

# UNIVERSITY OF BIRMINGHAM

## Research at Birmingham

### Dysfunctional Labor

Boatin, Adeline A.; Kenyon, Sara

DOI:

[10.1016/j.vaccine.2017.01.050](https://doi.org/10.1016/j.vaccine.2017.01.050)

License:

Creative Commons: Attribution-NonCommercial-NoDerivs (CC BY-NC-ND)

*Document Version*

Peer reviewed version

*Citation for published version (Harvard):*

Boatin, AA & Kenyon, S 2017, 'Dysfunctional Labor: Case Definition & Guidelines for Data Collection, Analysis, and Presentation of Immunization Safety Data', *Vaccine*, vol. 35, no. Issue 48, Part A, pp. 6538-6545.  
<https://doi.org/10.1016/j.vaccine.2017.01.050>

[Link to publication on Research at Birmingham portal](#)

#### General rights

Unless a licence is specified above, all rights (including copyright and moral rights) in this document are retained by the authors and/or the copyright holders. The express permission of the copyright holder must be obtained for any use of this material other than for purposes permitted by law.

- Users may freely distribute the URL that is used to identify this publication.
- Users may download and/or print one copy of the publication from the University of Birmingham research portal for the purpose of private study or non-commercial research.
- User may use extracts from the document in line with the concept of 'fair dealing' under the Copyright, Designs and Patents Act 1988 (?)
- Users may not further distribute the material nor use it for the purposes of commercial gain.

Where a licence is displayed above, please note the terms and conditions of the licence govern your use of this document.

When citing, please reference the published version.

#### Take down policy

While the University of Birmingham exercises care and attention in making items available there are rare occasions when an item has been uploaded in error or has been deemed to be commercially or otherwise sensitive.

If you believe that this is the case for this document, please contact [UBIRA@lists.bham.ac.uk](mailto:UBIRA@lists.bham.ac.uk) providing details and we will remove access to the work immediately and investigate.

1 **Dysfunctional Labor: Case Definition & Guidelines for Data Collection, Analysis, and Presentation**  
2 **of Immunization Safety Data**

3 Adeline A Boatin<sup>1</sup>, Linda O Eckert<sup>2</sup>, Michel Boulvain<sup>3</sup>, Chad Grotegut<sup>4</sup>, Barbra M Fisher<sup>5</sup>, Jay King<sup>6</sup>, Marie  
4 Berg<sup>7</sup>, Richard MK Adanu<sup>8</sup>, Uma Reddy<sup>9</sup>, Jason JS Waugh<sup>10</sup>, Manish Gupta<sup>11</sup>, Sonali Kochhar<sup>12</sup>, Sara  
5 Kenyon<sup>13</sup>

6  
7 The Brighton Collaboration Dysfunctional Labor Working Group.

8  
9 <sup>1</sup> Department of OB/GYN, Massachusetts General Hospital, Harvard Medical School, Boston, USA

10 <sup>2</sup> University of Washington, Seattle, WA

11 <sup>3</sup> Service d'obstétrique, Maternité HUG, Switzerland

12 <sup>4</sup> Division of Maternal-Fetal Medicine, Duke University, USA

13 <sup>5</sup> Maternal Fetal Medicine, Northwest Perinatal Center, Women's Healthcare Associates, LLC

14 Portland, USA

15 <sup>6</sup> Sanofi Pasteur, USA

16 <sup>7</sup> Institute of Health Care Science, University of Gothenburg, Gothenburg, Sweden

17 <sup>8</sup> University of Ghana School of Public Health, Ghana

18 <sup>9</sup> Pregnancy and Perinatology Branch, Eunice Kennedy Shriver National Institute of Child Health and  
19 Human Development, National Institutes of Health, USA

20 <sup>10</sup> Royal Victoria Infirmary, Newcastle Upon Tyne, United Kingdom

21 <sup>11</sup> Barts Health NHS Trust, London, United Kingdom

22 <sup>12</sup> Global Healthcare Consulting, India

23 <sup>13</sup> Reader in Evidence Based Maternity Care, Institute for Applied Health Research, University of  
24 Birmingham, United Kingdom.

25  
26  
27 \*Corresponding author: Adeline Boatin Tel:617 643 4928; Massachusetts General Hospital. Email:

28 adeline\_boatin@mgh.harvard.edu

29 secretariat@brightoncollaboration.orgmailto:secretariat@brightoncollaboration.org

30  
31 #Brighton Collaboration home page:

32 <http://www.brightoncollaboration.org><http://www.brightoncollaboration.org/>

33  
34 Disclaimer: The findings, opinions and assertions contained in this consensus document are those of the  
35 individual scientific professional members of the working group. They do not necessarily represent the  
36 official positions of each participant's organization (e.g., government, university, or corporation).  
37 Specifically, the findings and conclusions in this paper are those of the authors and do not necessarily  
38 represent the views of their respective institutions.

39  
40  
41 Keywords: dysfunctional labor, prolonged labor, abnormal labor, immunization, guidelines, case definition  
42

43 **1. Preamble**

44 **1.1. Need for Developing Case Definitions and Guidelines for Data Collection, Analysis, and**  
45 **Presentation for Dysfunctional Labor as an Adverse Event Following Immunization**

46 Vaccination during pregnancy is recommended for both maternal and neonatal benefit against a number  
47 of potential infections. The tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine is  
48 now routine recommended for pregnant women in each pregnancy not only for maternal benefit, but to  
49 confer passive antibody transfer to the newborn until infant immunizations can be given [1]. Influenza  
50 vaccinations are also strongly recommended for any pregnant woman, or women who might become  
51 pregnant during influenza seasons [2]. The safety of both these vaccinations has been well established.  
52 Efforts to develop new vaccinations for use during pregnancy represent a new opportunity to prevent  
53 common maternal and neonatal infections with severe morbidity and mortality. There is growing interest  
54 and research around maternal immunization against both Group B streptococcus (GBS) and Respiratory  
55 syncytial virus (RSV) as a public health strategy to prevent neonatal and infant infections worldwide [3, 4].  
56

57 Establishing the safety profile of any new vaccination requires careful surveillance of potential adverse  
58 effects and consistent terminology and definitions across context and time. The World Health  
59 Organization (WHO) defines an 'adverse event following immunization' (AEFI) as "any untoward medical  
60 occurrence which follows immunization and, which does not necessarily have a causal relationship with  
61 the use of the vaccine. The adverse event may be an unfavorable or unintended sign, an abnormal  
62 laboratory finding, a symptom or disease" [5]. Recognizing that vaccination is often temporally related to  
63 many events, abnormal findings or diseases, causality assessment between an AEFI and vaccination  
64 requires further rigorous assessment and study. Monitoring of a broad array of events, including those  
65 without established or suspected links to vaccine can therefore provide the initial basis for data with which  
66 such causality can be proven or disproven.  
67

68 Dysfunctional labor is relatively common occurrence during the intrapartum stage of pregnancy.  
69 Incidence estimates vary due to differences in definitions, but approximately 20% of labors are thought to  
70 be affected by this condition[6]. Though there are no reported links between dysfunctional labor and  
71 immunization, the measurement of this potential complication in association with vaccination is important  
72 to establish vaccine safety. Despite being relatively common, there is a lack of consensus on the criteria  
73 for the diagnosis of dysfunctional labor. Guidelines from professional obstetric societies differ in both the  
74 criteria used to define this process and when intervention should occur (Table 1.) The Brighton  
75 Collaboration has been developing standardized definitions for use in vaccine trials since 2001[7]. To  
76 further consistent terminology and definitions of outcomes and adverse events typically reported in  
77 vaccine trials, specifically for maternal immunization, standardized definitions of common obstetric  
78 outcomes are needed. The goal of this working group was therefore to provide a case definition for this  
79 term to facilitate surveillance and case ascertainment in vaccine trials.  
80

81 Labor is typically divided into three stages. The first stage of labor marks the onset of labor until full  
82 dilation of the cervix; the second stage, full dilation until delivery of the fetus, and the third, delivery of the  
83 placenta. In the 1950s, Friedman first described the first stage dividing this into latent and active phases  
84 of labor [8, 9]. His work first demonstrated the broad range of labor duration experienced by women and  
85 until recently provided the basis for defining normal progress and length of labor limits of normal labor  
86 duration. Recent evidence, however, from a larger more diverse population of women have challenged  
87 these historical durations [10].  
88

89 Dysfunctional or prolonged labor refers to prolongation in the duration of labor, typically in the first stage  
90 of labor. Diagnosis of delay in labor is dependent on careful monitoring of uterine contraction intensity,  
91 duration and frequency, cervical dilation and descent of the fetus through the pelvis. Dysfunctional labor  
92 can be an important contributor to maternal and perinatal mortality and morbidity if it remains  
93 unrecognized and untreated when needed. On the other hand, pre-emptive diagnosis of dysfunctional  
94 labor may lead to unnecessary interventions. Labor dysfunction is a leading indication for primary  
95 caesarean section and there is concern, that an over diagnosis may be a contributor to high and rising  
96 caesarean section rates [11].

97  
98 The pathophysiology of dysfunctional labor is multifactorial and complex and yet to be fully elucidated.  
99 Often, the exact etiology of dysfunctional labor is unknown. Broadly, etiology can be categorized into  
100 uterine contractile dysfunctions and abnormalities in the cephalopelvic ratio (i.e. the relation of the fetal  
101 size, presentation and position to the maternal pelvis). Both these causes can be influenced by a number  
102 of genetic and environmental factors including but not limited to maternal and gestational age, pre-  
103 pregnancy body mass index, pregnancy weight gain, physical activity, medical co-morbidities, parity, and  
104 obstetric complications (pre-eclampsia, premature rupture of membranes, chorio-amnionitis, placental  
105 abruption ) [12-15].

## 106 **1.2. Methods for the Development of the Case Definition and Guidelines for Data Collection,** 107 **Analysis, and Presentation for Dysfunctional Labor as an Adverse Events Following** 108 **Immunization**

109 Following the process described in the overview paper [16] as well as on the Brighton Collaboration  
110 Website <http://www.brightoncollaboration.org/internet/en/index/process.html>, the Brighton Collaboration  
111 *Dysfunctional Labor Working Group* was formed in 2015 and included members of clinical, academic,  
112 public health and industry background. The composition of the working and reference group as well as  
113 results of the web-based survey completed by the reference group with subsequent discussions in the  
114 working group can be viewed at:  
115 [http://www.brightoncollaboration.org/internet/en/index/working\\_groups.html](http://www.brightoncollaboration.org/internet/en/index/working_groups.html).

116  
117 To guide the decision-making for the case definition and guidelines, a literature search for publications in  
118 any language was performed using Medline, Embase and the Cochrane Libraries, including the terms  
119 dysfunctional, prolonged, delayed, obstructed, abnormal, augmented labor, arrest of dilation, labor  
120 dystocia AND vaccination' or 'vaccine' or 'immunization' OR 'immunize' OR 'inoculation. The search  
121 resulted in the identification of 172 references. All abstracts were screened for possible reports of  
122 dysfunctional labor following immunization. Two full text articles with potentially relevant material were  
123 reviewed in more detail, in order to identify studies using case definitions or, in their absence, providing  
124 clinical descriptions of the case material [17, 18]. This review resulted in no articles providing case reports  
125 or case definitions of dysfunctional labor following immunization.

126  
127 To further guide decision-making process, guidelines from major professional obstetric societies were  
128 reviewed and definitions of dysfunctional or prolonged labor summarized and provided to members of the  
129 working group for review (Table 1).

## 130 **1.3. Rationale for Selected Decisions about the Case Definition of Dysfunctional Labor as an** 131 **Adverse Event Following Immunization**

132  
133 Our focus throughout this process is to provide criteria for diagnostic certainty for the purpose of case  
134 definition rather than for the identification of time frames for intervention or management changes. This is  
135 a marked difference from the definitions provided in most guidelines where a timeframe or criteria are  
136 used to suggest when intervention and management changes should occur. Thus, a case meeting the

137 definitions provided may or may not warrant intervention, however it is not within the purview of this  
138 working group to provide such recommendations.

139  
140 We recommend criteria used in case ascertainment as defined below are restricted to term singleton  
141 pregnancies, i.e. at or after 37 completed weeks and before 42 weeks of pregnancy. The pathophysiology  
142 and course of labor in preterm, previable pregnancies or postdate pregnancies was felt to be sufficiently  
143 different that separate terminology and case definitions should apply. Both preterm labor and pregnancy  
144 loss have been separately defined by working groups though the Brighton collaboration [19, 20]. Despite  
145 similarities between labor in multiple vs. singleton gestations the working group felt the interaction  
146 between vaccination in a these different gestations may be different and thus warrant a separate  
147 consideration.

148  
149  
150 Definitions were formed separately for both the first stage and second stage of labor. Within the first stage  
151 we choose to focus on a definition of dysfunction once the established or active labor is reached. The  
152 definitions, therefore do not address potential dysfunction or protraction of the latent phase in the first  
153 stage of labor. Established labor describes the onset of active labor, (regular contractions and a cervical  
154 dilation of 4 centimeters (cm). This is distinct from the active phase of the first stage as described by  
155 Zhang et al where there is acceleration in the rate of dilation at 6cm. This stage of cervical dilation has  
156 since been used by United States professional societies as the basis for recommendations on a point  
157 before which unnecessary intervention should be avoided, rather than as a definition of established labor  
158 [21][10]. Established labor was also chosen as the starting time point as it includes all labors once they  
159 are established, regardless of whether they were initially induced or spontaneous. The requirement for  
160 regular contractions and cervical dilation of at least 4cm would mean that an induced labor that begins  
161 with foley catheter cervical ripening and achieves a mechanical dilation of 4cm, but without regular  
162 contractions is not considered in established labor. Similarly a multiparous woman with a cervix dilated to  
163 4cm but without any contractions would not be considered in established labor.

164  
165 We chose not to include the use of regional analgesia as a separate category within our definitions for  
166 both first and second stages of labor. We recognize that during routine clinical practice, the diagnosis of  
167 dysfunctional labor and potential subsequent intervention is often adjusted in the presence of regional  
168 analgesia. Current evidence suggests no impact of regional anesthesia on the first stage[22]. We  
169 recognize literature that shows that the second stage is longer in women with regional anesthesia [22],  
170 however for the purposes of case definition the working group considered regional analgesia a risk factor  
171 for a prolonged second stage rather than warranting separate categorization. As noted above, the scope  
172 of these definitions are for case ascertainment alone and not to prescribe or prevent intervention. Thus by  
173 excluding regional anesthesia as an influence on the case definition we do not mean to suggest any  
174 change in management decisions that might occur in women who do undergo regional anesthesia.

175  
176 In formulating a case definition that reflects diagnostic certainty we weighed specificity versus sensitivity.  
177 After reaching consensus, only two levels of definition were formed, both of which relate to diagnostic  
178 certainty around case definition, rather than clinical severity of a case. To make the diagnosis of  
179 dysfunctional labor, an examiner capable of reliably assessing uterine contractions, amniotic membrane  
180 status (intact vs. ruptured), cervical dilation, fetal station and a measure of time is required. The case  
181 definition has been formulated such that the level one definition is highly specific for the condition. As  
182 maximum specificity normally implies a loss of sensitivity, one additional diagnostic level has been  
183 included in the definition, offering a stepwise increase of sensitivity from level one to level two, while  
184 retaining an acceptable level of specificity at all levels. In this way it is hoped that all possible cases of  
185 dysfunctional labor can be captured. In the first stage of labor, certainty around ruptured membranes  
186 distinguishes between a level one and level two level of certainty. This second level of diagnostic  
187 certainty recognizes circumstances where the timing or certainty of rupture of membranes is unknown to  
188 the woman or her provider or is not documented in the medical record. In the second stage of labor,  
189 diagnostic certainty in level one and two are distinguished by certainty around the onset of active  
190 maternal effort i.e. pushing or visible baby after full dilation (cervix is reported at 10cm or no longer felt  
191 around the presenting part). This allows for variations in practice where women are allowed passive  
192 descent of the fetal head after full dilation or in cases where the onset of active pushing after full dilation

193 is not recorded. In both stages of labor, the working group determined a third level of definition would be  
194 not be specific enough to reliably measure cases of dysfunctional labor, therefore a third level of  
195 diagnostic certainty was not included.

196  
197 Influence of treatment on fulfillment of case definition

198 The Working Group decided against using “treatment” or “treatment response” towards fulfillment of  
199 dysfunctional labor case definition except in the second stage of labor. No distinction is made between  
200 spontaneous, augmented or induced labors, though recognizing, that induction may represent a risk  
201 factor for labor dysfunction. Similarly in the second stage of labor, no distinction is made for labors in  
202 which women receive regional anesthesia, though as noted above, it is recognized that this might  
203 represent a risk factor for prolonged second stage. We designed both level one and two definitions to be  
204 broad enough to include cases presenting differently due to appropriate and early treatment initiation.  
205 An exception is made for intervention for delivery in the second stage of labor, either by operative vaginal  
206 delivery or caesarean delivery for the indication of failure to progress or arrest of descent. This exception  
207 was made as it was felt practice patterns exist where early intervention is performed in the second stage  
208 and exclusion of these cases could result in underreporting of dysfunctional labor.

209  
210 Timing post immunization

211 Specific time frames for the onset of symptoms following immunization are not included in this definition.  
212 Due to the lack of a reported link between dysfunctional labor and immunization, and no postulated  
213 biological plausibility for a link, we felt a restrictive time interval from immunization to onset of  
214 dysfunctional labor should not be an integral part of such a definition. Furthermore, labor often occurs  
215 outside the controlled setting of a clinical trial or hospital. In some settings it may be impossible to obtain  
216 a clear timeline of the event, particularly in less developed or rural settings. In order to avoid selecting  
217 against such cases, the Brighton Collaboration case definition avoids setting arbitrary time frames.  
218 Therefore, we recommend that details of this interval should be assessed and reported as described in  
219 the data collection guidelines.

220 **1.4. Guidelines for data collection, analysis and presentation**

221 As mentioned in the overview paper, the case definition is accompanied by guidelines which are  
222 structured according to the steps of conducting a clinical trial, i.e. data collection, analysis and  
223 presentation. Neither case definition nor guidelines are intended to guide or establish criteria for  
224 management of ill infants, children, or adults. Both were developed to improve data comparability.

225 **1.5. Periodic review**

226 Similar to all Brighton Collaboration case definitions and guidelines, review of the definition with its  
227 guidelines is planned on a regular basis (i.e. every three to five years) or more often if needed.

228

229 **2. CASE DEFINITION OF Dysfunctional Labor**

230

231 **1. First Stage of Labor**

232 For both levels of diagnostic certainty, the woman is in established labor defined by regular contractions  
233 and cervical dilation of at least 4cm.

234 *Level 1 of diagnostic certainty*

235

236 Progress of less than 0.5 cm cervical dilation per hour, for at least 4 hours<sup>1</sup>, in women in established labor  
237 (i.e. have regular contractions and cervical dilation of at least 4cm) and with confirmed ruptured  
238 membranes<sup>2</sup>.

---

<sup>1</sup> “For at least 4 hours” was added to ensure adequate time allowed for progression. Thus a case where progression is less than 0.5cm in the first hour, but then subsequently speeds up would not meet the criteria for delayed or dysfunctional labor. It must be less than 0.5cm/hour averaged over 4 hours.

239  
240 *Level 2 of diagnostic certainty*  
241 Progress of less than 0.5cm cervical dilation per hour in women, for at least 4 hours, with established  
242 labor, (i.e. that is, regular contractions and cervical dilation of at least 4cm) without certainty of ruptured  
243 membranes.  
244  
245 **2. Second Stage of Labor**  
246 *Level 1 of diagnostic certainty*  
247 *Nulliparous women:*  
248 Full dilation<sup>3</sup> of the cervix  
249 AND  
250 onset of the active stage (active maternal effort (i.e. pushing) OR visible baby)  
251 AND  
252 greater than 2 hours of pushing  
253 OR use of instrument delivery for the indication of dystocia<sup>4,5</sup>  
254 OR caesarean delivery for the indication of dystocia<sup>5</sup>  
255  
256 *Multiparous women:*  
257 Full dilation of the cervix  
258 AND  
259 onset of the active stage (active maternal effort (i.e. pushing) OR visible baby)  
260 AND  
261 greater than 1 hour of pushing  
262 OR use of instrument delivery for the indication of dystocia<sup>4,5</sup>  
263 OR caesarean delivery for the indication of dystocia<sup>5</sup>  
264  
265 *Level 2 of diagnostic certainty*  
266 *Nulliparous women*  
267 Full dilation of the cervix in any phase of the second stage  
268 AND  
269 no delivery within 3 hours of full dilation  
270 OR use of instrument delivery for the indication of dystocia<sup>4,5</sup>  
271 OR caesarean delivery for the indication of dystocia<sup>4</sup>  
272 *Multiparous women*  
273 Full dilation of the cervix in any phase of the second stage  
274 AND  
275 no delivery within 3 hours of full dilation  
276 OR use of instrument delivery for the indication of dystocia<sup>4,5</sup>  
277 OR caesarean delivery for the indication of dystocia<sup>4</sup>

---

<sup>2</sup> Confirmed rupture of membranes is added to a level 1 of diagnostic certainty to exclude those women with advanced cervical exams who may have intermittent contractions but may not be in established labor.. For example, the multiparous woman with an advanced cervical exam.

<sup>3</sup> Full dilation of the cervix is described as 10cm dilated, or no palpable cervix around the presenting part of the fetus.

<sup>4</sup> Instrument delivery refers to delivery by forceps or vacuum/ventouse

<sup>5</sup> Dystocia indications include arrest of descent and failure to progress as opposed to indications for fetal well-being.

278 **3. GUIDELINES FOR DATA COLLECTION, ANALYSIS AND PRESENTATION OF**  
279 **DYSFUNCTIONAL LABOUR**

280 It was the consensus of the Brighton Collaboration *Dysfunctional Labor Working Group* to recommend the  
281 following guidelines to enable meaningful and standardized collection, analysis, and presentation of  
282 information about dysfunctional labor. However, implementation of all guidelines might not be possible in  
283 all settings. The availability of information may vary depending upon resources, geographical region, and  
284 whether the source of information is a prospective clinical trial, a post-marketing surveillance or  
285 epidemiological study, or an individual report of dysfunctional labor. Also, as explained in more detail in  
286 the overview paper in this volume, these guidelines have been developed by this working group for  
287 guidance only, and are not to be considered a mandatory requirement for data collection, analysis, or  
288 presentation.

289 **3.1. Data collection**

290 These guidelines represent a desirable standard for the collection of data on availability following  
291 immunization to allow for comparability of data, and are recommended as an addition to data collected for  
292 the specific study question and setting. The guidelines are not intended to guide the primary reporting of  
293 dysfunctional labor to a surveillance system or study monitor. Investigators developing a data collection  
294 tool based on these data collection guidelines also need to refer to the criteria in the case definition,  
295 which are not repeated in these guidelines.

296  
297 Guidelines numbers below have been developed to address data elements for the collection of adverse  
298 event information as specified in general drug safety guidelines by the International Conference on  
299 Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use [23] and  
300 the form for reporting of drug adverse events by the Council for International Organizations of Medical  
301 Sciences [24] and formulated by Jones et al[25]. These data elements include an identifiable reporter and  
302 patient, one or more prior immunizations, and a detailed description of the adverse event, in this case, of  
303 dysfunctional labor following immunization. The additional guidelines have been developed as guidance  
304 for the collection of additional information to allow for a more comprehensive understanding of  
305 dysfunctional labor following immunization.

306 **3.1.1. Source of information/reporter**

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

- 308  
309 1) Date of report.  
310  
311 2) Name and contact information of person reporting<sup>1</sup> and/or diagnosing the dysfunctional labor as  
312 specified by country-specific data protection law.  
313  
314 3) Name and contact information of the investigator responsible for the subject, as applicable.  
315  
316 4) Relation to the patient (e.g. Immunizer [clinician, nurse], family member [indicate relationship], other).  
317

318 **3.1.2. Vaccine/Control**

319 **3.1.2.1. Demographics**

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

- 321  
322 5) Case/study participant identifiers (e.g. first name initial followed by last name initial) or code (or in  
323 accordance with country-specific data protection laws).  
324  
325 6) Date of birth, age, and sex.  
326



327 7) For infants born to study participants: Gestational age and birth weight.

328 **3.1.2.2. Clinical and immunization history**

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

330

331 8) Past medical history, including hospitalizations, underlying diseases/disorders, pre-immunization  
332 signs and symptoms including identification of indicators for, or the absence of, a history of allergy to  
333 vaccines, vaccine components or medications; food allergy; allergic rhinitis; eczema; asthma.

334

335 9) Any medication history (other than treatment for the event described) prior to, during, and after  
336 immunization including prescription and non-prescription medication as well as medication or  
337 treatment with long half-life or long-term effect. (e.g. immunoglobulins, blood transfusion and  
338 immunosuppressants).

339

340 10) Immunization history (i.e. previous immunizations and any adverse event following immunization  
341 (AEFI)), in particular occurrence of an adverse event after a previous immunization.

342

343 **3.1.3. Details of the immunization**

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

345

346 11) Date and time of immunization(s).

347

348 12) Description of vaccine(s) (name of vaccine, manufacturer, lot number, dose (e.g. 0.25mL, 0.5 mL,  
349 etc) and number of dose if part of a series of immunizations against the same disease).

350

351 13) The anatomical sites (including left or right side) of all immunizations (e.g. vaccine A in proximal left  
352 lateral thigh, vaccine B in left deltoid).

353

354 14) Route and method of administration (e.g. intramuscular, intradermal, subcutaneous, and needle-free  
355 (including type and size), other injection devices).

356

357 15) Needle length and gauge.

358

359 **3.1.4. The adverse event**

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

362

363 Specifically document:

364

365 17) Clinical description of signs and symptoms of dysfunctional labor and if there was medical  
366 confirmation of the event (i.e. patient seen by physician).

367

368 18) Date/time of onset of established labour<sup>2</sup>, date/time of diagnosis of dysfunctional labor and final  
369 outcome including mode of delivery<sup>6</sup>.

370

371 19) Time interval since immunization

372

373 20) Concurrent signs, symptoms, and diseases.

374

375 21) Measurement/testing

- 376           • Values and units of routinely measured parameters (e.g. temperature, blood pressure) – in  
377           particular those indicating the severity of the event;  
378           • Method of measurement (e.g. type of thermometer, oral or other route, duration of measurement,  
379           etc.);  
380           • Results of laboratory examinations, surgical and/or pathological findings and diagnoses if  
381           present.  
382           • Include documentation of time and findings for cervical exam, onset of established labor, time of  
383           initiation and duration of regional analgesia if any, full dilation, onset of maternal pushing in the  
384           second stage, and time of delivery.  
385  
386 22) Treatment or intervention given for dysfunctional labor, especially if medication dosing, if procedure –  
387       type of procedure  
388  
389 23) Outcome<sup>6</sup> at last observation.  
390  
391 24) Exposures other than the immunization 24 hours before and after immunization (e.g. food,  
392       environmental) considered potentially relevant to the reported event.  
393

### 394       **3.1.5. Miscellaneous/ General**

- 395 25) The duration of surveillance for dysfunctional labor should be predefined based on  
396       • Biologic characteristics of the vaccine e.g. live attenuated versus inactivated component  
397       vaccines;  
398       • Biologic characteristics of the vaccine-targeted disease;  
399       • Biologic characteristics of dysfunctional labor including patterns identified in previous trials (e.g.  
400       early-phase trials); and  
401       • Biologic characteristics of the vaccinee (e.g. nutrition, underlying disease like immunodepressing  
402       illness).  
403  
404 26) The duration of follow-up reported during the surveillance period should be predefined likewise. It  
405       should aim to continue to resolution of the event, which in this case ascertainment would be after  
406       delivery is completed.  
407  
408 27) Methods of data collection should be consistent within and between study groups, if applicable.  
409  
410 28) Follow-up of cases should attempt to verify and complete the information collected as outlined in data  
411       collection guidelines 1 to 24.  
412  
413 29) Investigators of patients with dysfunctional labor should provide guidance to reporters to optimize the  
414       quality and completeness of information provided.  
415  
416 30) Reports of dysfunctional labor should be collected throughout the study period regardless of the time  
417       elapsed between immunization and the adverse event. If this is not feasible due to the study design,  
418       the study periods during which safety data are being collected should be clearly defined.  
419

### 420       **3.2. Data analysis**

421       The following guidelines represent a desirable standard for analysis of data on dysfunctional labor to  
422       allow for comparability of data, and are recommended as an addition to data analyzed for the specific  
423       study question and setting.  
424

- 425 31) Reported events should be classified in one of the following five categories including the three levels  
426       of diagnostic certainty. Events that meet the case definition should be classified according to the

427 levels of diagnostic certainty as specified in the case definition. Events that do not meet the case  
 428 definition should be classified in the additional categories for analysis.

429

430 **Event classification in 5 categories<sup>8</sup>**

431

432 **Event meets case definition**

433 1) Level 1: *Criteria as specified in the on dysfunctional labor case definition*

434 2) Level 2: *Criteria as specified in the on dysfunctional labor case definition*

435

436 **Event does not meet case definition**

437 **Additional categories for analysis**

438 3) Reported dysfunctional labor with insufficient evidence to meet the case definition<sup>9</sup>

439 4) Not a case of dysfunctional labor

440

441 32) The interval between immunization and reported dysfunctional labor could be defined as the  
 442 date/time of immunization to the date/time of onset<sup>2</sup> of the first symptoms and/or signs consistent with  
 443 the definition. If few cases are reported, the concrete time course could be analyzed for each; for a  
 444 large number of cases, data can be analyzed in the following increments:

445

446 **Subjects with dysfunctional labor by Interval to Presentation**

Interval*	Number
< 24h after immunization	
24h - < 72 h after immunization	
72h - <7 days after immunization	
7 days < 30 days after immunization	
More than 30 days	
<b>TOTAL</b>	

447

448 33) The duration of a possible dysfunctional labor could be analyzed as the interval between the  
 449 date/time of the first signs consistent with the definition and the delivery of t the fetus/es<sup>6</sup>. Whatever  
 450 start and ending are used, they should be used consistently within and across study groups.

451

452 34) The distribution of data (as numerator and denominator data) could be analyzed in predefined  
 453 increments (e.g. measured values, times), where applicable. Increments specified above should be  
 454 used. When only a small number of cases are presented, the respective values or time course can be  
 455 presented individually.

456

457 35) Data on dysfunctional labor obtained from subjects receiving a vaccine should be compared with  
 458 those obtained from an appropriately selected and documented control group(s) to assess  
 459 background rates of hypersensitivity in non-exposed populations, and should be analyzed by study  
 460 arm and dose where possible, e.g. in prospective clinical trials. Sample size to evaluate exposed  
 461 versus non-exposed populations should be calculated using background rates of dysfunctional labor  
 462 in the population to be studied.

463 **3.3. Data presentation**

464 These guidelines represent a desirable standard for the presentation and publication of data on  
 465 dysfunctional labor following immunization to allow for comparability of data, and are recommended as an  
 466 addition to data presented for the specific study question and setting. Additionally, it is recommended to  
 467 refer to existing general guidelines for the presentation and publication of randomized controlled trials,  
 468 systematic reviews, and meta-analyses of observational studies in epidemiology (e.g. statements of  
 469 Consolidated Standards of Reporting Trials (CONSORT), of Improving the quality of reports of meta-

470 analyses of randomized controlled trials (QUORUM), and of Meta-analysis Of Observational Studies in  
471 Epidemiology (MOOSE), respectively)[26-28].  
472

473 36) All reported events of on dysfunctional labor should be presented according to the categories listed in  
474 guideline 32.  
475

476 37) Data on possible on dysfunctional labor events should be presented in accordance with data  
477 collection guidelines 1-24 and data analysis guidelines 31-35.  
478

479 38) Terms to describe on dysfunctional labor such as “low-grade”, “mild”, “moderate”, “high”, “severe” or  
480 “significant” are highly subjective, prone to wide interpretation, and should be avoided.  
481

482 39) Data should be presented with numerator and denominator (n/N) (and not only in percentages), if  
483 available.  
484

485 Although immunization safety surveillance systems denominator data are usually not readily  
486 available, attempts should be made to identify approximate denominators. The source of the  
487 denominator data should be reported and calculations of estimates be described (e.g. manufacturer  
488 data like total doses distributed, reporting through Ministry of Health, coverage/population based data,  
489 etc.).  
490

491 40) The incidence of cases in the study population should be presented and clearly identified as such in  
492 the text.  
493

494 41) If the distribution of data is skewed, median and range are usually the more appropriate statistical  
495 descriptors than a mean. However, the mean and standard deviation should also be provided.  
496

497 42) Any publication of data on dysfunctional labor should include a detailed description of the methods  
498 used for data collection and analysis as possible. It is essential to specify:  
499

- 500 ● The study design;
- 501 ● The method, frequency and duration of monitoring for on dysfunctional labor;
- 502 ● The trial profile, indicating participant flow during a study including drop-outs and withdrawals to  
503 indicate the size and nature of the respective groups under investigation;
- 504 ● The type of surveillance (e.g. passive or active surveillance);
- 505 ● The characteristics of the surveillance system (e.g. population served, mode of report  
506 solicitation);
- 507 ● The search strategy in surveillance databases;
- 508 ● Comparison group(s), if used for analysis;
- 509 ● The instrument of data collection (e.g. standardized questionnaire, diary card, report form);
- 510 ● Whether the day of immunization was considered “day one” or “day zero” in the analysis;
- 511 ● Whether the date of onset<sup>2</sup> and/or the date of first observation<sup>3</sup> and/or the date of diagnosis<sup>4</sup> was  
512 used for analysis; and
- 513 ● Use of this case definition for on dysfunctional labor, in the abstract or methods section of a  
514 publication<sup>11</sup>.  
515

516

517 **Notes for guidelines**

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

520 <sup>2</sup>The date and/or time of onset is defined as the time post immunization, when dysfunctional labor is  
521 diagnosed. This may only be possible to determine in retrospect.

522 <sup>3</sup>The date and/or time of first observation of the first sign or symptom indicative for dysfunctional labor  
523 can be used if date/time of onset is not known.

524 <sup>4</sup>The date of diagnosis of an episode is the day post immunization when the event met the case definition  
525 at any level.

526 <sup>5</sup>The end of an episode is defined as the time the event no longer meets the case definition at the lowest  
527 level of the definition.

528 <sup>6</sup> E.g. recovery to pre-immunization health status, spontaneous resolution, therapeutic intervention,  
529 persistence of the event, sequelae, death.

530 <sup>7</sup>An AEFI is defined as serious by international standards if it meets one or more of the following criteria:  
531 1) it results in death, 2) is life-threatening, 3) it requires inpatient hospitalization or results in  
532 prolongation of existing hospitalization, 4) results in persistent or significant disability/incapacity, 5) is a  
533 congenital anomaly/birth defect, 6) is a medically important event or reaction.

534 <sup>8</sup>To determine the appropriate category, the user should first establish, whether a reported event meets  
535 the criteria for the lowest applicable level of diagnostic certainty, e.g. Level three. If the lowest  
536 applicable level of diagnostic certainty of the definition is met, and there is evidence that the criteria of  
537 the next higher level of diagnostic certainty are met, the event should be classified in the next category.  
538 This approach should be continued until the highest level of diagnostic certainty for a given event could  
539 be determined. If the lowest level of the case definition is not met, it should be ruled out that any of the  
540 higher levels of diagnostic certainty are met and the event should be classified in additional categories  
541 four or five.

542 <sup>9</sup>If the evidence available for an event is insufficient because information is missing, such an event should  
543 be categorized as "Reported dysfunctional labor with insufficient evidence to meet the case definition".

544 <sup>10</sup>An event does not meet the case definition if investigation reveals a negative finding of a necessary  
545 criterion (necessary condition) for diagnosis. Such an event should be rejected and classified as "Not a  
546 case of dysfunctional labor".

547 <sup>11</sup>Use of this document should preferably be referenced by referring to the respective  
548 link on the Brighton Collaboration website (<http://www.brightoncollaboration.org>).

549

550

551  
552

553 **4. ACKNOWLEDGEMENTS**

554 SK was supported by the NIHR Collaborations for Leadership in Applied Health Research and Care West  
555 Midlands initiative. The views expressed are those of the author(s) and not necessarily those of the NHS,  
556 the NIHR or the Department of Health. The authors are grateful for the support and helpful comments  
557 provided by the Brighton Collaboration and the reference group (see  
558 <https://brightoncollaboration.org/public/what-we-do/setting-standards/case-definitions/groups.html> for  
559 reviewers), as well as other experts consulted as part of the process. The authors are also grateful to Jan  
560 Bonhoeffer, Jorgen Bauwens of the Brighton Collaboration Secretariat and Sonali Kochhar of Global  
561 Healthcare Consulting for final revisions of the final document. Finally, we would like to acknowledge  
562 the Global Alignment of Immunization Safety Assessment in Pregnancy (GAIA) project, funded  
563 by the Bill and Melinda Gates Foundation.  
564

565 **Table 1: Summary of Professional Guidelines**

566

Professional Organization	Year Published	First Stage		Second Stage	
		Nulliparous	Multiparous	Nulliparous	Multiparous
NICE [29]	2014	Normal: 8-18hours Suspected delay: <2cm in 4 hours, with delay confirmed with progress of less than 1cm 2 hours later.	Normal: 5-12 hours Delay :<2cm in 4 hours OR slowing in progress of labor	Birth expected within 3 hours of start of active second stage Delay: 2 or more hours	Birth expected within 2 hours of start of active stage Delay: 1 or more hours
ACOG/SMFM [11]	2014	Normal <20 hours Arrest: 6cm dilation and 4 hours or more of adequate contractions or 6 hours or more of inadequate contractions	Normal < 14 hours Arrest: 6cm dilation and 4 hours or more of adequate contractions or 6 hours or more of inadequate contractions	No maximum time frame Permit at least 3 hours of pushing	No maximum time frame. Permit at least 2 hours of pushing
RANZCOG [30]	2014	Prolonged if: <1cm/hr in active phase	Prolonged if: <1cm/hr in active phase	>2 hours	>1 hour
WHO [31]	2014	<0.5cm to 1cm/hr during the active phase	<0.5cm to 1cm/hr during the active phase	N/A	N/A
SOGC [32]	1995	<0.5cm/hour over a 4 hour period	<0.5cm/hour over a 4 hour period	2 hours if no regional anesthesia	N/A
FIGO [33]	2012	N/A	N/A	No more than 3 hours of active pushing	No more than 2 hour of active pushing

567

568

569 5. REFERENCES

570

- 571 1. Updated recommendations for use of tetanus toxoid, reduced diphtheria toxoid and  
572 acellular pertussis vaccine (Tdap) in pregnant women and persons who have or  
573 anticipate having close contact with an infant aged <12 months --- Advisory Committee  
574 on Immunization Practices (ACIP), 2011. MMWR Morb Mortal Wkly Rep, 2011. **60**(41):  
575 p. 1424-6.
- 576 2. Grohskopf, L.A., et al., *Prevention and control of seasonal influenza with vaccines:  
577 recommendations of the Advisory Committee on Immunization Practices (ACIP) --  
578 United States, 2014-15 influenza season.* MMWR Morb Mortal Wkly Rep, 2014. **63**(32):  
579 p. 691-7.
- 580 3. Munoz, F.M. and P. Ferrieri, *Group B Streptococcus vaccination in pregnancy: moving  
581 toward a global maternal immunization program.* Vaccine, 2013. **31**: p. D46-D51.
- 582 4. Munoz, F.M., *Respiratory syncytial virus in infants: is maternal vaccination a realistic  
583 strategy?* Current opinion in infectious diseases, 2015. **28**(3): p. 221-224.
- 584 5. World Health Organization, *Causality assessment of an adverse event following  
585 immunization (AEFI): user manual for the revised WHO classification.* 2013, World  
586 Health Organization: Geneva.
- 587 6. Zhu, B.P., et al., *Labor dystocia and its association with interpregnancy interval.* Am J  
588 Obstet Gynecol, 2006. **195**(1): p. 121-8.
- 589 7. Brighton Collaboration. *Brighton Collaboration - Our Story.* [cited 2016 June 29th];  
590 Available from: <https://brightoncollaboration.org/public/who-we-are/our-story.html>.
- 591 8. Friedman, E.A., *The graphic analysis of labor.* American Journal of Obstetrics and  
592 Gynecology, 1954. **68**(6): p. 1568-1575.
- 593 9. Friedman, E.A., *Primigravid Labor: A graphicostatistical analysis.* Obstetrics &  
594 Gynecology, 1955. **6**(6): p. 567-589.
- 595 10. Zhang, J., et al., *Contemporary patterns of spontaneous labor with normal neonatal  
596 outcomes.* Obstetrics and gynecology, 2010. **116**(6): p. 1281.
- 597 11. Caughey, A.B., et al., *Safe prevention of the primary cesarean delivery.* American  
598 journal of obstetrics and gynecology, 2014. **210**(3): p. 179-193.
- 599 12. Sheiner, E., et al., *Risk factors and outcome of failure to progress during the first stage  
600 of labor: A population-based study.* Acta obstetrica et gynecologica Scandinavica, 2002.  
601 **81**(3): p. 222-226.
- 602 13. Selin, L., G. Wallin, and M. Berg, *Dystocia in labour--risk factors, management and  
603 outcome: a retrospective observational study in a Swedish setting.* Acta obstetrica et  
604 gynecologica Scandinavica, 2008. **87**(2): p. 216-221.
- 605 14. Kjaergaard, H., et al., *Risk indicators for dystocia in low-risk nulliparous women: a study  
606 on lifestyle and anthropometrical factors.* Journal of Obstetrics and Gynaecology, 2010.  
607 **30**(1): p. 25-29.
- 608 15. Kjærgaard, H., et al., *Obstetric risk indicators for labour dystocia in nulliparous women: a  
609 multi-centre cohort study.* BMC pregnancy and childbirth, 2008. **8**(1): p. 1.
- 610 16. Kohl, K.S., et al., *The development of standardized case definitions and guidelines for  
611 adverse events following immunization.* Vaccine, 2007. **25**(31): p. 5671-4.
- 612 17. Orenstein, L.A., et al., *Background rates of adverse pregnancy outcomes for assessing  
613 the safety of maternal vaccine trials in sub-Saharan Africa.* PLoS One, 2012. **7**(10): p.  
614 e46638.
- 615 18. Salam, R.A., et al., *Impact of Haemophilus influenzae type B (Hib) and viral influenza  
616 vaccinations in pregnancy for improving maternal, neonatal and infant health outcomes.*  
617 Cochrane Database Syst Rev, 2015(6): p. CD009982.
- 618 19. Harrison, M.S., et al., *Pathways to preterm birth: Case definition and guidelines for data  
619 collection, analysis, and presentation of immunization safety data.* Vaccine, 2016.



- 620 20. Da Silva, F.T., et al., *Stillbirth: Case definition and guidelines for data collection,*  
621 *analysis, and presentation of maternal immunization safety data.* Vaccine, 2016.
- 622 21. Spong, C.Y., et al., *Preventing the first cesarean delivery: summary of a joint Eunice*  
623 *Kennedy Shriver National Institute of Child Health and Human Development, Society for*  
624 *Maternal-Fetal Medicine, and American College of Obstetricians and Gynecologists*  
625 *Workshop.* Obstet Gynecol, 2012. **120**(5): p. 1181-93.
- 626 22. Anim-Somuah, M., R. Smyth, and L. Jones, *Epidural versus non-epidural or no*  
627 *analgesia in labour.* Cochrane database syst rev, 2011. **12**.
- 628 23. International Conference on Harmonisation of Technical Requirements for Registration  
629 of Pharmaceuticals for Human Use (ICH), *Guidelines for Clinical Safety Assessment*  
630 *(E2a-e)*(Accessed at: <http://www.ich.org/>).
- 631 24. Council for International Organizations of Medical Sciences (CIOMS), *Reporting form*  
632 *for International Reporting of Adverse Drug Reactions,*. Accessed at  
633 <http://www.cioms.ch/>.
- 634 25. Jones, C.E., et al., *Guideline for collection, analysis and presentation of safety data in*  
635 *clinical trials of vaccines in pregnant women.* Vaccine, 2016.
- 636 26. Moher, D., et al., *Improving the quality of reports of meta-analyses of randomised*  
637 *controlled trials: the QUOROM statement. Quality of Reporting of Meta-analyses.*  
638 *Lancet*, 1999. **354**(9193): p. 1896-900.
- 639 27. Moher, D., et al., *The CONSORT statement: revised recommendations for improving the*  
640 *quality of reports of parallel-group randomized trials.* JAMA, 2001. **285**(15): p. 1987-91.
- 641 28. Stroup, D.F., et al., *Meta-analysis of observational studies in epidemiology: a proposal*  
642 *for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group.*  
643 *JAMA*, 2000. **283**(15): p. 2008-12.
- 644 29. National Collaborating Centre for Women's and Children's Health, *Intrapartm Care: Care*  
645 *of health women and their babies during childbirth,* in *Clinical Guidline 190;* . 2014,  
646 National Institute for Health and Care Excellence.
- 647 30. The Royal Australian and New Zealand College of Obstetricians and Gynaecologist,  
648 *Provision of routine intrapartum care in the absence of pregnancy complications.* 2014,  
649 RANZCOG.
- 650 31. World Health Organization, *Recommendations for augmentation of labour.* 2014, World  
651 Health Organization: Geneva.
- 652 32. Society of Obstetricians and Gynaecologists of Canada, *Dystocia,* in *Clinical Practice*  
653 *Guidelines for Obstetrics.* 1995.
- 654 33. Motherhood, F.S. and C. Newborn Health, *Management of the second stage of labor.* Int  
655 *J Gynaecol Obstet*, 2012. **119**(2): p. 111-6.
- 656