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Guideline for collection, analysis and presentation of safety data in clinical trials of vaccines in pregnant women

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Abstract

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Disclaimer

The findings, opinions and assertions contained in this consensus document are those of the individual scientific professional members of the working group. They do not necessarily represent the official positions of each participant's organization (e.g., government, university, or corporation). Specifically, the findings and conclusions in this paper are those of the authors and do not necessarily represent the views of the World Health Organization or the Centers for Disease Control and Prevention.

Conflict of interests

PTH is an investigator for clinical trials done on behalf of St Georges, University of London, London, UK, sponsored by vaccine manufacturers. He is a consultant to Novartis and Pfizer on group B streptococcus vaccines but receives no personal funding for this activity. KME has conducted maternal vaccination studies for Group B streptococcal vaccines funded by Novartis, with the funding to her university. PN is working as a regulatory consultant for industry and WHO. For maternal immunization, PN has been consulted by Novartis V&D. The other authors have no conflicts of interest to declare.

Vaccination during pregnancy is increasingly being used as an effective approach for protecting both young infants and their mothers from serious infections. Drawing conclusions from published studies in this area can be difficult because of the inability to compare vaccine trial results across different studies and settings due to the heterogeneity in the definitions of terms used to assess the safety of vaccines in pregnancy and the data collected in such studies.

The guidelines proposed in this document have been developed to harmonize safety data collection in all phases of clinical trials of vaccines in pregnant women and apply to data from the mother, fetus and infant. Guidelines on the prioritization of the data to be collected is also provided to allow applicability in various geographic, cultural and resource settings, including high, middle and low-income countries.

Keywords

Adverse event; Immunization; Pregnancy; Guidelines; Clinical trials; Vaccines Safety

1. Preamble

1.1. Background and need for this guidelines

Three-quarters of all neonatal deaths worldwide occur during the first week of life, with the first 24 h being the most critical period [1,2]. In the first months of life, transplacentally delivered maternal antibodies are crucial for the infant's protection against infectious diseases. The main objective of immunization in pregnancy is the prevention of infections in mothers and infants at a time when they are most susceptible to morbidity and mortality from these infections. Other objectives of immunization in pregnancy may include reducing the severity of infections in previously non-immune pregnant women, which, for some infections [3], can be more severe than in non-pregnant women [4,5], as well as preventing infections in the fetus [6].

Recommendations already exist in a number of countries to vaccinate pregnant women against tetanus [7], influenza [8–11] and pertussis [12–16], while other vaccines are recommended where there is perceived benefit [17].

Vaccinating pregnant women is a potential strategy for preventing specific infections in infants and many vaccines are currently in various stages of clinical trials. Examples include vaccines against group B streptococcus (GBS) [18], respiratory syncytial virus (RSV) [19] and *Streptococcus pneumoniae* [20,21].

In the United States, the National Institutes of Health have supported studies of vaccines in pregnant women since the 1980s. Aside from a few small prospective clinical trials, most studies have been observational because pregnancy is typically an exclusion criterion for participation in research. In March 2004, the first International Neonatal Vaccination workshop was held in Virginia (USA) to further explore the immunology and safety of immunization strategies to expand protection of neonates against vaccine-preventable diseases [22]. The participants found it difficult to draw conclusions from the studies reviewed during the workshop because of the inability to compare vaccine trial results across

different studies and settings, in part because critical information was either lacking or inconsistently collected. One of the conclusions of the workshop was that the data collected and presented from vaccine trials in both neonates and pregnant women should be harmonized. Similarly, at an international meeting on vaccination in pregnancy in 2012 [23], it was noted that there were no widely accepted guidelines for data collection in studies of vaccination in pregnancy. This lack of harmonization was also evident when evaluating the studies conducted during the 2009–2010 H1N1 influenza pandemic, when vaccines were administered to large numbers of pregnant women worldwide [24]. Efforts to develop widely accepted guidelines for the assessment of safety of vaccines in pregnant women have subsequently evolved with the recognition that immunization in pregnancy appears to be a generally safe and effective strategy to protect both mothers and infants against potentially life-threatening infectious diseases [25–28].

A detailed analysis of the available guidelines from regulatory agencies and others including the Food and Drug Administration (FDA), European Medicines Agency (EMA) and International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) reinforced the evidence of the lack of harmonization and the minimal guidance available for safety monitoring (Appendix 1). The EMA has outlined specific requirements for evaluating vaccines in pregnant women, including: criteria to select medicinal products, including vaccines, for which active surveillance in pregnancy is necessary, guidance on how to monitor accidental or intended exposure to medicinal products during pregnancy and specific requirements for reporting and presenting data on adverse outcomes of exposure during pregnancy [29]. In the FDA and ICH guidelines, only general guidance was available, but specific requirements are now emerging with the inclusion of available data on maternal immunization in the product labeling [30].

The guidelines proposed in this document have therefore been developed to harmonize data collection for safety monitoring in the course of clinical trials of vaccines in pregnant women. These guidelines may also assist in the ongoing assessment of safety surveillance of vaccines already recommended for use in pregnant women, however the focus of these recommendations is data collection in clinical trials. Guidance on the prioritization of the data to be collected is also provided to promote collection of at least a minimal set of high-priority parameters in various settings, including low- and middle-income countries (LMIC).

1.2. Relationship of this guidelines to other guidelines

Internationally accepted general recommendations for the analysis and reporting of vaccine trial data already exist and should be consulted where appropriate. These include the CONSORT statement [31,32] and its extension for safety reporting in randomized vaccine trials [33] as well as the Brighton Collaboration guidelines for collection, analysis and presentation of vaccine safety data in pre- and post-licensure clinical studies [34,35]. Complementary to these general guidelines for data collection are a glossary of terms, tables of key disease concept definitions, and standardized case definitions for key obstetric and neonatal events for safety monitoring of vaccines in pregnant women. These are available on the Brighton Collaboration website (www.brightoncollaboration.org). The current guidelines also build on specific guidance documents developed for harmonizing safety assessment in

trials of vaccines in pregnant women in the United States [36–39] and specifically aim for applicability in all resource settings.

1.3. Use of these guidelines

It was the consensus of the Brighton Collaboration Working Group that the following guidelines are a desirable standard for collection of vaccine safety data in clinical trials involving pregnant women. These guidelines are intended for all parties involved in the planning, evaluation, and implementation of relevant studies including investigators, research networks, ethics committees and sponsors. The ability to implement these guidelines depends on a number of factors, such as the availability of resources, the availability of epidemiological information, the types of vaccines under study and the vaccine trial design.

These guidelines are intended to be applicable in diverse geographic, administrative, and cultural regions, regardless of the differences in the availability of health care resources. The group recognizes that implementation of all guidelines might not be possible in all settings and has therefore prioritized the collection of data to take account of this. It is acknowledged that guidance given the highest priority may be challenging to implement in resource-limited settings. In these circumstances, investigators would need to make a detailed assessment of whether sufficient resources can be provided in order to undertake a clinical trial assessing safety of vaccines in pregnancy. It is important to emphasize that, regardless of the local availability of health care resources, the trial sponsor is responsible to ensure the provision of standard care if an adverse event does occur.

These guidelines are intended to be used alongside the complementary data collection matrix (a collection of variables to be included in a case report form [CRF]) [40].

The proposed guidelines are not intended to guide or establish criteria for management of ill infants, children, or adults. They are not regulatory in nature and are not mandatory; the data collected in individual clinical trials will be dependent on the pre-specified aims and objectives, study setting and resources. These guidelines are not intended to replace established or mandated processes of adverse event reporting. The intention is to optimize and harmonize the use of data obtained from participants in clinical trials. The scientific purpose is to give added value to the reported results of individual trials by improving data accuracy and comparability. Additional data may be collected, analyzed, and presented as deemed necessary by investigators, ethics committees, regulators, and/or sponsors. Shared data collection tools and protocols should be designed to further optimize safety reporting and to facilitate data collection and analysis according to the guidelines presented in this document. A directory to available tools promoting harmonization is maintained at brightoncollaboration.org.

1.4. Development process of guidelines

Following the standard Brighton Collaboration process [41], a Working Group was formed in November 2004 to develop guidelines for assessment of safety in maternal and neonatal immunization studies. This Working Group included 32 members from developed and developing countries, with pertinent professional backgrounds ranging from public health

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organizations to regulatory authorities, academic institutions and scientists from vaccine manufacturers. Working Group members had expertise in immunization programs, immunology, vaccine trials and regulatory affairs, as well as obstetrics, pediatrics and infectious diseases. The Working Group conducted regular conference calls over the course of 2 years, elicited written comments from participants from the 1st International Neonatal Vaccination Workshop in Virginia, and incorporated their comments. This initiative led to broad initial guidelines considering both neonatal and maternal immunization based on the contributions of the Working Group members and other experts in the field of maternal and neonatal immunization, as well as on a critical literature review of published data.

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In the light of increased research and regulatory activities around immunization of pregnant women, the guidelines were reviewed and updated again during 2012–2014. This included an updated literature review, as well as a specific call made through the Brighton Collaboration membership to identify any recent or emerging guidelines. Input was also sought from experts attending a maternal immunization consultation meeting at the World Health Organization (WHO) in July 2014 based on the work of two interdisciplinary Brighton Collaboration Task Forces [42]. In the frame of the GAIA project (Global Alignment of Immunization Safety Assessment in pregnancy; www.gaia-consortium.net), supported by the Bill & Melinda Gates Foundation, the Working Group re-convened to derive targeted guidelines for the assessment of the safety of vaccines in pregnant women and to finalize these guidelines following structured peer-review by the broad global Brighton Collaboration Reference Group [41]. This guideline should be considered as a ‘living document’, which will be reviewed periodically and updated to take account of emerging data and feedback from investigators implementing these guidelines, these will be available at www.brightoncollaboration.org.

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1.4.1. The systematic literature review—The literature search was performed using English and non-English citations for maternal and neonatal guidelines, in the context of immunization, over the period from 1966 to October 2014. The search terms used within PubMed (National Institute of Health, US, National Library of Medicine) were: “immunization, vaccination, neonate, neonatal, perinatal, maternal, pregnant and pregnancy”, which led to the identification of more than 500 potentially relevant articles, which were further narrowed down by immediate relevance for this guideline to 250 original articles and review papers. This included the 74 studies of vaccines in pregnant women reviewed in depth as part of the review of the current practice of adverse event reporting [24]. The review did not identify any publications on the standardization of data collection in trials of vaccines in pregnant women until 2012. Since then, four publications have become available based on the work surrounding vaccines in pregnant women at the U.S. National Institutes of Health [36–39]. In addition to the peer-reviewed scientific literature, the systematic review identified the available regulatory and other professional guidance documents (listed in Appendix 1).

1.4.2. Rationale for overall structure of the guidelines—The guideline document emphasizes the following five aspects of data collection for pregnancy vaccine trials:

- i. Clinical trial site background data collection

- ii. Pre-vaccination screening data
- iii. Vaccine- and immunization-related data
- iv. Follow-up monitoring data (including birth-related and neonatal data)
- v. Adverse event monitoring data (including maternal, fetal and infant)

While all outcomes of a vaccine trial in pregnancy need to be monitored, the Working Group acknowledges that it might not be practical to pre-define and solicit all possible clinical and laboratory outcomes. However, a core dataset should be collected in all vaccine trials in pregnancy, where feasible. Thus, each of these main sections has been further divided into subsections based on two priority levels for data collection:

Priority 1: Essential: data considered essential for the understanding of the trial results and/or required by national and/or international regulatory authorities;

Priority 2: Complementary: data considered complementary and important but not essential.

The Working Group emphasized the need to record essential clinical data, in particular all evidence used to make a specific diagnosis. For any individual vaccine trial, additional data may be collected depending on the capacities at a given vaccine trial site and the importance of those data for the primary or secondary objectives of the trial as determined by the investigators, research networks, ethics review committees and sponsors.

1.4.3. Specific data to be collected—Through the GAIA project a large number of clinical terms relevant to trials of vaccination in pregnancy were identified. Amongst these terms a limited number have been identified that require standardization and a (growing) subset of these have been formally defined [43]. Investigators are encouraged to review this list and classify adverse events following immunization (AEFIs) according to these case definitions. Additionally, as part of this initiative a data collection matrix for use in clinical trial protocols (a collection of variables to be included in a CRF) has been developed [40], as well as an automated case classification tool [44]. Investigators are encouraged to use these for harmonization and data comparability purposes.

2. Guidelines

2.1. Clinical trial site background data collection: Collection of relevant public health data on mothers and neonates

- 1 Specify the background rate of key maternal, fetal, neonatal and infant conditions in the population from which trial participants are selected or, alternatively, in a population that is most similar to the study population. A comprehensive list of conditions is available [43]. A recommended minimal list of events (Priority 1) is specified below:
 - Maternal and fetal conditions: rates of maternal death, spontaneous abortion or miscarriage, stillbirth, preterm delivery and common obstetric outcomes (cesarean section, eclampsia/preeclampsia and preterm labor)

- Neonatal and infant conditions: rates of congenital anomalies, rates of small for gestation age (SGA), low birth weight, prematurity and neonatal death

If not available, investigators are encouraged to collect the above data in preparation for the clinical trial.

- 2 Indicate the source of available background data (e.g., Ministry of Health or District/Provincial epidemiological data, previous studies in comparable study settings, or observational data collected from study locality in preparation for clinical trial) (Priority 1).

2.2. Pre-vaccination screening data

2.2.1. Maternal demographic data—This section defines data that should be collected on all participants prior to vaccination, typically during the screening visit for the vaccine trial.

- 3 Study participant identifiers (initials for the given and family), or code, or as otherwise specified in country-specific data protection laws (Priority 1)
- 4 Date of birth of pregnant woman (specify calendar used if not Julian calendar, specify most accurate known date of birth if actual date not known by mother [e.g., month and year]) and age at the time of screening (Priority 1)
- 5 The assessment of race (i.e., shared genetically determined physical characteristics) and ethnicity (i.e., shared sociological characteristics) should be based on locally accepted principles, which should be summarized (Priority 1). Selected genetic host factors, which are of potential importance for vaccine responses (e.g., Human Leukocyte Antigen [HLA] haplotypes), may transcend other descriptive means of demographic categorization, and should be assessed in such cases (Priority 2)
- 6 Other demographic details, including maternal educational level (Priority 1), household geographic location (Priority 1), environment (urban, suburban, rural) (Priority 2) and consanguinity (Priority 2).
- 7 Surrogate indicators of socioeconomic status appropriate to local and cultural setting (e.g., type of housing, number of people in the home, size of home, household income, maternal occupation and household assets) (Priority 2)

2.2.2. Maternal medical and obstetric history—This section defines data that should be collected and recorded for all vaccine trial participants. Permission to review the maternal prenatal obstetric and general medical records should be included in the consent document.

- 8 General medical history, including pre-existing non-obstetric conditions, previous surgery, and hospitalizations (Priority 1)
- 9 Obstetric medical history: order of the current pregnancy, gravity, parity, attendance at antenatal visits and results of any routine tests obtained during pregnancy to assess pregnancy and the fetus (e.g., congenital anomalies,

ultrasound, amniocentesis). For prior pregnancies, document dates of delivery or termination of pregnancy, history of multiple pregnancies, pregnancy complications, history of cesarean section (elective or emergency), pregnancy outcome(s) (live birth, still birth or abortion) and history of previous early-onset neonatal infection (Priority 1)

- 2 Infections: results of any routine antenatal screening tests for infections (Priority 1). Additionally, laboratory investigations should be performed for infections that may have impact on the immunogenicity, efficacy and safety of pregnancy vaccines or aid interpretation of events that occur in the mother, fetus, neonate or infant (Priority 1). These infections include, but are not limited to, human immunodeficiency virus (HIV) 1 and 2, malaria (where relevant), syphilis, tuberculosis (where relevant), Zika virus (where relevant), hepatitis B virus, rubella, hepatitis C virus, group B streptococcus, toxoplasmosis, genital herpes simplex virus infections and other sexually transmitted infections (Chlamydia, gonococcus, etc.). Additionally, background data on the target infection for specific vaccine studies will be required (Priority 1), e.g., GBS colonization and GBSuria in a subject participating in a GBS vaccine trial
- 11 Other acute non-infectious medical conditions during the present pregnancy e.g., hematologic, including anemia, metabolic, endocrine, gynecological, rheumatological, cardiovascular, renal, gastrointestinal, pulmonary or neurological conditions and any other health condition of potential importance for the immunogenicity and safety of vaccines; this includes results of non-routine laboratory testing during pregnancy relevant to such medical conditions (Priority 1)
- 12 Medication history: medication taken up to 1 month prior to pregnancy and study vaccination, including prescription and non-prescription drugs, herbal and homeopathic preparations and nutritional supplements [45]. A comprehensive list of known teratogens is available [46,47] (Priority 1)^{2,3}
- 13 History of allergies, including adverse drug reactions: allergen and a description of the reaction
- 14 Vaccination history: recorded vaccines administered up to 1 year prior to enrollment and study vaccination together, as well as date of administration (Priority 1)

2.2.3. Maternal screening examination and investigations—The following parameters should be assessed for each trial participant:

- Nutritional status of the mother (ideally prior to and during this pregnancy, but at enrollment as a minimum), assessed by the most reliable, locally available

²Note history of drug abuse, cigarette and alcohol use in pregnancy, and all exposures to potential teratogens that have occurred during pregnancy.

³The interval of the medication history pre-conception and during pregnancy (note trimester) should be based on the possible duration of acute and chronic medication effects and relevance to the vaccine trial. This will apply particularly for medication with a long half-life or long-term effects, such as immunoglobulins, blood transfusions, or immuno-suppressants

methods, including measurement of height and weight to establish body mass index (BMI) or other validated nutritional indicators (Priority 1)

- Resting Heart Rate (beats per minute), systolic and diastolic blood pressure (mmHg), respiration rate (breaths per minute), body temperature (°C or °F) (Priority 1)
 - Abnormalities on general physical examination
 - General appearance, generalized dermatological signs, cardiovascular signs, respiratory signs, hematological signs, gastrointestinal signs, urogenital signs, musculoskeletal signs, neurological signs, ocular/ visual signs, endocrine/ metabolic signs (Priority 1)
- Abnormalities on obstetric examination
 - Scars from previous deliveries, fundal height, documentation of fetal heart tones and fetal movement (if applicable) (Priority 1)
- Laboratory examinations
 - Full blood count, differential, Urea, Creatinine, AST*, ALT*, GGT*, Bilirubin, Na, K, Cl, Glucose (*or equivalent according to local laboratory) (Priority 1)
 - Baseline laboratory investigations for infections that may have impact on the immunogenicity, efficacy and safety of pregnancy vaccines or aid interpretation of events that occur in the mother, fetus, neonate or infant (Priority 1). These infections include, but are not limited to, human immunodeficiency virus (HIV) 1 and 2, malaria (where relevant), syphilis, tuberculosis (where relevant), Zika virus (where relevant), hepatitis B virus, rubella, hepatitis C virus, GBS, toxoplasmosis, herpes simplex virus infections and other sexually transmitted infections (e.g., Chlamydia, gonococcus). Where relevant, the results of previous routine tests may be used (with prior ethics approval). Additionally, investigations relevant to the target infection for specific vaccine studies may be required (Priority 1) (e.g., GBS colonization in a subject participating in a GBS vaccine trial)
 - Urine: protein, glucose, bacterial culture (Priority 2)

2.2.4. Fetal data—This section defines data that should be collected and recorded on all vaccine trial participants.

- 15** Presence of fetal growth restriction (IUGR)⁴ (Priority 1)
- 16** Any fetal anomaly noted before vaccination of the mother (e.g., by ultrasound or other screening tests [specify test]) (Priority 1)

⁴See case definition and guidelines at brightoncollaboration.org.

- 17 Gestational age (i.e., number of weeks mother was pregnant at the time of vaccination⁵) (Priority 1)

2.3. Vaccine and immunization data

- 18 Storage conditions of the vaccine. Study vaccines need to be stored and managed per manufacturer and sponsor requirements and accountability, and appropriate storage conditions must be maintained until administration of the vaccine (Priority 1)

For all vaccine trial participants, the following information should be collected and recorded:

- 19 Description of the administered vaccine(s)⁶: Name of the vaccine(s), manufacturer, lot number, expiry date, actual dose volume (Priority 1). Diluents should be described with their lot numbers, and expiry dates (where appropriate)
- 20 Prior to vaccination, maternal vital signs should be obtained, including blood pressure, heart rate, respiratory rate and temperature (Priority 1). Vaccine should only be administered if these parameters are within the specified normal ranges for the study. Vaccine administration should be deferred in women with febrile or non-febrile acute illnesses at the time of vaccination (Priority 1)
- 21 Date, time and route of immunization (e.g., oral, intramuscular, intradermal, subcutaneous). This should include the anatomic location of the vaccine application (Priority 1)
- 22 Gestational age (i.e., number of weeks mother was pregnant at time of each dose received [see GAIA preterm birth case definition for gestational age algorithm⁵]) (Priority 1)
- 23 Simultaneous administration of other vaccines, and their indication (e.g., mass immunization campaign, routine vaccine) (Priority 1)
- 24 The type of healthcare provider who has immunized the participant (e.g., physician, nurse, other) (Priority 2)

2.4. Follow-up monitoring data

This section defines data that should be collected and recorded for all vaccine trial participants.

- 25 Duration of follow-up to assess safety of vaccination in pregnancy should be predefined in the study protocol. The Working Group recommend that the minimal follow-up time period for safety of the mother is until 6 months after delivery or the early termination of pregnancy; the minimal follow-up time period for the infant is 1 year after birth (Priority 1). It is recognized that there are significant logistical challenges associated with follow-up of the infant until

⁵See case definition and guidelines at brightoncollaboration.org.

⁶The study protocol should specify the recommended dose, number of doses (if part of a series of immunizations against the same disease or condition), multi or mono-dose, pre-filled syringe and the construct and components of the vaccine including the number and type of antigens included in the vaccine, carrier(s), adjuvant (including adjuvant manufacturer) and preservatives used, as well as the device type (e.g., needle, spray, micro-needle patch).

1 year of age; where a shorter follow-up duration is pre-specified, there should be adequate justification for this, for example, based on biological characteristics of the vaccine, the vaccine-targeted disease or of the AEFI, including patterns identified in previous trials. There may also be reasons for extending safety follow-up further, based on the above factors, or the characteristics of the vaccine recipient (e.g., nutrition, underlying diseases such as immune-depressing illnesses and other pre-existing conditions), or the intention to assess child development and late-onset outcomes as part of the Risk Management Plan (which may require follow-up until 5 years of age or more).

- 26 Safety follow-up should include a symptom diary for a minimum of the first 7–14 days after each dose and regular follow-up contacts during the first year (Priority 1) (for example, follow-up at 1 month after each dose, at delivery, and at 2, 6 and 12 months, depending on the trial). Some or all of the follow-up may be in-person or through other contact (e.g., by telephone), depending on the trial. The first 2 weeks includes recording of solicited and unsolicited acute local and systemic AEFI. The follow-up contacts include recording of solicited and unsolicited systemic AEFI and any signs and symptoms indicative of vaccination failure.

2.4.1. Maternal data—This section defines data that should be collected and recorded after vaccination for all vaccine trial participants.

- 27 New-onset medical conditions, surgery required, and hospitalizations (Priority 1)
- 28 Nutritional status of the mother assessed by the most reliable, locally available methods including measurement of height and weight to establish BMI, or other validated nutritional indicators; this should be assessed in each trimester and at delivery (Priority 1)
- 29 Pregnancy monitoring: antenatal attendance, including routine tests to assess pregnancy and the fetus (e.g., tests for congenital anomalies, ultrasound, amniocentesis) (Priority 1)
- 30 Infections: results of any routine antenatal screening tests for infections (Priority 1). Additionally, the results of laboratory investigations for infections that may have impact on the immunogenicity, efficacy and safety of pregnancy vaccines or aid interpretation of events that occur in the mother, fetus, neonate or infant (Priority 1). These infections include, but are not limited to, human immunodeficiency virus (HIV) 1 and 2, malaria (where relevant), syphilis, tuberculosis (where relevant), Zika virus (where relevant) hepatitis B virus, rubella, hepatitis C virus, Group B streptococcus, toxoplasmosis, genital herpes simplex virus infections and other sexually transmitted infections (e.g., Chlamydia, gonococcus). Additionally, data on the target infection for specific vaccine studies will be required (Priority 1) (e.g., GBS colonization in subject participating in a GBS vaccine trial)

- 31 Other acute non-infectious medical conditions during the pregnancy (e.g., hematologic, including anemia, metabolic, endocrine, gynecological, rheumatological, cardiovascular, renal, gastrointestinal, pulmonary or neurological conditions and any other health condition of potential importance for the immunogenicity and safety of vaccines); this includes results of non-routine laboratory testing during pregnancy relevant to such medical conditions (Priority 1)
- 32 Medication history: medication received during pregnancy, including prescription and non-prescription drugs, immunobiological agents, herbal and homeopathic preparations and nutritional supplements [45]. A comprehensive list of known teratogens is available [47] (Priority 1)⁷
- 33 Vaccination history: any vaccines administered since study vaccination with date of administration (Priority 1)

2.4.2. Fetal data—This section defines data that should be collected and recorded on all vaccine trial participants.

- 34 Presence of fetal growth restriction⁸ (IUGR) (Priority 1)
- 35 Any congenital anomaly noted (e.g., by ultrasound or other tests [specify test]) (Priority 1)

2.4.3. Birth related and neonatal data—This section defines data that should be collected and recorded for all vaccine trial participants.

- 36 Specify the place of delivery including geographic location (e.g., city, country) and the setting (e.g., home, clinic, hospital) (Priority 1)
- 37 Specify the mode of delivery: normal spontaneous vaginal delivery, elective versus emergency (or semi-elective), cesarean section (Priority 1)
- 38 Specify presence and type of health care assistant at delivery: physician, midwife, other (Priority 2)
- 39 Specify length of first stage of labor, length of second stage of labor (Priority 2)
- 40 Specify date and time of rupture of membranes (Priority 2)
- 41 Specify date and time of birth (Priority 1)
- 42 Perinatal maternal laboratory tests as required to assess maternal safety (Priority 1)
- 43 Specify key findings of fetal monitoring during labor (Priority 2)
- 44 Any medical treatment given to the mother during delivery (e.g., antibiotic prophylaxis) (Priority 2)

⁷Note history of drug abuse, cigarette and alcohol use in pregnancy, and all exposures to potential teratogens that have occurred during pregnancy.

⁸See case definition and guidelines at brightoncollaboration.org.

- 45 Birth-related vitality status: live birth, stillbirth, neonatal death⁸ (Priority 1)
- 46 Specify singleton or multiple birth (Priority 1)
- 47 Need for resuscitation at birth (Priority 1)
- 48 APGAR Score: measured at 1, 5 and 10 minutes (Priority 1)
- 49 Birth weight, length and head circumference (Priority 1)
- 50 Specify abnormalities (e.g., SGA) (Priority 1)⁹
- 51 Sex: Male, female or indeterminate (Priority 1)
- 52 Gestational age: Total Maturity Score (confirmation by external physical characteristics [see GAIA preterm birth case definition for gestational age algorithm¹⁰]) (Priority 1)
- 53 Nutrition: The type of feeds (e.g., breast milk (mother/donor), formula feeding, parenteral nutrition, mixed feeding) and their respective start and stop times should be recorded in months of age (Priority 2)
- 54 Key findings on neonatal examination (Priority 1): General appearance (syndromic or normal), generalized dermatological signs, cardiovascular signs, respiratory signs, hematological signs, gastrointestinal signs, urogenital signs, musculoskeletal signs, neurological signs (including audiological test results), neurodevelopmental signs, ocular/visual signs, endocrine/metabolic signs.
- 55 Presence of congenital malformations or birth injuries¹¹ (Priority 1)
- 56 Presence of congenital or acute infection in the neonate¹² (Priority 1)
- 57 Any medical or surgical treatment given to the neonate (e.g., antibiotic treatment, exchange transfusion, intravenous flu-ids, steroids or other immunosuppressive therapies, herbal remedies (Priority 1)
- 58 Vaccinations (and specific dates) received by the neonate during the follow-up period (Priority 1)
- 59 Neonatal laboratory tests as indicated in the relevant protocol; should be reflective of the need for assessment of potential toxicities, and should include, at a minimum, full blood count, differential, transaminases, bilirubin, glucose, blood urea nitrogen and creatinine (Priority 1)

2.5. Data collection for AEFI (Priority 1)

The Working Group recommends referring to general Brighton Collaboration guidelines and template AEFI report forms [34,35]. Data collection should be in line with the general drug safety guidelines by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (<http://www.ich.org>) and

⁹See case definition and guidelines at brightoncollaboration.org.

¹⁰See case definition and guidelines at brightoncollaboration.org.

¹¹see case definition and guidelines at brightoncollaboration.org.

¹²see case definition and guidelines at brightoncollaboration.org.

the ethical standards in research and reporting requirements for drug adverse events by the Council for International Organizations of Medical Sciences (CIOMS, <http://www.cioms.ch>). Pertinent legally binding international and national guidelines as well as regulatory requirements need to be followed.

Internationally standardized terminology and case definitions for AEFI should be used for case verification and follow-up. The Working Group recognizes and emphasizes that AEFI may be temporally associated with, but not necessarily caused by, administration of a vaccine. The following guidelines outline requirements for collecting high-quality information on reported AEFI, without regard to whether there is a causal relationship to a prior immunization.

Causality assessment of individual AEFI reports should be based on verified and well-documented cases. For the causality assessment of AEFIs, investigators should consider biological plausibility of adverse events based on safety data from pre-clinical toxicology studies, as well as experiences with prior maternal vaccine trials and where applicable post-licensure safety data for other maternal vaccines [48]. Widely accepted causality assessment algorithms should be pre-specified and followed for reporting purposes [48]. The Working Group recognizes and recommends that causality assessment may also be done by (comparative) quantitative analytic methods (e.g., time series) during the trial and should be performed for AEFI regardless of individual report causality assessment by investigators [48].

2.5.1. Specific data collection for maternal AEFI—This section applies to the mother and is in addition to the data collected and recorded for all mothers in Section 2.4.1.

For local adverse events, refer to Brighton Collaboration case definition for data collection for a local reaction at or near the injection site [49]. For systemic adverse events, refer to relevant Brighton Collaboration case definitions for appropriate guidance on data collection [43]. For adverse events that might constitute a clinical vaccination failure, refer to the CIOMS case definition [50] for additional guidance on data collection.

- 60** Criteria fulfilled to meet a case definition and other signs or symptoms indicative of solicited and unsolicited AEFI
- 61** Detailed clinical description of the event, including the quality of symptoms (e.g., type of pain)
- 62** Date and time of: onset, first observation, diagnosis, end of an episode and final outcome
- 63** Concurrent signs, symptoms, and diseases other than the event described
- 64** Recurrence of event after initial AEFI
- 65** Onset or occurrence of similar event prior to immunization
- 66** Values and units of routinely measured parameters (cm, °C, etc.) - in particular, those indicating the severity of the event

- 67 Method of measurement (e.g., type of thermometer, oral or other specific route, duration of measurement)
- 68 Results of laboratory examinations, surgical and/or pathological findings and diagnoses
- 69 Treatment given for the AEFI (i.e., systemic and/or local site treatment)
- 70 Outcome at last observation of each AEFI should be clearly described (e.g., recovery to pre-immunization health status, spontaneous resolution, therapeutic intervention, persistence of the event, sequelae, death, or description of any other outcome)
- 71 Medical review of the event (i.e., patient seen by physician)
- 72 Presence or absence of concurrent local disease outbreaks or environmental exposures pertinent to the AEFI
- 73 Further doses given and the outcome (i.e., re-vaccination)

2.5.2. Specific data collection for AEFI in fetus / neonate / infant born to a vaccinated mother—This section applies to the fetus and neonate / infant born to a mother vaccinated in pregnancy and is in addition to the data collected and recorded, as specified, in Sections 2.4.2 and 2.4.3. Refer to relevant Brighton Collaboration case definitions for appropriate guidance on data collection [43]. For adverse events that might constitute a clinical vaccination failure refer to general guidelines [50] for additional guidance on data collection.

- 74 Criteria fulfilled to meet a case definition and other signs or symptoms indicative of an AEFI
- 75 Detailed clinical description of the event including the quality of symptoms
- 76 Date and time of: onset, first observation, diagnosis, end of an episode and final outcome
- 77 Concurrent signs, symptoms, and diseases other than the event described
- 78 Values and units of routinely measured parameters (cm, °C, etc.) - in particular those indicating the severity of the event
- 79 Method of measurement (e.g., type of thermometer, oral or other specific route, duration of measurement)
- 80 Results of laboratory examinations, surgical and/or pathological findings and diagnoses
- 81 Treatment given for the AEFI (i.e., systemic and/or local site treatment)
- 82 Outcome at last observation of each AEFI should be clearly described (e.g., recovery to pre-immunization health status, spontaneous resolution, therapeutic intervention, persistence of the event, sequelae, death, or description of any other outcome)

- 83 Medical review of the event (i.e., patient seen by physician)
- 84 Presence or absence of concurrent local disease outbreaks or relevant environmental exposures

2.5.3. Duration of follow-up after an AEFI in vaccinated mother and neonate / infant born to a vaccinated mother

- 85 The duration of follow-up for AEFI should be predefined in the protocol
- 86 Follow-up of reported events should be sufficient to attempt to verify and complete the collection of information as outlined in the relevant sections. In particular, for all cases at any level of diagnostic certainty and for reported events with insufficient evidence, all signs and symptoms indicative of the respective AEFI should be recorded

2.6. Data analysis

See Section 2.2 of the “Guidelines for collection, analysis and presentation of vaccine safety data in pre- and post-licensure clinical studies” [34].

- 87 Reported safety outcomes could be classified in one of the following categories. Events that meet the AEFI case definition should be classified according to the levels of diagnostic certainty, as specified in the relevant case definition, using Brighton Collaboration definitions if available. Events that do not meet the case definition at any of the levels of diagnostic certainty to make the diagnosis of a given AEFI could be classified in the additional categories for analysis.

Event classification

Event meets the case definitions (Main categories)

1. Level 1 of diagnostic certainty
2. Level 2 of diagnostic certainty
3. Level 3 of diagnostic certainty Event does not meet the case definition (Additional categories for data analysis)
4. Reported [AEFI] with insufficient evidence to meet the case definition
5. Not an event of [AEFI]

- 88 The interval between immunization and an AEFI should be specified by using the date/time of immunization and either the date/time of onset or first observation or diagnosis, whichever is most appropriate for the AEFI. Whatever dates are used, they should be used consistently within and across study groups
- 89 The duration of an AEFI, if applicable, should be analyzed as the interval between date/time of onset or first observation or diagnosis and the end of episode or final outcome. Whatever start and ending dates are used, they should be used consistently within and across study groups

- 90 If a given AEFI occurs intermittently, the event corresponding to the greatest magnitude of adverse event should be used as the basis for categorization. Also, the frequency and pattern of re-occurrence (e.g., periodicity) should be analyzed
- 91 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 during AEFI). Analysis may also include other characteristics like qualitative patterns of criteria defining the event (e.g., periodicity, frequency, fever-days.
- 92 The distribution of data (as numerator and denominator data) should be analyzed in predefined increments (e.g., measured values, times), where applicable. When the number of cases reported is too small for stratification, the respective values or time course should be described for each case
- 93 AEFI should be analyzed by study arm and dose
- 94 Results obtained in subjects receiving a vaccine under study ideally should be compared with those obtained from appropriately selected and documented control groups

2.7. Data presentation

See also Section 2.3 of the “Guidelines for collection, analysis and presentation of vaccine safety data in pre- and post-licensure clinical studies” [34].

The following guidelines represent a desirable standard for presentation or publication of analyzed AEFI data to allow comparability in vaccine safety. They are not guidelines for primary reporting of AEFI to a study monitor. Additional information collected and analyzed may be presented depending on the study question and setting. It is recommended to also refer to existing guidelines, including CONSORT (Consolidated standards of reporting trials), QUORUM (Improving the quality of reports of meta-analyses of randomized controlled trials), TREND (Transparent reporting of evaluations with non-randomized designs), STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) and MOOSE (Meta-analysis of observational studies in epidemiology) for presentation and publication of randomized, controlled trials, meta-analyses, non-randomized designs, observational studies, and systematic reviews of vaccine safety studies, respectively [51–55].

- 95 Terms to describe an AEFI, such as “low-grade”, “mild”, “moderate”, “high”, “severe” or “significant”, are highly subjective, prone to wide interpretation, and should be avoided unless validated or clearly defined
- 96 Safety data should be presented with numerator and denominator (and not only in percentages or graphical illustrations) and by lot or vaccine, if applicable
- 97 If the median and range are the appropriate statistical descriptors, and the distribution of data is skewed, then the mean and standard deviation should also be provided to permit meta-analysis

- 98 The incidence of events meeting the case definition should be presented and clearly identified as such in the text
- 99 Any publication of AEFI data should include as detailed as possible a description of the methods used for data collection and analysis. It is essential to specify:
- the study design;
 - the study group(s) including comparison group(s); e.g., cumulative incidence rate: 10 cases of a given AEFI among 1 million doses administered; or incidence rates: 3 cases of a given AEFI on day 1, 2 cases on day 2, 10 cases on day 3 following immunization, or 0 cases after the first dose, 1 case after the second dose, 10 cases after the third dose;
 - the instrument of data collection (e.g., standardized questionnaire, diary card);
 - the method, frequency, and duration of monitoring for AEFI;
 - whether the day of immunization was considered “day one” or “day zero” in the analysis;
 - whether the date of onset and/or the date of first observation and/or the date of diagnosis, and the end of episode and/or final outcome were used for analysis;
 - the data analysis plan per protocol, and the statistical plan; and any amendments to these sections of the protocol added during the study;
 - the trial profile, indicating participant flow during a study, including drop-outs and withdrawals to indicate the size and nature of the respective groups under investigation;
 - Reference of the AEFI case definition used (Brighton or other) for AEFI in the abstract or methods section of a publication.

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Appendix A. Supplementary material

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