WHO Meeting to Develop Brighton Collaboration Definitions of Key Terms Used for Monitoring the Safety of Immunization in Pregnancy in Mothers and Newborn Children

WHO Headquarters, Geneva, Switzerland, 24-25 July 2014

Executive Summary

The WHO Initiative for Vaccine Research held a consultation to facilitate harmonization of key events for monitoring vaccine safety in pregnant women and newborn children. The meeting was held jointly with the Brighton Collaboration, and participants included a multidisciplinary group with expertise in vaccine safety, immunization during pregnancy, epidemiology, paediatric and obstetrical infectious diseases, vaccine clinical trials and vaccine regulation. Observers included representatives from the pharmaceutical industry. Multidisciplinary stakeholder groups from WHO also contributed to the meeting as Secretariat. The specific meeting objectives were to review existing case definitions and guidance documents to prioritize key terms for continuous monitoring of immunization safety in pregnancy. This interim set of key terms and any other terms identified during the meeting would undergo further revision by the Brighton Collaboration after the meeting. Additional meeting goals were to develop interim case definitions for these key terms and to recommend next steps towards harmonized data collection and well informed data interpretation.

Participants discussed key terms proposed by WHO consultants. These key terms were chosen for discussion based on four criteria: (1) frequency – incidence and reporting rate of events, (2) severity of health outcome, (3) public health relevance – including potential impact and also concern in low- and middle-income countries, and (4) measurability in different settings. Using existing definitions and descriptions, consultants proposed and reached consensus on several key terms supporting the use of interim case definitions. Among 23 Fetal/Neonatal terms selected for discussion during the meeting, 13 were considered to be priority outcomes, 9 were considered as outcomes, and 2 were considered enabling terms. A total of 16 Maternal/Pregnancy terms were discussed during the meeting, of which 10 were considered to be priority outcomes, 2 were considered outcomes, and 4 were considered enabling terms. In total, 39 events were discussed, of which 23 were considered priority outcomes, 11 additional outcomes, and 6 enabling terms.

In the final session, the group proposed several obstetric and neonatal key terms which need further harmonization and definition development. Finally, the “way forward” was outlined and generally agreed upon. Brighton Collaboration will proceed to take the key terms through further harmonization processes and consensus building. As these terms may be revised through subsequent Brighton Collaboration processes, the terms will be maintained and regularly updated on the Brighton Collaboration website at http://brightoncollaboration.org/public/resources/standards/case-definitions/pregnancy.html.
Session 1: Introduction, Background and Procedures

Joachim Hombach, WHO Initiative for Vaccine Research (WHO/IVR), opened the meeting by explaining WHO’s overall mandate to remove obstacles to implementing maternal influenza immunization as requested by its Strategic Advisory Group of Experts. He also described the meeting rationale to harmonize key events of special interest for evaluation of vaccine safety in pregnancy and newborn children.

Justin Ortiz (WHO/IVR) read out all declared interests reported by meeting participants and explained the objectives and procedures of the meeting:

- To review existing case definitions and guidance documents
- To prioritize events of special interest for continuous monitoring of immunization safety in pregnancy
- To develop interim case definitions for these events
- To recommend a core data set of key terms of events to be collected when monitoring the safety of immunization in pregnancy

The aim of developing an interim set of standardized key terms was to inform vaccine safety monitoring both in clinical studies and post-licensure surveillance. The terms and definitions are not developed to guide diagnosis or treatment of patients or other aspects of clinical care. Neither are they developed to determine severity or causality, nor to redefine outcomes for non-vaccine clinical epidemiologic studies. The meeting expected outcomes were:

- Consensus list of interim key terms to define events of interest
- Interim set of consensus definitions
- Consensus set of data to be collected
- List of areas where consensus remains to be built

The key terms would be further revised by the Brighton Collaboration through its standard procedures after the meeting.

Patrick Zuber, WHO Safety and Vigilance (WHI/SAV), described the Global Vaccine Safety Initiative (GVSI) and the work that has been done within GVSI concerning maternal immunization. He explained the Global Vaccine Safety Blueprint, the strategic plan of the GVSI for strengthening vaccine safety activities globally through the coordinated efforts of major stakeholders. The major objectives of the strategic plan are the following:

- To assist low and middle income countries (LMIC) to have at least minimal capacity for vaccine safety activities
- To enhance capacity for vaccine safety assessment in countries that introduce newly-developed vaccines, that introduce vaccines in settings with novel characteristics, or that both manufacture and use prequalified vaccines
- To establish a global vaccine safety support structure.

He emphasized the global need for harmonized definitions for adverse events (AEs).

Jan Bonhoeffer (Brighton Collaboration Foundation and Meeting Chairperson) highlighted the timeliness of the meeting and explained that it addresses an urgent need to harmonize the definitions of key terms to monitor the safety of immunization in pregnancy. He explained the mission of the Brighton Collaboration to enhance the science of vaccine research by providing standardized, validated, and objective methods for monitoring safety profiles and benefit-risk ratios of vaccines. The development of standardized case definitions and guidance documents promotes a shared understanding, common language, and data comparability within and across studies, sites, and vaccines. Case definitions are intended to be applicable to clinical trials, observational studies, spontaneous reporting, and in different geographic and cultural settings -- with specific attention to LMIC. Case definitions are developed primarily for use at the data analysis stage. They may, however, be used to inform data collection indirectly in studies and surveillance.

Mirjana Nesin (US National Institutes of Health) presented the US National Institutes of Health Division of Microbiology and Infectious Diseases (NIH/DMID) toxicity tables for grading and reporting adverse events (AEs) in clinical trials enrolling pregnant women. At NIH, when studies in pregnant women began 20-30 years ago, AE reporting and definitions were not consistent. For this reason NIH is establishing standardized definitions. The process began in 2011 and has continued to the present. The process endeavoured to achieve agreement on high level (not detailed) case definitions, grade events on degree of toxicity, and harmonize case definitions. Four working groups published three papers in Vaccine in 2013; six more manuscripts will be published in a Clinical Infectious Diseases supplement in 2014. As a result of this work, tools were developed which can help to improve protocol design. Definitions can be applicable in different settings, but the focus of this effort is high-resource settings and on healthy women. Nesin said the NIH work was complementary to the work being discussed in this meeting, but different in scope.

Steven Hirschfield, (US Public Health Service, National Institute of Child Health and Human Development), gave a talk via teleconference entitled “Child Health Research Terminology: Experience of the Eunice Kennedy Shriver National Institute of Child Health and Human Development”. His group began a terminology harmonization initiative several years ago. He said that current complex medical terminology has general deficiencies for child health. National Institute of Child Health and Human Development has attempted to harmonize systems and has coordinated terminology working groups. He explained the methodology and the approach to adoption and dissemination. In summary, he said that a harmonized child health-oriented terminology with international participation is under development. Important factors in this process include the consistency of concepts and terms, as well as a greater precision analysis. As such, the terminology should be precise, uniform, consistent,
sustainable, and should include tools/training for its implementation. Challenges identified in this process include: cultural challenges of adjusting and demonstrating the need to adopt updated terminology, the need to prepare training tools, and implementation.

Next, Philipp Lambach (WHO/IVR) gave an overview of WHO’s preparatory activities for this meeting. These include undertaking systematic literature reviews of AEs during pregnancy and the newborn period, developing a stakeholder survey identifying institutions and key terms used in AE surveillance, and supporting Brighton Collaboration Taskforces to develop an interim set of key events for monitoring. He further outlined the planned process to develop a set of interim key terms at the meeting.

Mark Katz (WHO/IVR Consultant) explained a stakeholder survey. In all, 446 individuals were contacted by WHO, and 500 individuals were contacted through Brighton Collaboration, together comprising over 400 institutions. Individuals were asked whether they were using case definitions for adverse events following immunization (AEFI) in studies or surveillance systems, and, if so, what case definitions were being used. Overall, 41% of individuals and 40% of institutions responded. There were responders from all WHO regions. Responders included obstetric and gynaecologic societies, paediatric societies, research groups, pregnancy registries, government agencies, regulatory authorities, public health institutes, vaccine manufacturers and other international organizations. All responses were collected, collated, and analysed.

Saad Omer (Emory University) presented a systematic review of definitions for AEFI during pregnancy and the newborn period. In the final review, 74 papers were included. Most studies were related to influenza vaccine, followed by Tdap and yellow fever vaccines. In all, 74 unique case definitions were identified describing 35 AEs. The majority of AEs monitored in published studies lacked case definitions. Overall, 25 of 74 studies did not provide any AE definition, and few definitions included severity strata. The most common AEs included miscarriage, spontaneous abortion, preterm birth, and still birth. The main finding of the systematic literature review was the heterogeneity of outcome definitions, safety assessment methods, and data collection methods, as well as the lack of reporting consistency of safety data within and across studies.

Omer suggested the following recommendations:

1. Case definitions should be of sufficient detail and consistency of language to avoid ambiguity
2. Frequency analysis may inform standardization efforts where multiple case definitions for a given AE are available
3. Efforts should be made to encourage:
   a. Consistent reporting in the methods section of AE definitions used or specific classifications by schemes or codes
   b. Consistent reporting in results of all AEs defined
4. Standardized definitions and shared guidance for collection, analysis, and presentation of safety data for prospective and retrospective studies should be developed for
monitoring the safety of immunization in pregnancy studies and programs surveillance

WHO/IVR obstetric and paediatric consultants, Linda Eckert (University of Washington) and Flor Munoz (Baylor College of Medicine), explained the procedures of the Brighton Collaboration Maternal and Neonatal Taskforces. The Taskforces developed a landscape analysis and harmonization process to produce interim definitions of key terms for paediatric and obstetric outcomes for vaccine safety surveillance. WHO and the Taskforces worked for over four months to identify sources with information relevant to the assessment of safety of vaccines during pregnancy. They reviewed material from all the identified sources, including material obtained through the landscape analysis, literature reviews, ongoing clinical trials, and research protocols. Some important sources of data included the Brighton Collaboration draft document on safety of vaccines in pregnancy, WHO documents addressing immunization during pregnancy and global surveillance on adverse events following immunization, the National Children Study, the National Institutes of Health, the Global Alliance on Prevention of Prematurity (GAPPS), the International Classification of Diseases (ICD-9, ICD-10), CTCAE, MedDRA and other terminology databases, pregnancy and congenital anomaly registries, vaccine safety and pharmacovigilance surveillance systems, vaccine safety surveillance programs, investigators of current and planned clinical trials, and the pharmaceutical industry.

Key terms were selected based on frequency, severity, public health relevance, public concern, measurability, and comparability. Documents were developed with tables that included key terms, synonyms of those terms, concept definitions (simple, common definitions), and descriptive definitions (detailed definitions, including assessment guidelines based on available resources). Key terms were classified according to five categories as they related to:

1) Maternal Health
2) Pregnancy
3) Delivery/Labour/Postpartum period
4) Fetal
5) Neonatal

Eckert and Munoz identified key terms and definitions for discussion in the deliberative sessions of the meeting. Selection of the terms was based on their relevance for the assessment of safety of vaccines during pregnancy. The goals of the discussion were to agree on the inclusion/exclusion of the key terms; suggest terms/synonyms for inclusion; agree on concept definitions; and present a detailed description of term diagnostic criteria for discussion as needed. The detailed description of the terms will be utilized in the development of future Brighton Collaboration definitions. At the end of the deliberative sessions, participants would be asked to determine if the terms selected were considered priority outcomes, non-priority outcomes, or enabling terms useful in the overall assessment of vaccine safety.
Sessions 2 and 3: Maternal and Neonatal Deliberative Session

Munoz and Eckert led the discussion of the selected key terms. The Brighton Collaboration Taskforces and meeting participants prioritized the key terms based on the following four criteria:

1. Frequency (incidence rate of events and reporting rate of events)
2. Severity (severity of individual health outcome)
3. Public health relevance (potential public health impact and potential for concern in LMIC)
4. “Measurability” in different settings

It was highlighted that consensus formation on concepts and definitions should consider existing descriptions and definitions and should allow for comparability to and merging with existing data. The value of backward comparability was acknowledged. However, it was agreed that priority should be a forward looking approach, considering that this is an emerging field of research and program monitoring and cyclical revision of definitions is likely to occur. This general approach was adopted by the plenary, and discussion of each term concluded with a consensus decision about whether the term should be included as a key term, and, if so, what the interim case definition should be.

Fetal and Neonatal Events:
A total of 62 terms were identified by the Neonatal Taskforce for potential discussion. Among these, a total of 23 terms were selected for discussion during the meeting, of which 13 were considered to be priority outcomes, 9 were considered as non-priority outcomes, and 2 were considered enabling terms (terms that assist in the assessment of safety or of other priority events).

Maternal Health, Pregnancy, Delivery and Postpartum Period Events:
A total of 45 terms were identified by the Obstetric Taskforce for potential discussion. Among these, a total of 16 terms were discussed during the meeting, of which 10 were considered to be priority outcomes, 2 were considered outcomes, and 4 were considered enabling terms.

In total, 39 events were discussed, of which 23 were considered priority outcomes, 11 outcomes, and 6 enabling terms. The list of events by priority category is included in Appendix A.

Session 4: Key Terms – Additional Discussion

Munoz and Eckert asked the group for suggestions about other key terms and adverse events that should be considered. Responses included the following:

- Pregnancies: molar and ectopic pregnancies, antepartum bleeding, threatened abortion
- Uterus, placenta and chorion: chorioamnionitis, uterine rupture
- Maternal: anaemia in pregnancy
- Maternal or neonatal: cardiomyopathy, seizures and neurological disorders respiratory distress, purpura, auto-immune disorders
- Laboratory parameters: liver function parameters; kidney function
- Neonatal: failure to thrive, jaundice, apnoea/bradycardia
• Postpartum, lactation: mastitis, lactation, postpartum infections
• Long term/late events: autism, developmental delay, allergies/hyper-sensitivities
• Special populations: HIV-positive women (e.g. CD4 count)

It was noted that most of these terms were included in the list of terms selected by the Obstetric and Neonatal Taskforces, but were not discussed during the meeting due to time constraints. These terms would be further reviewed for inclusion in future efforts by Brighton Collaboration.

**Session 4: Conclusions and Way Forward**

Bonhoeffer invited participants to propose next important steps in follow-up to the meeting. The following recommendations were generally agreed on:

1. The phrase “key terms” could be used rather than “adverse events” or “events of special interest” given their respective regulatory implications.
2. There is a need for standardized case definitions for an exhaustive set of events. Until these become available, interim definitions should be made available and shared for widest possible use.
3. Brighton Collaboration was the open global platform and mechanism to lead efforts of definition standardization given their previous work on standardizing case definitions at international level and their expertise on consensus building.
4. An overall evaluation framework should be developed:
   a. A public consultation should be implemented for review and feedback on the outputs of the meeting.
   b. Interim case definitions should be evaluated at least regarding usefulness, applicability, and reduction of inter-rater variability.
   c. Implementation in simple observational studies (e.g., incidence rate studies) should be pursued and to allow for assessment of applicability and positive predictive values of the definitions and usefulness of terminologies, guidance and tools.
   d. Case definitions could be incorporated into NIH toxicity tables and tested in clinical trials.
5. Tools should be developed to facilitate implementation at various levels and may include:
   a. A data collection tool, such as a case report form/data collection list.
   b. A glossary of enabling terms.
   c. Ontologies of the terms, keeping multilingual data collection in mind.
   d. Disease code mapping for key events should be performed to support case identification.
6. There is a need for guidance(s) for harmonized collection, analysis, and presentation of data in prospective and retrospective data ascertainment.
7. Guidelines should be shared with various stakeholder groups for review and comment
   a. This should be done as part of focused stakeholder consultations.
   b. The Council for International Organizations of Medical Sciences (CIOMS) is considering the establishment of a dedicated working group on immunization in pregnancy which may review and potentially recommend the use of standardized case definitions, guidelines, and tools. The existing CIOMS vaccine pharmacovigilance working group may be able to include the topic with review of the Brighton Collaboration case definitions in their next work plan starting 2017.
8. Population-based health care data sources should be identified and incidence rates of key outcomes should be determined (even if outcome definitions differ from those developed by this group) with a particular focus on LMIC while using advanced databases as benchmarks.

9. The utility of identified databases in LMIC for observational studies including incidence rate, signal substantiation, and hypothesis testing studies should be assessed.

10. Ideally, background rates of key events should be established that are country-specific or site-specific while using common definitions. In practice, this is limited by lack of resources and capacity constraints.

11. Optimal models for conducting post-licensure association studies in LMIC should be assessed including comparison of data collection methods, approaches to meta-analysis and pooling, and performance evaluation of comparative analytic methods to inform interpretation of results from real concerns.

12. Dissemination strategies should be considered
   a. The meeting report should be circulated to all participants and for dissemination to their respective institutions
   b. Participants should raise awareness of this and subsequent efforts within their institutions and professional networks
   c. The two Taskforces should finalize work and publish concepts
   d. Brighton Collaboration should make the terms, disease concepts, interim case definitions, guidance, and tools via a dedicated resource platform at its website for immediate use by interested parties.
   e. Funders should be informed about this ongoing process so that they can inform their investigators about the process and availability of interim case definitions.

13. The Global Advisory Committee on Vaccine Safety is WHO’s principle advisory body on vaccine safety issues. The committee acknowledged the development of global standards for vaccine safety monitoring by the current initiative. Their further endorsement will be critical for acceptance and sustainability of any recommended guidelines and standards.

Justin Ortiz thanked all participants and observers for their involvement in the meeting. He asked the observers to exit the room and then asked remaining meeting participants whether they felt decisions were made with undue influence by observers to the meeting. No participant responded that he or she felt influenced by meeting observers. Ortiz then closed the meeting.
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Appendix
Key Terms Prioritization and Concept Definitions

FETAL AND NEONATAL EVENTS KEY TERMS/CONCEPT DEFINITIONS

Updated terms can be found at the Brighton Collaboration website: