethargic or unconscious
Normal eyes	Eyes are sunken	Eyes are sunken
Drinks normally, not thirsty	Thirsty, drinks eagerly	Drinks poorly, or not able to drink
Skin pinch goes back quickly	Skin pinch goes back slowly	Skin goes back very slowly
Fluid deficit as a % of body weight < 5 % or < 50 ml/kg body weight	Fluid deficit as a % of body weight of 5-10 % OR 50-100 ml/kg body weight	Fluid deficit as a % of body weight of > 10% OR > 100ml/kg body weight

**Table 2: Grading of severity based on symptoms of diarrhea**

<b>Grade 1</b>	<b>Grade 2</b>	<b>Grade 3</b>
Less than 4 stools per day with no limitation to activities of daily living (ADLS) <sup>‡</sup> (75)	4-6 stools per day with or without minimal interference with ADLS	7 stools or more per day with interference with ADLS or with visible blood in stool*
<sup>‡</sup> limitations in a person's ability to engage in work, school, play, or other activities for health reasons		
* This is visible blood in stool in the absence of hemorrhoids		
NB. These numbers are arbitrary cut-offs based on experience by working group members and communication with other investigators.		

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

- 27) Treatment given for the diarrhea (e.g., intravenous fluids, oral rehydration solution, or medication).
- 28) 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<sup>9</sup> (46).
- 29) Record the frequency of diarrhea stools/day, patterns or re-occurrence, or if intermittent diarrhea occurs include dates whenever possible.
- 30) The outcome<sup>8</sup> 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 (i.e., any intervention, including e.g., intravenous fluids, antimicrobial agents);
  - Diarrhea still present;
  - 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**

- 31) 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 (e.g., adjuvants);
- 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).

32) 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 unfeasible, the study period during which safety data are being collected and/or included in the database should be clearly defined.

33) Follow-up of reported events should attempt to verify and complete the collection of information as outlined in the data collection guidelines 1 through 30.

### **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.

34) Reported events should be classified in one of the following three categories. When events meet the case definition, it should be classified according to the one level 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.

#### ***Event classification in three categories<sup>10</sup>***

Event meets case definition

*Main category*

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

Event does not meet case definition

*Additional categories*

- 2) Insufficient evidence for diarrhea<sup>11</sup>
- 3) Not a case of a diarrhea<sup>12</sup>

35) The interval between immunization and diarrhea could be defined as the date/time of immunizations to the date/time of onset<sup>4</sup> or first observation<sup>5</sup> or diagnosis<sup>6</sup>, whichever is most appropriate for diarrhea. Whatever dates are used, they should be used consistently within and across study subjects and described.

The following time intervals, where n = the number of subjects with diarrhea newly present (date of onset or date of first observation or date of diagnosis), and N = the Number of all subjects with diarrhea or all study subjects.

Time interval	<u>n</u> number of subjects with diarrhea newly present at the specified time interval/ <u>N</u> Number of all subjects with diarrhea or <u>N</u> Number of all study subjects (%) (Specify which was used)
≤24 hours	n/N _____ (%)
25 – ≤48 hours	n/N _____ (%)
49 – ≤72 hours	n/N _____ (%)
73 hours – ≤7days	n/N _____ (%)
>7days - ≤14 days	n/N _____ (%)
>14 - ≤28 days	n/N _____ (%)
> 28 days	n/N _____ (%)

36) The duration of diarrhea, if applicable, could be analyzed as the interval between date/time of onset<sup>4</sup> or first observation<sup>5</sup> or diagnosis<sup>6</sup> and the end of episode<sup>7</sup> or final outcome<sup>8</sup>. 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 35.

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 (60)); persistent diarrhea (i.e., episode of diarrhea that lasts >14 days to ≤28 days (61, 62)); and chronic diarrhea (i.e., episode of diarrhea that lasts >28 days (60, 63, 64)) should be analyzed.

- 37) If the diarrhea occurs intermittently, the event corresponding to the greatest magnitude, i.e., the number of stools/day could be used as the basis for analysis. Also the frequency and pattern of re-occurrence (e.g., periodicity) can be analyzed.
- 38) If more than one measurement of a particular parameter is taken 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 like qualitative patterns of criteria defining the event (e.g., periodicity, frequency, fever-days, etc).
- 39) 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 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 also 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], 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) (76-78).

- 40) All reported events on diarrhea should be presented according to the categories listed in guideline 34.
- 41) Data on diarrhea should be presented in accordance with data collection guidelines 1-33 and data analysis guidelines 34-39.
- 42) 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.

- 43) The distribution of data (as numerator and denominator data) should be presented in the predefined time increments as listed in the analysis guideline 35. If the number of cases is small, the exact time course could be presented for each case.
- 44) The incidence<sup>13</sup> and prevalence<sup>14</sup> of events meeting the case definition should be presented and clearly identified as such in the text.
- 45) If the distribution of data is skewed, the median and range are the more appropriate statistical descriptors than a mean.

- 46) 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
    - The type of surveillance (e.g., passive or active surveillance);
    - The characteristics of the surveillance system (e.g., population served, mode of report solicitation); and
    - The search strategy in surveillance databases;
  - Comparison group(s), if used for analysis;
  - Whether the day of immunization was considered “day one” or “day zero” in the analysis;
  - Whether the date of onset<sup>4</sup> and/or the date of first observation<sup>5</sup>, and/or the date of diagnosis<sup>6</sup>, end of episode<sup>7</sup> or final outcome<sup>8</sup> was used for analysis. Whatever dates are used, they should be used consistently within and across subjects and described; and
  - Reference of the case definition(s) used (Brighton Collaboration or other) in the abstract or methods section of a publication<sup>15</sup>.

### Notes for Guidelines

<sup>1</sup> If the reporting center is different from the vaccinating center, appropriate and timely communication of the adverse event should occur.

<sup>2</sup> 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](http://www.hermetic.ch/cal_stud/cal_art.html#Julian_Calendar)

<sup>3</sup> 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 (79).

<sup>4</sup> 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.

- <sup>5</sup> The date and/time of first observation of the first sign or symptom indicative for diarrhea can be used, if date/time of onset is not known.
- <sup>6</sup> The date of diagnosis of an episode is the day the event met the case definition.
- <sup>7</sup> The end of an episode is defined as the time the event no longer meets the case definition.
- <sup>8</sup> An AEFI 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.
- <sup>9</sup> See the 5-point grading of diarrhea adapted from Sack *et al* (46) and a demonstration on You Tube at: <http://www.youtube.com/watch?v=I8KMwWR2ZDk> . This demonstration was developed by this working group and posted on You Tube for ease of access of the information globally.
- <sup>10</sup> If Level 1 of the case definition is not met, the case should be classified as category 2 or 3. A distinction should be made between missing and 'known' to be absent. If information about a criterion is missing, the case should be classified according to the information available as mentioned above. If a criterion is known to be absent, the case should be classified according to category 2 or 3.
- <sup>11</sup> If the evidence available for an event is insufficient because information is missing to make a determination at any level of diagnostic certainty, such cases should be categorized as "reported event of diarrhea with insufficient evidence to meet the case definition".
- <sup>12</sup> An event does not meet the case definition if investigation reveals a negative finding of a necessary criterion for classification in Level 1. Such an event should be classified as "Not a case of diarrhea".
- <sup>13</sup> E.g., total of 10 cases of diarrhea in 2000 study participants or 1 case per million; use as appropriate.
- <sup>14</sup> E.g., cases of diarrhea on day 1: 2 cases, day 2: 10 cases, day 3: 3 cases, etc.
- <sup>15</sup> Use of this document should be referenced by referring to the link on the Brighton Collaboration website (<http://www.brightoncollaboration.org>).

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**Appendix A: Table of Variables Describing Diarrheal Episodes:**

<b>Variable</b>	<b>Type of variable</b>	<b>Categorization or score suggested</b>	
<b>1. Age</b>	Numerical	Suitable categorization age is 0-5 years, and 5 years and above with the preference of listing actual age if known. (15, 18, 47-55)	
<b>Diarrhea/stool/nausea or vomiting associated characteristics</b>			
<b>2. Dehydration</b>			
Dehydration in children	Use the WHO (9) grading that is based on treatment plans A, B, and C No dehydration [A] Some dehydration [B] Severe dehydration [C]	2 or more signs in B or C below (under assessment of diarrhea patients) = some dehydration 2 or more signs in C below = severe dehydration	
<b>Assessment of diarrhea patients for dehydration in children: Details of signs and symptoms</b>			
<b>Look at:</b>	<b>No dehydration [A]</b>	<b>Some dehydration [B]</b>	<b>Severe dehydration [C]</b>
<b>Look at condition <sup>a</sup></b>	Well. alert;	Restless, irritable	Lethargic or unconscious
Eyes <sup>b</sup>	Normal	Sunken	Sunken
Thirst	Drinks normally, not thirsty	Thirsty , drinks eagerly	Drinks poorly, or not able to drink
Feel: Skin Pinch <sup>c</sup>	Goes back quickly	Goes back slowly	Goes back very slowly
<sup>a</sup> Being lethargic and sleepy are not the same. A lethargic child is not simply asleep: the child’s mental state is dull and the child cannot be fully awakened; the child may appear to be drifting into unconsciousness. <sup>b</sup> In some infants and children the eyes normally appear somewhat sunken. It is helpful to ask the mother if the child’s eyes are normal or more sunken than usual. <sup>c</sup> The skin pinch is less useful in infants or children with marasmus or kwashiorkor, or obese children. Note: Mention any presence of acidosis and electrolyte imbalance if present.			
<b>Estimating fluid deficits in assessment of children for dehydration</b>			
<b>Assessment</b>	<b>Fluid deficit as a % of body weight</b>		<b>Fluid deficit in ml/kg body weight</b>
Some dehydration [B]	5-10%		50-100ml/Kg
Severe dehydration [C]	>10%		>100ml/kg
<b>Variable</b>	<b>Type of variable</b>	<b>Categorization or score suggested</b>	
<b>3. Visual stool consistency scale</b>	The working group recommends (as applicable given the study setting) the use of a 1- 5 point visual stool scale (46). See demonstration at:		

	<a href="http://www.youtube.com/watch?v=I8KMwWR2ZDk">http://www.youtube.com/watch?v=I8KMwWR2ZDk</a> ).	1-5 levels
<b>4. Duration of diarrhea</b>	Hours, days etc	See Vesikari <sup>‡</sup> Numerical score (45) in appendix C
<sup>‡</sup> “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”.		
<b>5. Maximum number of diarrhea stool/24 h</b>	Numerical	See Appendix C
<b>6. Vomiting: Duration of vomiting</b>	Hours, days	See Appendix C
<b>7. Max number vomiting episodes/24 h</b>	No of episodes	See Appendix C
<b>8. Nausea</b>	Yes/No	
<i>NB. It would not be easily ascertained in the very young</i>		
<b>9. Stool examination [microscopy, culture or other test etc to identify pathogen]</b>		Describe causative pathogen depending on study and availability of laboratory capacity
<b>10. Presence of mucus in stool</b>		Yes/No
<i>NB. The bacteriology of mucus was considered non-specific to etiologic pathogens</i>		
<b>11. Presence of gross blood in stool</b>		Yes/No
<b>12. Laboratory evidence of blood in stool</b>		Yes/No
<b>Other characteristics</b>		
<b>9. Fever</b>	Continuous variable	Fever is defined as the endogenous elevation of at least one measured body temperature of 38 <sup>0</sup> C. (80)
NB: The value of 38 <sup>0</sup> C is accepted as reflecting an abnormal elevation of temperature, irrespective of device, anatomic site, age or environmental conditions.		
<b>13. Presence of rectal prolapse</b>		Yes/No
<b>14. Tenesmus</b>		Yes/No
<i>NB. It would not be easily ascertained in the very young</i>		
<b>15. Convulsions/seizures</b>	Presence and 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 (81)
<b>16. Attacks of persistent crying</b>		Presence of crying which is continuous AND unaltered for $\geq 3$ hours or likely to be altered for $> 3$ hours or likely to be continuous in infants and children (82)
<b>17. Presence of intussusception</b>		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 (83)
<b>18. Cramping</b>		Yes/No
<i>NB. It would not be easily ascertained in the very young and their description of cramping could be different such as "my tummy hurts"</i>		

## 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/reporter

	Assessing	Reporting
a. Medical provider including professional status		
b. Parent/self		
c. Other		

### B. Vaccinee/control

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 <sup>1</sup>	____/____/____ (mm / dd / yyyy) <sup>1</sup>	Unknown
<sup>1</sup> All dates, specify type of calendar used, the common Julian calendar is preferred		
c. Age	----- years-----months	Unknown
d. Sex	M [ ] F [ ]	Unknown [ ]
If female, pregnancy status	Non-pregnant [ ] Pregnant [ ]	Unknown [ ]
e. Race/Ethnicity (if appropriate)		Unknown [ ]

f. Infants ( $\leq$ 12 months of age)	Gestational age -----Years  Birth weight  -----kg/or -----ounces  Weight at assessment  -----kg/or-----ounces  Length of infant  -----cm/ or -----inches	Unknown [ ]   Unknown [ ]   Unknown [ ]   Unknown [ ]	
<b>2. Clinical / immunization history</b>			
a. Relevant past medical conditions including hospitalizations, underlying disease, immunological disorders, or recent travel that may affect the evaluation of diarrhea as an AEFI?  Such diseases or disorders include: <ul style="list-style-type: none"> <li>• Gastrointestinal infections [GI] of infestations</li> <li>• Non-GI infections such as meningitis, bacterial sepsis:</li> <li>• Ear [otitis media]</li> <li>• Respiratory [Pneumonia]</li> <li>• Urinary [UTI]</li> <li>• Systemic illnesses e.g., Malaria in endemic areas</li> <li>• Food allergy etc*</li> <li>• Recent travel history</li> </ul> <i>NB. Additional conditions are listed in section 1.3.8 in the preamble section of this document</i>	Yes [ ]	No [ ]	Unknown
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	Yes [ ]	No [ ]	Unknown

treatment with long half- life (e.g., immunoglobulins, blood transfusion, immunosuppressants) (excluding treatment given for adverse event )			
If YES, please specify (including the dates/and or times of their administration if available)			
<p>c. Nutritional history: in infants, any recent dietary changes in feeding habits or change from breast feeding to use of formula-include. [yes] [no] [unknown]</p> <p>If yes, mention the possible change dates if known and list the foods currently taken by infant.</p>			
<p>d. Immunization history: indicate if history is:</p> <p>verbal [ ] or documented [ ] Unknown [ ]</p> <p>If documented, attach immunization record, be exact on information on vaccines, [e.g., if combination vaccines, list all components and dates of administration].</p>			
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)?	Yes [ ]	No [ ]	Unknown
If yes, please list the vaccine(s) involved and a description of diarrhea, number in series, and dates of administration if available.			

### C. Details of the immunization

1. Timing		
a. Date of immunization <sup>1</sup>	<p>____/____/____</p> <p>(mm / dd / yyyy)</p>	Unknown

b. Time of immunization <sup>2</sup>	_____ am / pm (check which)			Unknown
<sup>2</sup> Specify if 12 or 24 hour clock was used. The 24 hour clock is preferred since it eliminates the am and pm differences.				
<b>2. Vaccine details</b> If >1 vaccine was given				
Vaccine	1	2	3	4
a. Trade name				
b. Manufacturer				
c. Lot number				
d. Diluents, their lot number and expiration date [if available]				
e. Vaccine presentation	Singledose vial [ ] Multidose-vial [ ]	Singledose vial [ ] Multidose-vial [ ]	Singledose vial [ ] Multidose-vial [ ]	Singledose vial [ ] Multidose-vial [ ]
f. Volume (mL)				
g Dose number				
h. If combined vaccine, specify : <ul style="list-style-type: none"> <li>antigen components ----- -----</li> <li>if vaccine was administered as separate injection sites concomitantly Yes[ ] No [ ]</li> </ul>				
i. Route of administration	Oral [ ]  Other (specify)  Unknown [ ]	Oral [ ]  Other (specify)  Unknown [ ]	Oral [ ]  Other (specify)  Unknown [ ]	Oral [ ]  Other (specify)  Unknown [ ]

j. Person who immunized the subject	Nurse [ ] Other health care provider (specify) Unknown [ ]	Nurse [ ] Other health care provider (specify) Unknown [ ]	Nurse [ ] Other health care provider (specify) Unknown [ ]	Nurse [ ] Other health care provider (specify) Unknown [ ]
k. Describe any information the reporter finds relevant to the evaluation of the diarrhea.				

**D. The adverse event**

<b>Diarrhea/stool/nausea or vomiting associated characteristics</b>			
1. Presence of frequent bowel movement? If yes, continue to sub-sections below. Answer as appropriate	Yes	No	Insufficient evidence
2. Maximum number of stools per day?	-----[Number]		Unknown
3. Please check the following if present.			
a. Presence of dehydration?	Yes	No	Unknown
If yes, describe severity of diarrhea <sup>3</sup> based on dehydration	mild	Mod erate	Severe
<sup>3</sup> Use the WHO criteria in Guideline 26			
b. Describe severity of diarrhea <sup>4</sup> based on symptoms	Grade 1	Grade 2	Grade 3
<sup>4</sup> Use the 1-3 grading based on symptoms of diarrhea in Guideline 27			
c. Are the stools looser than normal?	Yes	No	Unknown
If yes, using the describe the grade using a 1-5 point visual scale; 1=normal, 2=soft, 3= “runny or takes the shape of container”, 4=brown liquid, and 5=hard stool <sup>5</sup> (46)			
<sup>5</sup> See this visual 5 point scale is demonstrated at: <a href="http://www.youtube.com/watch?v=I8KMwWR2ZDk">http://www.youtube.com/watch?v=I8KMwWR2ZDk</a>			
d. Duration of diarrhea	-----Hours -----days No		Unknown
e. Presence of vomiting?	Yes	No	Unknown

If yes, maximum number of vomiting episodes	-----[Number]	Unknown	
f. Duration of vomiting	-----Hours -----days	Unknown	
g .Presence off nausea?	Yes	No	Unknown
h. Was stool examination done?	Yes	No	Unknown
If yes, list any relevant results and pathogen obtained including lab evidence of blood in stool			
i. Presence of mucus in stool?	Yes	No	Unknown
j. Presence of gross blood in the stool?	Yes	No	Unknown
k. Presence of abdominal cramping?	Yes	No	Unknown
<b>Other characteristics</b>			
l Presence of fever <sup>6</sup> ?	Yes	No	Unknown
If yes, record highest temperature	----- <sup>0</sup> C ----- <sup>0</sup> F		
m. Presence of rectal prolapse?	Yes	No	Unknown
n. Presence of intussusception <sup>6</sup> ?	Yes	No	Unknown
o. Presence of tenesmus?	Yes	No	Unknown
p. Presence of attacks persistent crying in infants <sup>6</sup> ?	Yes	No	Unknown
q. Presence of seizures <sup>6</sup> ?	Yes	No	Unknown
r. Presence of abdominal cramping?	Yes	No	Unknown
s. Other description (specify)			
<sup>6</sup> Refer to the specific Brighton document for a more comprehensive description of the adverse event. Specific documents can be downloaded freely at: <a href="http://www.brightoncollaboration.org/internet/en/index/definition___guidelines.html">http://www.brightoncollaboration.org/internet/en/index/definition___guidelines.html</a>			
4. Timing of the Diarrhea	Date <sup>1</sup>	Time <sup>2</sup> (check am or pm)	

a. Onset of diarrhea:	___/___/___ (mm/dd/yyyy)	_____ am/pm	Unknown
b. 1st Observation:	___/___/___ (mm/dd/yyyy)	_____ am/pm	Unknown
c. Diagnosis	___/___/___ (mm/dd/yyyy)	_____ am/pm	Unknown
5 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 37 on suggested time intervals in section 3 of this document.			
9. 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			
Outcome unknown [ ]			
Any other outcome, (specify)			
9. Outcome at last follow-up			
<b>E. Miscellaneous</b>			
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](mailto:secretariat@brightoncollaboration.org)

**Appendix C: Table showing the Vesikari numerical Scoring Systems for Severity of Rotavirus Diarrhea: A = Score Given, B= % Distribution of cases in the present material (45)**

Symptom or Sign	9 Points (Hjelt et al. [84])		14 Points (Flores et al [41])		20 Points (Now Proposed)	
	A	B	A	B	A	B
Duration of diarrhea (days)						
1	1	24%	1	25%		
1-4					1	22%
2-4	2	28%	2	49%		
>4	3	48%	3	26%		
5					2	40%
≥6					3	38%
Max no. diarrheal stools/24 h						
1-3	1	12%	1	12%	1	23%
4-5	2	34%	2	34%	2	29%
≥6	3	40%	3	40%	3	35%
Duration of vomiting (days)						
1					1	31%
2					2	25%
1-2	1	55%	1	55%		
≥3	2	32%	2	32%	3	32%
Max no. vomiting episodes/24 h						
0					0	12%
1					1	28%
2-4					2	32%
≥5					3	28%
Fever						
<37.0°C						
<37.5°C	0	20%				
<38.1°C			0	34%		
>37.5°C	1	80%				
37.1°C-38.4°C					1	15%
≥38.1°C			1	66%		
38.5°C-38.9°C					2	28%
≥39°C					3	34%
Dehydration						
None			0	66%	0	66%
1-5%			2	28%	2	28%
≥6%			3	6%	3	6%
Treatment						
None			0	82%	0	30%
Polyclinical						
Rehydration					1	51%
Hospitalization			2	19%	2	19%

