Stakeholders Meeting on Maternal Interventions Vigilance: Safety Monitoring and Surveillance in Vaccine and other Research Settings

20-21 November 2017
Domaine de Penthes
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Background

There is increasing evidence that maternal immunization has the potential to improve health outcomes for both mothers and their babies. As a number of promising vaccines are in the process of development, there is need to ensure that mechanisms are in place for appropriate safety monitoring. The Stakeholders Meeting on Maternal Interventions Vigilance was organized by the World Health Organization (WHO) to assess current vigilance methods for maternal immunization and other interventions in pregnancy and to propose a roadmap for harmonization of vigilance across programmes.

In background information for the meeting, WHO noted that safety monitoring of vaccines administered during pregnancy will require “enhanced vigilance mechanisms and standardized case definitions of key events in pregnant women and newborns”. However, there are numerous medical interventions during pregnancy and early childhood, requiring that immunization and safety monitoring of vaccines should be harmonized with a range of methods by a range of stakeholders.

The Stakeholders Meeting on Maternal Interventions Vigilance was convened as a result of collaboration between four technical departments of WHO (Immunization, Vaccines and Biologicals; Essential Medicines and Health Products; Reproductive Health and Research; and Maternal, Newborn, Child and Adolescent Health). Those core organizers were also guided by advice from a further six WHO departments, covering all health issues relating to pregnancy and newborn health. 1

Specifically, the meeting set out to:

- review current methods or methodologies to monitor outcomes of maternal immunization and other interventions, with a particular focus on pharmacovigilance;
- assess these vigilance methodologies and identify where harmonization is needed;
- assess their global applicability for maternal immunization and other interventions;
- propose coordination mechanisms and a roadmap to support their harmonization across programmes and partners working on improving pregnancy and early childhood health outcomes.

Opening

Dr Patrick Zuber, Dr Elizabeth Mason

Dr Zuber welcomed participants to Geneva and introduced the two-day agenda which was accepted without discussion. The agenda of the meeting is contained in Annex 1. Participants then introduced themselves around the room. The list of participants is contained in Annex 2. Dr Zuber then introduced the Chair of the meeting, Dr Elizabeth Mason.

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1 The 10 departments involved were, in alphabetical order: Essential Medicines and Health Products (EMP); Global Malaria Programme (GMP); Global TB programme (GTB); HIV/AIDS (HIV); Information, Evidence and Research (IER); Immunization, Vaccines and Biologicals (IVB); Maternal, Newborn, Child and Adolescent Health (MCA); Nutrition for Health and Development (NHD); Reproductive Health and Research (RHR); and the Special Programme for Research and Training in Tropical Diseases (TDR).
The Chair formally opened the meeting, noting that it was timely in view of the advances being made to facilitate and implement maternal immunization for prevention of a number of conditions. Recent examples, as in the case of the outbreak of Zika virus disease in the Americas, highlighted the need for new effective interventions of which safe vaccines could be a key part. The Chair called for a fruitful discussion that would result in defining coordination mechanisms that will be further developed to ensure harmonized methodologies for vigilance and outcome monitoring to improve both maternal and newborn health.

Introductory session

Need for harmonized vigilance approaches for pregnancy interventions and recent initiatives – a partner’s perspective

Dr Sonali Kochhar

Pregnancy is a time of increased health vulnerability for both women and fetuses and therefore the safety of interventions during that period is a paramount consideration. Many interventions are currently made during pregnancy, and those interventions and the tools used to monitor their safety vary around the world, making it impossible to compare data. For instance, different terms and codes are used in health-care records. Clinical and investigative practices also vary according to local economic status and social norms, complicating availability of and access to important data. Consequently, vigilance approaches for all pregnancy interventions (including those related to vaccines) should be harmonized.

If new maternal vaccines are introduced, there will be a need for appropriate active safety surveillance systems, which currently do not exist in many countries. Various initiatives exist to help harmonize vigilance approaches related to pregnancy interventions, including the Brighton Collaboration (BC) process which uses a standard format for case definitions to determine diagnostic certainty. The BC case definitions have been recommended by WHO, United States Centers for Disease Control and Prevention (CDC), FDA and EMA etc. Following the 2014 WHO international conference on standardization of key terms for maternal immunisation (MI), the Global Alignment of Immunization Safety Assessment in Pregnancy (GAIA) project was formed to develop standards and tools for MI and Maternal and Child Health (MCH) harmonized vigilance with a specific focus on LMIC needs. GAIA uses the BC process and has developed 21 case definitions for key obstetric and neonatal outcomes, enabling terms (e.g. gestational age assessment algorithm), guideline for collection, analysis and presentation of safety data in clinical trials of MI, map of disease codes across terminologies e.g. MedDRA, ICD10, SNOMed, NCI, NLM (UMLS) codes and an online tool for automated case classification (single or batch classification). These are all globally applicable. The GAIA definitions are being used in clinical studies, epidemiological studies to assess background rates of events, AEFI surveillance, pregnancy registries and maternal and perinatal birth outcomes assessments. They can be used for monitoring not only maternal immunization but also other maternal and child health programmes.

The International Society for Pharmacoepidemiology (ISPE) vaccine special interest MI Group project assessed the use of health facilities to diagnose obstetric and neonatal outcomes in LMIC. The study, conducted in 65 villages 120 kilometres from Kampala (Uganda) has shown that some GAIA definitions could be used even in settings with very limited resources. Additionally, the Immunising Pregnant women and Infants Network (IMPRINT) is working to tackle key challenges for use of vaccines in pregnancy and new-borns. One of the grants is to evaluate the field performance and validate some GAIA case definitions and enabling term to harmonize safety monitoring for MI in LMIC. Several initiatives for harmonized vigilance are ongoing and speed, quality and implementability in HIC and LMICs is of essence. Progress is constrained by funding and logistics.
Integration and coordination of pregnancy interventions with existing Maternal Neonate Child Health (MNCH) services and surveillance will strengthen existing programs, leverage infrastructure, and minimize disruption of routine MNCH services

Discussion:
Support was expressed by participants for harmonization of surveillance definitions and methods related to pregnancy interventions. It was pointed out that passive surveillance systems are not designed to measure adverse events in pregnancy; rather, active surveillance systems need to be added to the routine controls during pregnancy. There was also an explanation that the Brighton definitions were developed specifically to achieve diagnostic certainty and not for causality assessment. Before applying any definitions it would be important to understand the use they were created for.

Maternal immunization safety monitoring in low- and middle-income countries: a roadmap for programme development
Dr Eve Lackritz

Global efforts are underway to develop, evaluate, and implement new vaccines targets for use in pregnant women, particularly in low- and middle-income countries (LMIC) where burden of disease is the greatest. Maternal immunizations are developed to establish protective immunity in pregnant women and transfer protective immunity to the fetus and young infant, protecting infants during a vulnerable period prior to infant immunization. As these efforts move forward, systems are needed that can monitor the effectiveness of vaccines and identify, evaluate and respond to potential adverse events following immunization (AEFI) among both pregnant women and their offspring. These systems may be difficult to implement in LMICs, where surveillance for complications of pregnancy and adverse birth outcomes, and regulatory systems, may be lacking.

The Global Alliance to Prevent Prematurity and Stillbirth (GAPPS) and a coalition of technical experts conducted a landscape review, funded by the Bill & Melinda Gates Foundation, to evaluate systems in LMICs for tracking outcomes in mothers and their offspring. Based on input from a large, multidisciplinary group of experts and a stakeholders’ meeting, a report was developed that outlined a strategy for development pharmacovigilance systems to monitor safety of pregnant women and infants in LMICs, building on current infrastructure and addressing critical gaps. It also reviewed monitoring systems for maternal and child health programmes and strategies for monitoring adverse events in both mothers and infants over time.

The report identified a number of priority recommendations and an implementation plan. A complex array of organizations and national government entities has made important contributions and commitments to monitoring health of pregnant women and newborns, and safety and effectiveness of maternal immunizations. If harnessed, coordinated, and strengthened, a coherent strategy would have an important impact on safety monitoring in pregnant women and newborns. Areas of emphasis included enhanced methods for monitoring outcomes of pregnant women and newborns, as well as strategies for strengthening pharmacovigilance systems specifically for vaccine use in pregnancy. Strategies were highlighted whereby existing maternal, newborn and child health (MNCH) surveillance systems could be leveraged and strengthened, such as those for birth defects and civil registration, and identify priority variables that should be tracked. Pregnant women and their offspring are a vulnerable population and have been excluded from research. Excluding pregnant women from research has resulted in significant unintended consequences, leaving the field of obstetrics lacking evidence-based strategies to protect the health of pregnant women and data to assess the safety and efficacy of vaccines and medications in this population.
Discussion:
There was general support for strengthening MNCH surveillance and sentinel surveys, in addition to strengthening pharmacovigilance systems in LMICs. Ideally these efforts could be advanced together as part of the same system. The question of benefit and risk was raised because data on both are needed to assess the potential of a vaccine or medical intervention. It was pointed out as an example that, for pertussis, many countries do not have accurate incidence rates of infection, making it difficult to assess risk and benefit of a vaccine. In addition, data on concomitant drug use, environmental exposure, and comorbidities are not collected in a systematic way, making it difficult to accurately investigate causation of an AEFI. Improved integration of research and MNCH programs is needed to strengthen evidence-based healthcare practices, monitor safety of drugs and vaccines, and enhance overall monitoring of health threats to pregnant women, the fetus, and newborns.

Monitoring of maternal and early childhood outcomes

WHO landscape of monitoring outcomes of pregnancy
Dr Allisyn Moran

Monitoring pregnancy outcomes is important for clinical interventions and surveillance as well as vigilance for health products. Even so, there are limited amounts of data on pregnancy outcomes from both areas, with challenges around complete birth registration, misclassification of mortality and morbidity, systematic analysis, clear definitions, assessment and measurement methodology, and the variability of collected information. Currently, 14 groups from 10 different WHO departments are working on various aspects of pregnancy outcomes. The Maternal, Child and Adolescent Health and the Reproductive Health Research Departments have collaborated to produce a series of documents in collaboration with partners. The “Every Newborn Action Plan” (ENAP) and Ending Preventable Maternal Mortality (EPMM) outline the importance of collecting data regarding outcomes related to maternal and newborn survival and well-being. In addition, there are guidance documents on Maternal Death Surveillance and Response and perinatal audit and response, which emphasize the importance of tracking maternal and perinatal mortality, diagnosing the cause of death, and using the information to improve the quality of care. In the independent Expert Review Group (iERG) report, monitoring for action is a conceptual framework stressing the need for leadership, resources and strengthening institutions to improve monitoring of maternal and child and adolescent outcomes. There is ongoing work on tracking maternal morbidity using clear definitions and standard tools. Another initiative is the Indicator Framework for the Global Strategy for Women’s, Children’s and Adolescent’s Health 2016-203, which defines indicators for monitoring maternal, child and adolescent outcomes. The WHO Department of Information, Evidence and Research developed the International Classification of Diseases for Maternal Mortality (ICD-MM) which provides the codes for all deaths during pregnancy, childbirth, and the puerperium in collaboration with the Reproductive Health Research Department. MCA and RHR have collaborated on the International Classification of Disease for Perinatal Mortality (ICD-PM), which provides standards code for perinatal deaths. The WHO Open Smart Register Platform looks at e-registries. The Nutrition Department has developed a Toolkit of standards and norms for birth defect surveillance, which has been implemented in several regions and countries. The Tropical Disease Research partnership supports a WHO central repository of information on maternal outcomes in low- and middle-income countries after different exposures to different medications. Two WHO departments that work on vaccines and vaccine safety have produced guidelines on clinical evaluation of vaccines. Last, but not least, the Global Vaccine Safety Multi Country Collaboration project aims at assessing the feasibility and applicability of selected GAIA case definitions pertaining to neonatal outcomes, mainly in low and middle income countries. Despite ongoing collaborative efforts, all these activities face data limitations in terms of quantity and quality, incomplete...
reporting, and misclassification. There is a lack of systematic analysis, clear definitions, assessment which results in great variability of the information collected. In addition, there are a variety of systems, strategies and plans to implement these programs at the country level.

Beyond WHO, there are a variety of other stakeholders who actively contribute to data generation and this slide only presents a sample of those that regulatory interact with us. This is very encouraging as it shows that there is a broad commitment to improve maternal and newborn health, but in the same time it stresses even more the challenges faced. The major challenges being faced are the recording of data across different health system levels using different tools and platforms, different definitions and classifications for maternal and neonatal outcomes, the need for standardized definitions and measurement (e.g. of gestational age), disaggregation of data, and the applicability of standards to LMICs. It was concluded that both the quantity and quality of data need to be improved, and harmonization in all steps of monitoring maternal and neonatal outcomes is paramount.

Discussion:
Developments towards a more unified approach to monitoring care in pregnancy were welcomed. A number of related issues were raised, such as moving Zika virus interventions from an emergency response to a long-term strategy, and research on the prevention of certain conditions with folic acid. A central registry on the effects of medicines and vaccines during pregnancy is also being developed in countries by the Special Programme for Research and Training in Tropical Diseases (TDR). WHO’s HIV programme reminded participants that it had long been working on the safety of medicines during pregnancy (although data are nevertheless difficult to come by on a global scale), while the department of Reproductive Health and Research (RHR) reported efforts to digitize medical record systems on pregnancy. While appreciation was expressed for these various efforts, the programmes’ managers were urged not to forget the concerns of the women themselves.

Pregnancy and early childhood outcomes monitoring through health and demographic surveillance systems
Dr Peter Waiswa

The INDEPTH Network (Better Health Information for Better Health Policy) is a network of 49 independent Health and Demographic Surveillance Sites (HDSS) that carry out longitudinal research on populations in urban and rural areas of LMICs. INDEPTH sites are located in 18 countries in Africa, Asia and Oceania, with some 3.8 million people being monitored regularly. Focus areas include sexual and reproductive health as well as MNCH, with working groups supervising each area.

INDEPTH’s MNCH working group is coordinated by Makerere University in Uganda and deals with the generation of data on MNCH, including pregnancies and outcomes as well as causes of death. The purpose of the working group is to improve pregnancy and outcome tracking in order to provide a better platform for testing precision public health approaches across the research pipeline. Data collection and validation are similar across sites but there are slight differences, such as in the use of village health workers to collect health data. Pregnancy surveillance is the prime feature of all activities, and not just a part of a disease-based system. Core indicators that are collected regularly are pregnancy, stillbirth, neonatal death, infant deaths, maternal deaths, live births, and women delivering at a health facility, maternal age and causes of death. Meeting participants were shown infant mortality rates in different locations, as well as the differences in rates of stillbirth, neonatal mortality and infant mortality at the different sites. Cause-specific mortality rates were shown for prematurity, congenital anomalies, asphyxia, infection, and other causes and indeterminate at different sites.
One HDSS site in Iganga, Uganda, has piloted the use of GAIA definitions for obstetric outcomes (hypertensive disorders, maternal death, pathways to preterm birth, postpartum haemorrhage and non-reassuring fetal status) and neonatal outcomes (congenital anomalies, neonatal death, neonatal infection, preterm birth and stillbirth). Results have shown that it is possible to derive data on maternal and neonatal conditions at both hospitals and health centres and in the surrounding areas. However, although this capability exists, and a comprehensive system of data collection is possible in situations with limited resources, the system can be improved by strengthening data collection. Some sites in the MNCH working group are already doing work on immunization, though not specifically on maternal immunization, but they have expressed interest in it.

Discussion:
The importance of training was emphasized. It was explained that there is a standard toolkit for training field workers and visits to all INDEPTH sites include checks on training, which is evaluated in the field, and checks on whether data are consistent. A community health system provides data on gestation rates but in some areas estimates have to be used. The case definitions are validated for specificity and sensitivity by the relevant working group. The collection of data of abortion is possible at some sites but others present difficulties depending on the local culture and religion.

Maternal immunization safety in the context of MNCH interventions
Dr Ajoke Sobanjo-ter Meulen

Intervening early in the life course is essential to achieving the under-5 mortality targets of the Sustainable Development Goals (SDGs). Compared to the average 2-4% annual U5MR reduction observed in sub-Saharan Africa during the Millennium Development Goal era, substantial acceleration will be needed to attain the 6-9% reduction per year required to attain the SDG targets by 2030. Some 2.6 million babies are estimated to have been stillborn in 2015, 98% of them in LMICs. In sub-Saharan Africa, up to 50% of stillbirths may be infection-related, with syphilis as the main cause of stillbirths and Group B Streptococcus (GBS) as a significant contributor to perinatal mortality. Most of the mortality burden occurs in infants too young to be vaccinated, and immunologic protection against infectious diseases in this age group is primarily reliant on antibody transferred via the placenta from the mother to her infant, or given passively to the infant at birth. Vaccines administered during pregnancy, such a GBS vaccine, are one of few interventions that can be given early enough to potentially protect against infection-associated preterm death and stillbirth, as well as early neonatal sepsis. Maternal vaccination would complement existing MNCH interventions in the continuum of mother-infant care.

A comprehensive global GBS disease burden modelling study estimated that in 2015 there were 319,000 infants <3 months of age with GBS disease, as well as 90,000 (UR 36,000-169,000) deaths and at least 10,000 (UR 3000-27,000) children with disability related to GBS meningitis. There were at least 33,000 (13,000-52,000) pregnant or post-partum women with GBS sepsis and 57,000 (UR 12,000-104,000) stillbirths due to GBS disease per year. Intrapartum antibiotic prophylaxis (IAP) is available to pregnant women in high income countries; however its potential impact is limited to early-onset GBS disease. Advantages of maternal vaccination over IAP include the possible leverage off existing antenatal care platforms, the reduction of adverse outcomes for invasive disease in pregnant and postnatal women, unborn babies, and infants, and prevention of the less clearly measured burden from non-invasive disease, including, for example, preterm birth [Lawn JE et al.; Seale et al., CID 2017].

Development of a maternal vaccine against Group B Streptococcus is now supported by industry and global partners, representing considerable progress compared with some years ago when liability concerns were preventing manufacturers from pursuing licensure for vaccines for use in pregnancy.
Following the thalidomide scandal in the 1970s regulations were put in place to exclude pregnant women from clinical trials with a focus on risk avoidance. Now that extensive experience has been gained by maternal immunization programs such as the maternal and neonatal tetanus elimination program, and influenza and pertussis maternal vaccination is implemented in several countries, policy recommendations are being changed to overcome gaps and barriers. Notably, respiratory syncytial virus (RSV) vaccine is the first vaccine that has entered phase 3 clinical trials in pregnant women.

Human data are needed to advance the evidence base to inform treatment decisions in pregnant women to improve maternal and infant health outcomes. However, a study in the United States found that while large numbers of women take prescription medicines and over-the-counter medicines during pregnancy, most industry-sponsored trials exclude pregnant women. Facilitated by the Zika epidemic, mothers' interests in the welfare of their babies are now strengthening the highlighting the potential benefit of maternal immunization, as well as the acceptability of testing experimental vaccines in pregnant women.

The WHO global vaccine safety blueprint has recommended alignment of post-marketing safety surveillance system for both vaccines and medicines. Efforts to harmonize the safety monitoring of adverse pregnancy outcomes across vaccines and medicines are critical to enable appropriate benefit-risk assessment of interventions in pregnancy. This requires close collaboration between the vaccines and the maternal-neonatal- and child health (MNCH) expert communities. Similarly, vaccines and MNCH programs will need to work jointly on effectively implementing maternal immunization via antenatal care. In 2017, preliminary data in a WHO-led study highlighted the potential for the Expanded Programme on Immunization (EPI) in strengthening antenatal care services in the context of administering tetanus vaccine to pregnant women.

Discussion:
Participants welcomed moves towards maternal immunization. Comments included a call for the monitoring of effects and potential adverse events of maternal vaccination to be integrated into clinical surveillance since vaccination cannot be monitored separately. The fact that harm may be done to unborn children not just by infections but also by medicines was said to represent a challenge that must be dealt with. It was suggested that science-based stories are needed to demonstrate not only the importance of health care during pregnancy but also to show the need to protect pregnant women and their offspring. All maternal tetanus programmes currently are required to investigate for possible effects on the infant.

Maternal and early childhood outcomes terminologies

ICD-11 definitions of pregnancy outcomes
Dr Robert Jakob, Dr Doris Chou

ICD-10 has been published in 43 languages and is used in over 100 countries, with 12 modifications\(^1\). However, it is now 25 years old and was never designed for electronic use. ICD-11 is now in the final stages of development as the international standard for reporting and measuring health and health services (e.g. mortality and morbidity statistics, quality and safety, primary care, health-care costs, progress towards the SDGs, clinical documentation). ICD-11 incorporates more elements than ICD-10, plus improved usability, index, improved comparability of translations, and links to other

classifications. 2017 has been dedicated to ICD-11 quality assurance, and in June 2018 WHO will release a version for implementation.

ICD-11 has 26 chapters, a pattern of functioning (from the International Classification of Functioning, or ICF), traditional medicine, extension codes, and multiple languages. The extension codes allow for more detail (e.g. severity, temporality, etiology, biological indicators, differential diagnosis, present on admission etc.), and each entry includes a clinical description of the disease or condition. Thus, there is the basic ICD but also much more detail for recording or for other specific purposes. Links with other classifications aim to ensure semantic interoperability – so that there is one term for each concept. The use and potential of the online ICD browser were explained.

WHO’s Department of Reproductive Health and Research (RHR) looked at the existing ICD-10 chapters relating to its area of work and through a specialized technical advisory group (the Genito-urinary Reproductive Medicine TAG), reviewed and proposed technical inputs to improve the Chapters. For instance, not all ICD-10 codes included a definition, but all ICD-11 codes will include one; additionally, the review identified relevant conditions which did not have an ICD code. One outcome of the RHR review of relevant ICD-10 codes was the ICD-MM, which is intended to assist in the appropriate use of the ICD. Lessons learned during the RHR revision included engagement with stakeholders in the long term, the need to ensure “telescoping” from the big picture to the closer view, and communication. As partners move ahead with maternal immunization they should all aim to collect data conforming to a standardized definition to ensure that results can be compared and combined.

Discussion:
Participants welcomed the introduction to the latest ICD classification. The discussion period chiefly consisted of requests for further details of the functionality of ICD-11. All ICD-11 entries, including abortion, have a short definition and also a longer definition that includes aspects of what the disease or condition may involve. ICD-11 has some 5,000 categories that can be expanded to 15,000 but, with extension codes of categories and conditions, the number can expand to millions. For instance, ICD-11 includes intestinal cancer both under cancer and under the digestive system. The classification can be used at different levels with different levels of detail. Training materials will also be issued. ICD-10 and ICD-11 map together very well. ICD-11 was initially developed with working groups looking for scientific improvements and modifications in a very open process, followed by field-testing. All ICD entries focus on the descriptive scientific term, with the possibility that entries relating to sensitive issues may be changed in some countries (keeping a single standard international definition). Two years ago the last country using ICD-8 switched to ICD-10. A number of countries are still using ICD-9, and certainly several versions of ICD will be operating in parallel. ICD-10 updates will stop in 2019. WHO no longer updates ICD-9, because that revision was put in the public domain and a number of codes have been changed by the issuers.

MedDRA and Safety Monitoring of Pregnancy and Neonatal Outcome
Dr Judy Harrison

The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) developed the Medical Dictionary for Regulatory Activities (MedDRA) in the 1990s to support the exchange of regulatory information. ICH is the owner of MedDRA which in fact is more of a terminology than a dictionary. MedDRA facilitates the exchange of regulatory information worldwide. MedDRA is used in the development of data standards for safety monitoring, the collection of regulatory data, and the development of guidelines for data interpretation. MedDRA is based on a hierarchical structure that categorizes medical terms by body system, organ, and function. MedDRA also includes a comprehensive list of adverse events and other medical terms, such as abnormalities, procedures, and diagnoses. MedDRA is used in a variety of industries, including pharmaceuticals, medical devices, and clinical research, to ensure consistent and accurate data collection and analysis. It is important to ensure that the coding system used for data collection is robust and comprehensive, and that it is used consistently across organizations and countries. This will allow for more accurate and reliable data analysis and will facilitate the sharing of data across industries and borders.
of clinical information through standardization, supporting data entry and retrieval and analysis of clinical information about human medical products.

MedDRA is used in regulatory authority and industry databases, the WHO Programme for International Drug Monitoring, individual case safety reports and summaries, clinical study reports, company safety information and marketing applications, as well as for a number of other purposes. It contains data on medical conditions, indications, investigations (tests, results), medical and surgical procedures, medical history, medication errors, product use and quality issues, and other patient-related and product-related information. It has a five-level hierarchy, with 27 System Organ Classes that expand through the other levels to 78,026 Lowest Level Terms. A medical concept can be represented in multiple System Organ Classes. MedDRA is now available in 11 languages.

MedDRA is provided free of charge to regulators, non-profit groups, academics and health-care providers. Others pay a subscription. Commercial subscribers pay according to their revenue. The database is maintained through requests from users for new terms or for changes to existing terms. New versions are produced two times a year. Training is provided free to subscribers, with 4,400 persons being trained in 2016.

Participants were shown the MedDRA terms on pregnancy and neonatal outcomes. Spreadsheets on congenital conditions, preterm birth, stillbirth and abortion were provided for the meeting’s breakout sessions. Coding is done using the Lowest Level Terms (most specific) and analysis is carried out at the medical concept level (Preferred Term level) and at higher levels in the hierarchy. Standardised MedDRA Queries (SMQs) are groupings of terms from one or more System Organ Classes; they are tools used to support signal detection and monitoring. The intention is to maximize the likelihood that all terms related to a specific medical condition of interest are identified. The SMQ on pregnancy and neonatal topics contains nine other SMQs within it. MedDRA is integrated with other terminologies, such as the US National Institute of Child Health and Human Development’s pediatric adverse event terminology with 1,338 MedDRA terms.

Discussion
Participants welcomed the information on MedDRA and particularly praised the grouping of terms by concept.

The GAIA project – standardized case definitions of adverse events following maternal immunization
Dr Jan Bonhoeffer

Brighton Collaboration is a global network of some 600 partners trying to develop standard case definitions by looking at three levels of diagnostic certainty – i.e. definite, probable and possible. Funding comes from a range of partners, including WHO, CDC, the European Commission and the Bill and Melinda Gates Foundation. WHO and CDC have both recommended the use of Brighton case definitions. Each definition derives from a standard process that involves a volunteer working group and a varied number of reviewers (which may vary from 5 or 6 to well over 100).

The GAIA project similarly brings together a large variety of stakeholders. It grew out of concern expressed by WHO and others in 2014 that there was heterogeneity of study methods and national harmonization efforts. So far 65 key outcomes have been delineated and 21 definitions (11 neonatal and 10 obstetric) have been prioritized and published. It was noted that the GAIA definitions increase accuracy, precision and comparability. Of the 21 GAIA case definitions already published, there are 45 sub-definitions. Every GAIA case definition can be mapped to the event group, the
event, to various stratifications, or to levels of certainty. The definitions are designed to classify regardless of source.

Discussion:
There was appreciation for the efforts of GAIA to produce standard definitions. Each GAIA working group consists of persons with expertise, and once they are on board a rigorous scientific process is begun based on Cochrane methodology. A participant noted that over 70% of common maternal conditions do not have a systematic review – and, where systematic reviews exist, most of the papers come from the same small number of countries.

GACVS reviews of the safety of vaccines in pregnancy
Dr Marion Gruber

WHO’s Global Advisory Committee on Vaccine Safety (GACVS) was established in 1999 to enable WHO to respond promptly, efficiently and with scientific rigour to vaccine safety issues. In 2011, the Strategic Advisory Group of Experts on immunization (SAGE) requested for GACVS to provide support to a review of evidence on the safety of vaccination during pregnancy and lactation. The GACVS pregnancy subgroup carried out a literature review (cut-off point May 2013) on the safety of vaccination in pregnancy focusing on vaccines available at that time. Most of the data came from observational studies, case series and passive surveillance systems. The subgroup also considered theoretical considerations and experimental data. Pregnancy outcomes considered included maternal morbidity and mortality, miscarriage/stillbirth, prematurity, small size for gestational age, congenital anomalies. Of note, GACVS conclusions regarding safety of vaccination in pregnancy were based on expert discussion and consensus rather than on a systematic review and/or grading system.

Based on the data reviewed GACVS found no evidence of adverse pregnancy outcomes following immunization of pregnant women. It was noted that studies varied in the outcomes measured and definitions applied which led GACVS to recommend that harmonized definitions for pregnancy outcomes be developed.

WHO and Brighton Collaboration convened two task forces in 2014 to review terminologies and definitions relating to the safety of vaccines administered to pregnant women, as well as a global stakeholder survey of relevant terms and safety assessment methods. Later that year, WHO held an expert consultation to review obstetric and paediatric adverse event case definitions and guidance, to prioritize terms for key events for continuous monitoring of immunization safety in pregnancy, to develop concept definitions, and to recommend a core data set of key terms of events to be collected. Overall, 39 key terms were reviewed and prioritized and consensus concept definitions were endorsed. The consultation also recommended development of guidance for data collection, analysis and presentation of safety data, tools for harmonized data collection, data sharing and use of health care data sets to strengthen safety surveillance. The Global Alignment of Immunization Safety Assessment in Pregnancy (GAIA) network was formed to establish a globally shared understanding of outcomes and approaches to monitoring safety of vaccines used in pregnancy with particular focus on low- and middle income countries.

In June 2016 GACVS reviewed guidelines developed by the GAIA project. The Committee considered the GAIA guidelines timely and useful and noted that they should provide for flexibility regarding core data collection requirements as data collection in certain settings may not be feasible. Challenges related to infrastructure, availability of background data, changes in background rates or clinical standards in various settings should also be acknowledged, including the fact that the presence of researchers will affect some pregnancy-related outcomes. GACVS noted the possibility of updating these guidelines which may also be applicable for safety monitoring in the context of
observational studies. Furthermore, to test and facilitate their implementation, the Committee stressed the need for field-testing and review, the generation of practical tools for investigators, capacity-building/training and a dissemination strategy. Participants in the present meeting were shown the GAIA guidelines for collection, analysis and presentation of safety data in clinical trials of vaccines in pregnant women.

Discussion:
The GAIA definitions can be used for clinical purposes, for medicines or vaccine safety, background rates or disease monitoring. However, the definitions were developed specifically for case verification and not for case identification. It was noted that the GAIA definitions are gaining in importance. Some European countries have now incorporated the GAIA definitions into electronic passive reporting forms.

Breakout groups – applicability of existing terminologies
Participants were divided into four breakout groups in order to: 1) examine four pregnancy or early childhood health outcomes and assess their applicability, and 2) compare corresponding terminology systems. Each group addressed these issues in terms of one of the following topics: abortion, congenital anomalies, stillbirth, and preterm birth. Each group was asked to record its discussions according to a standard format. Following the discussions, each breakout group reported its discussions and findings to the plenary. The main findings are summarized according to the five dimensions summarized in the following table.

Discussion:
The issue of major versus minor congenital anomalies was raised. While all congenital anomalies are defects and need attention from a medical perspective, the fact that major anomalies will have a greater impact on a child’s life than minor ones means that it is important to distinguish between them from a public health perspective. There was a comment that we tend to discuss the different outcomes of pregnancy separately although they are all related, and a further comment that it is important to know the difference between major and minor anomalies because in the literature it is not always clear what is being referred to when rates of anomalies are reported. Photographs of congenital anomalies would be important to help in identification, but it can be culturally difficult to obtain them.

A further issue was raised of how to assess gestational age. It is not possible to do an ultrasound in all settings, but one way to assess gestational age at birth is to measure foot length. It was reported that, when the meningitis vaccine Menafrivac was used in a mass campaign in Burkina Faso, surveillance involved assessment of some 1000 vaccinated pregnant women. Four were found to have problems, but all these four had visited medical services only at the end of their pregnancies. The assessment of gestational age is important, as issues such as stillbirth, miscarriage and spontaneous abortion are all related to it.
### Table – Summary of work group deliberations

<table>
<thead>
<tr>
<th>Breadth of circumstances affecting the identification of the outcome</th>
<th>Core data elements required to confirm the outcome for each system</th>
<th>Challenges related to the clinical settings measuring the outcome</th>
<th>Applicability of different systems in the context of different types of studies</th>
<th>Aspects of available terminologies requiring further field-testing and review</th>
</tr>
</thead>
</table>
| **Group 1: Abortion** | • Early pregnancy loss may not be recognized or reported.  
• Pregnant women may not present for prenatal care during the first trimester, so early pregnancy loss or more accurate gestational estimation via ultrasound may be missed.  
• For cultural reasons, it may not be possible to differentiate spontaneous from induced abortion if based on maternal self-report or based on documentation in medical records.  
• Second-trimester spontaneous abortions ("late abortions") may have different etiologies than early pregnancy loss.  
• Some settings lack access to ultrasound, staff trained in ultrasound or pregnancy laboratory tests. | • Gestational age  
• Actual product of conception  
• Weight of product of conception  
• Pregnancy test (preferable)  
• Ultrasound (preferable). | • Clinical trials usually do not recruit women in their first trimester of pregnancy, making it difficult to assess this outcome via clinical trials.  
• Spontaneous adverse event reporting is not helpful due to biases, except as a means of generating potential safety signals.  
• Prospective observational studies can be used to study inadvertent exposures among pregnant women (i.e. follow-up outcomes among women of childbearing age exposed to medical products of interest).  
• Prospective observational studies (i.e. prospective cohort studies, pregnancy registries, active surveillance) can be designed to assess abortion risk associated with exposures.  
• HDSS sites are useful as sentinel sites for studying the risk of abortion but findings may not be generalizable. | • There are inconsistencies in the cut-offs used for gestational age between spontaneous abortion and stillbirth (e.g. < 22 weeks for spontaneous abortion and ≥ 28 weeks for stillbirth). What about the period between 22 weeks and 28 weeks?  
• Further clarification is needed on harmonization of terminologies and definitions (including definitions of early and late spontaneous abortion).  
• Determination of first-trimester spontaneous abortions needs clarification (e.g. Should it be based on the last menstrual period? When do you start counting gestation? What if there is no “last period”).  
• The proposed gestational age algorithm should be field-tested.  
• It is important to map the various definitions/classifications  
• Different terms used (e.g. spontaneous abortions, abortions, miscarriages, fetal loss) lead to confusion in field studies and surveillance and in reporting of findings. |
| Group 2: Congenital anomalies | • An infinite number of conditions exist.
• There are existing systems to classify congenital anomalies.
• Classification is influenced by local and cultural conditions (e.g. autopsy, prenatal diagnosis, termination of pregnancy).
• Presence or absence of local expertise and diagnostic resources affect identification. | • An accepted descriptor or case definition
• A “gold standard” diagnostic evaluation or test (evaluation by an expert or a specific diagnostic/confirmary test)
• Outcome-dependent (e.g. prenatal diagnosis only, fetal demise, prematurity-related, postnatal presentation)
• Objective-dependent
• Might require a combination of elements. | • Awareness and expertise (of health care personnel, community health workers, parents) are required to recognize there is a problem.
• In most areas, congenital anomalies may not be identified
• In certain areas only external anomalies can be detected.
• Resources are required.
• There needs to be access to the infant (which may be prevented in some cultures).
• Inability to keep mothers in hospital post-discharge and to follow up with personnel able to identify the problem (as with identification of danger signs). | • Terminology is not consistent.
• There is poor specificity: the actual diagnosis is needed, not just a code label.
• MedDRA for research versus ICD for coding and observational studies: it may be necessary to combine these to complement each other or add new coding to identify the outcome and avoid misclassification, depending on the type of study.
• Misclassification is a concern (non-differential misclassification can be addressed by increasing specificity).
• Sample size effect. | • All available terminologies should be tested and reviewed in different settings.
• There is a need to focus on relevant outcome-based objectives for data utilization.
• Validation should be based on an agreed gold standard.
• Sensitivity/specificity, PPV (positive predictive value)/NPV (negative predictive value).
• Standard operating procedures are needed for evaluation. |

| Group 3: Stillbirth | • The settings are product monitoring, pregnancy monitoring or outcome monitoring.
• The studies required are pre-licensure and post-licensure clinical trials, and prospective and retrospective observational studies.
• There is a tendency to report | • Both ICD-11 and GAIA definitions require similar data elements, though GAIA is more elaborate than ICD-11.
• ICD-10 and ICD-11 definitions differ in structure and criteria.
• GAIA definitions tend to be more based on signs | • For assessment of gestational age, levels 1, 2 and 3 of the GAIA definition requires level 1 of the GA assessment; otherwise it goes to level 4.
• Reporting the diagnosis can be challenging for cultural and political reasons – i.e. “blame culture”. Diagnosis reporting also depends on | • ICD-11 and GAIA definitions are both applicable in clinical trials and prospective studies.
• In retrospective studies, ICD codes are applicable to case identification, while GAIA definitions are more applicable to case verification but can | • Clarification is needed for differentiation between antepartum and intrapartum stillbirth.
• For GAIA definitions, checklists of signs and symptoms need to be field-tested. |

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¹ Group 2 considered 6 differing definitions of congenital anomalies and, for the purposes of its discussions, defined “congenital anomaly” as a condition of prenatal origin that is present at the time of live birth or fetal demise, or in utero, and that affects or has the propensity to affect the health, survival or physical or cognitive functioning of the individual. The group pointed out that the GAIA definition gives no direction on how to define multiple birth defects in one infant, and there is a need to be able to ascertain outcome with some level of specificity (diagnosis) and not just at a high level.
| Group 4: Preterm birth | Live births as stillbirths to minimize blame.  
- It is often unclear how to differentiate late abortions from stillbirth at field level.  
- It is unclear who can assess stillbirths; capacity-building will be needed. | And symptoms, and can be used to inform data collection following preparation of a checklist of symptoms.  
- Reporting based on signs and symptoms can address some of the concerns.  
- Workload (impacts reporting). | Potentially be used for case identification.  
- Applicability is enhanced in electronic systems. |
| --- | --- | --- | --- |
| - Cultural attitudes in some regions will lead to late antenatal consultations.  
- Reporting of last menstrual period could be influenced by the local culture.  
- Access to health care is an important factor in the identification of the parameters.  
- Contraception methods may influence the identification of last menstrual period, and contraception differs from region to region and country to country. | - Last menstrual period (plus estimate of certainty)  
- First trimester examination  
- Second trimester fundal height  
- Ultrasound (plus estimated time of examination)  
- Physical examination of the newborn  
- Birthweight  
- Electronic data collection, if possible. | - Obtaining the right data (quality and quantity)  
- Recording the right data  
- Reporting the right data  
- Training/supervision/capacity workload. | - Prospective data are no problem.  
- For retrospective data, obtaining timing of the last menstrual period is difficult but other parameters should be in the dossier.  
- Capacity-building is needed to always collect these basic data. |
Assessing case definitions

Multicentre assessment of definitions to measure early childhood morbid conditions

Dr Thomas Verstraeten

There is a need for safety surveillance of new vaccines to be used during pregnancy in low and middle income countries, and hence also a need to standardize definitions for obstetric and neonatal health outcomes. A simulation exercise was undertaken in 34 sites, located mostly in Africa and Asia, to select sites for a study to assess the applicability of the GAIA case definitions. Participants were shown how the sites were selected and how an additional aim of the future study was to estimate the site-specific minimum detectable risk for each health outcome.

More specifically, the study under preparation will estimate the minimum detectable odds ratio for a future case-control study and the minimum detectable relative risk for a future cohort study, based on the number of cases identified at each site during the study period, the total number of live births, and the level of maternal immunization coverage. For each health outcome, the applicability of the GAIA case definition will be assessed by calculating the proportion of cases identified that can be classified according to each GAIA case definition level of diagnostic certainty. The study will also identify factors that influence the applicability of the GAIA case definitions and will assess which missing data elements are preventing classified cases from meeting a better level of diagnostic certainty. The observational prospective hospital/health centre-based study period is expected to last for one year.

The study population will consist of all children delivered at the hospital, and their mothers. The GAIA case definitions to be assessed are those for low birthweight, neonatal death, neonatal infection, preterm birth, small for gestational age, stillbirth and congenital microcephaly. Maternal immunization status for tetanus or other vaccines administered during pregnancy will be ascertained for all mothers of identified cases of the health outcome of interest.

Discussion:
Part of the learning will be to find how many cases each site can identify. This will help in the future to know how many sites need to be enlisted to study sufficient cases. The number of sites per country varies. If some women choose to go back to their homes to deliver, they will indeed be lost to the study. Most sites use paper-based records but the aim is not to change the systems in the sites at this stage. Rather, the aim is to see what is feasible in the present situation.

Assessment of definitions for pregnancy and early childhood morbid conditions in industrialized countries

Dr Miriam Sturkenboom

The speaker explained that VACCINE_GRID, of which she is president, is a charity that was established to facilitate global collaboration in the conduct of studies for estimation of vaccine effects. The organization is managing a study on the evaluation of 10 GAIA definitions in high income countries. The initial “assumed implementability” of the definitions by maternal immunization investigators present at the IABS stakeholder meeting in Washington in 2016 was fairly positive for randomized control trials, but less so for observational studies in both low as well as high resource settings. Since the Gates Foundation and WHO focus on low income settings, the investigators decided to focus on high-resource settings. The study is funded by NVPO through a research grant with the University of Cincinatti, principal investigator is Dr. Steve Black.
The aim of the study is to evaluate whether cases (from routine care and clinical trials) can be classified according to the GAIA definitions, retrospectively. The definitions need to be evaluated in this context because of the need for background rates of events to inform whether observed case reports after introduction of the maternal immunization program (which hopefully will use the same classification) are more than expected, and to enable the pooling of data across studies (whether randomized control trials or observational). With different coding systems being used in different places, the study is designed to evaluate the ability to use GAIA maternal and neonatal outcome definitions. Its five main objectives are to assess ability to identify and classify cases retrospectively, to assess the Brighton Collaboration level of diagnostic certainty, to compare the classification by investigator and tool, and to estimate the positive predictive value of the ICD-9, ICD-10 and MedDRA codes.

The study is focused on seven sites in Australia, the United Kingdom and United States, looking for both maternal and neonatal outcomes in hospital medical records, clinical trial documents, and maternal immunization studies. Code Mapper\textsuperscript{1} was used to map the codes of ICD-9 and ICD-10, READ, and MedDRA. A data collection form will be provided for each outcome of interest, and training of the data abstractors will utilize dummy cases. The study is currently under way, the final report is expected in June 2018.

Maternal and early childhood outcomes surveillance systems

Global systems for monitoring congenital abnormalities.

Dr Cynthia Moore

Considerations for surveillance of malformations include whether the population source is population-based or hospital-based, pregnancy outcomes and clinical phenotypes, surveillance methods, and data source (single or multiple). Several tools exist for the surveillance of birth defects, including Birth defects surveillance: Atlas of selected congenital anomalies by WHO, CDC and the International Clearinghouse for Birth Defects Surveillance and Research.

The USA has the National Birth Defects Prevention Network, a voluntary organization that develops guidelines and national standards, advances multistate projects, and raises public awareness. The International Clearinghouse for Birth Defects Surveillance and Research has 42 surveillance programmes in 36 countries. In Europe there is European Surveillance of Congenital Anomalies (EUROCAT) which has 43 registries in 23 countries. South-East Asia has the Newborn and Birth Defects Database (NBBD), with over 250 hospitals in the region reporting defects. The Latin American Collaborative Study of Congenital Malformations (ECLAMC) has a programme of clinical and epidemiological investigation of developmental congenital anomalies, as well as a research programme and a permanent monitoring system.

In several locations antiretroviral treatment programmes started reporting birth defects, as did some perinatal health programmes. Surveillance to evaluate folic acid intervention in China in the 1990s reported some birth defects, as did a United States Department of Defense military study of women who had been given anthrax vaccine. More recently a rapid population-based surveillance programme was conducted to identify birth defects consistent with Zika virus infection. This resulted in pregnancy and infant registries being set up to monitor pregnancy and infant outcomes in

Colombia, Puerto Rico and the USA. Limitations of birth defects surveillance include the fact that it relies on retrospective data, and many of the defects are rare which means that active surveillance is very costly. It is usually easier to look for specific birth defects than for defects in general.

Discussion:
The overview of congenital malformation monitoring was welcomed. In discussion of the congenital malformation database used by CDC, it was noted that some of the definitions used are old and have been in the recording system over a long period. Definitions may vary slightly according to what the data are needed for. However, ICD codes have been added. The point was made that this is a very large and valuable dataset and that it would be even more useful if it could be made comparable with data from other sources. For the past 15 years prenatal diagnosis has been added to the data. It was pointed out that the Bill & Melinda Gates Foundation has been looking at the CDC approach to see how it might be applied to low-resource settings, but one of the challenges is to find out how to examine without ultrasound. Autism and other neuro-developmental disorders are also a major issue since a number of teratogens are linked to them. In conclusion the Chair emphasized the need to distinguish between causality in utero and causality in the post-natal period.

Attempts at harmonizing reporting on pregnancy outcomes

Dr Khalid Khan

Journals are important elements in the acceptance or rejection of definitions. Participants were shown examples of journal articles reporting the same issues by different definitions. It was suggested that some researchers are cherry-picking what they want to report. In addition, depending on the sample size, extreme results can be generated. Such issues have been noted by editors of women’s health journals. In 2014 the CROWN (Core Outcomes in Women’s and Newborn Health) initiative was launched to encourage researchers to develop core outcomes in women’s health. The intention was, and is, to form a consortium to promote core outcomes in gynaecology and obstetrics and to encourage the reporting of results according to those core outcomes. Over 80 journals are participating in this process in different countries and languages.

There are 32 ongoing projects to define core outcome sets in women’s health. This is done by developing a long list of potential core outcomes, obtaining stakeholder (including patients) consensus, confirming the final core outcome set, agreeing definitions and disseminating them. So far 13 core outcome sets have been published and 13 trials have adopted these outcome sets as a basis for their protocols. CROWN will also disseminate the GAIA definitions.

Discussion:
The suggestion to include patients in the consensus-building attracted some comment, as did the process of disseminating the definitions and persuading researchers to use them. The latter point was said to be an ongoing process. It was stressed that there is a need to move toward standardization of definitions so that effective comparisons can be made. Participants were informed that a WHO meeting in 2014 defined a number of core outcomes. With regard to maternal vaccination, obstetricians have never really been part of vaccination programmes. For vaccination there have to be very precise definitions, and much of the future process in this area must be to bring obstetricians up to speed on this issue. The GAIA definitions are important because they enable comparisons across settings and across companies. The Chair said it is unacceptable to have 150 studies on the induction of pregnancy with 80 of them not mentioning what happens to the mother, as shown in one meta-analysis, or not mentioning what happens to the baby.

Use of public health registries in assessing pregnancy outcomes

Dr Alain Labrique
Digital pregnancy registers are intended to be integrated, prospective routine health information systems that collect a consistent set of data on incident and prevalent pregnancies, including complications, as well as maternal and neonatal outcomes. They are often integrated into routine systems and should not be confused with pregnancy exposure registries which monitor the safety of medications, devices and services used during pregnancy and which record pregnancy outcomes systematically as related to those exposures or devices.

Health services around the world have a culture of capturing and reporting data, but not necessarily of data use – especially in real-time. In Bangladesh, for instance, our research showed that one cadre of frontline health worker had to deal with 19 different registers, and hundreds of data fields, consuming massive amounts of their time. Globally, there are a significant number of legacy (often paper-based) systems with a lot of client-level health data which are usually inaccessible to health workers and supervisors striving to improve service coverage and quality. Additionally, paper health records are often not standardized and variability in data recording can lead to important variations in quality. Households are visited by multiple health workers who do not interact with each other, leading to redundant, and often conflicting data being captured. Data should be collected for a purpose – to support the workflow and efficiency of health workers and to improve the quality of care for those the health workers aim to serve.

Data collection, screening for outcomes, delivering services and reporting do not have to be separate functions. There is a tendency to think of registers in terms of static paper ledger systems, but digital registers have the capacity to be altogether different. In this new digital era, strong integrated information systems are both necessary and possible, with digital tools adding value at different levels and across domains. Even in resource-limited environments, rudimentary systems can be implemented which use global technical and semantic standards with common data elements and shared denominators. Digital registers are, to begin, efficient data capture instruments, which reduce errors in entry (by preventing the entry of invalid codes). Relevant data can be shared across workers who are authorized to have access to information about changes in client health. Data can be aggregated at multiple levels, eliminating time-consuming reporting tasks and indicators can be formulated based at the individual, group or geographic level. Finally, the ‘real-time’ availability of data supports supervisory monitoring actions that seek to ensure service coverage as well as reduce inequities in service receipt.

Digital pregnancy registries are the focus of a programme on which Johns Hopkins School of Public Health and the JHU Global mHealth Initiative are working with WHO. Digital registries function by combining unique identification, digital service records, electronic decision support, work-planning management and optimization, and automated indicator-based reporting. An integrated software package facilitates this. The aim is to optimize the experience of pregnant women and their children who are the targets of government-delivered antenatal and postnatal care.

This digital system replaces the nineteen paper registers, moving from over 450 fields of data captured continuously, to a mere 50-60 fields required in one digital system, saving a great deal of time and effort. Where this system has been introduced, community health workers use mobile devices (android tablets) to improve coverage and quality by combining both supply-side strengthening and demand-side inputs. While the digital register serves to optimize and facilitate the health workers’ tasks, the system automatically sends text message reminders to client personal phones to prompt timely, appropriate care-seeking behaviors. In the example presented, over 12,000 families have been registered and GPS-located in 6 weeks and results so far have been positive. Pilot study results suggest that antenatal care coverage rates may be increased 3-fold with significant benefits to both mother and newborn, and postnatal care rates also doubled as a result.
Results also show that it is possible to capture denominators, systematic workflows can be implemented, pregnancies can be identified, outcomes can be captured, and individuals in communities can be involved in triggering vital events. This system, known as OpenSRP-mCARE, is presently being evaluated at large scale in one of the largest digital health randomized trials ever undertaken, with over 12,000 pregnancies being enrolled.

The optimal enterprise architecture to facilitate digital registries was shared, illustrating the importance of a standards-based approach to system development. The use of common standards to store data allows information to be shared across unrelated information systems with relative ease. Various agencies are involved in developing the Open Smart Register Platform (OpenSRP), which includes electronic client record forms (which are flexible so that new data fields and use-cases can be added as appropriate). The platform includes the ability to share between different cadres of health workers such as nutritionists, vaccinators and midwives. At present the OpenSRP system is developing modules for maternal and child health, cognitive development, growth and nutrition, TB monitoring and for routine immunization tracking.

**Discussion:**
There was considerable interest in the OpenSRP-mCARE system and the possibilities it offers in low-resource settings. There was discussion as to whether the system used in Bangladesh could be used for pharmacovigilance. It currently is not used for that purpose but it has been used for tracking vaccines by lot numbers. The system is interoperable with DHIS2 (the District Health Information System, version 2, which is used to collect routine health data from the government health facilities of Bangladesh). There has been agreement on sharing of semantic libraries to make raw data available in various forms and language. The people who work on Open-SRP mCARE are usually community health workers with education from Grade 8 up to bachelor level. The importance of establishing common definitions for variables and indicators was stressed. Participants were referred to the Open Concept Lab for more details on semantic libraries. On the issue of privacy, the system can be adapted to national guidelines.

**Evolving needs for assessing pregnancy interventions**

**A regulator’s perspective on harmonization needs for pregnancy interventions**

*Dr Steve Anderson*

Any vaccination during pregnancy must take into account other vaccines and medications that have been received. Post-marketing pharmacovigilance in the USA includes passive surveillance, pregnancy exposure registries, and active surveillance using large medical databases. Nevertheless, many pregnancy outcomes for medicines and vaccines are poorly captured. The system of passive surveillance in the USA, operated by the Vaccine Adverse Event Reporting System (VAERS), was described, as were its limitations – such as the lack of denominator data, underreporting of adverse events, and biases in reporting (e.g. following media reports). Pregnancy exposure registries are usually maintained by the manufacturer as a post-marketing commitment. They tend to be small (200–300 entries) unless there is a specific safety concern.

As for active surveillance, the US Food and Drug Administration (FDA) has 170 million persons in its PRISM database. CDC has also an active surveillance database (the Vaccine Safety Datalink) with 10 million persons. However, large databases present some challenges since not all conditions are systematically captured. Adverse events in pregnancy, such as spontaneous abortion, are not captured if they occur outside of the knowledge of a health-care provider or health facility.
Standardization of case definitions is critical for comparisons across studies. The US databases are starting to use the GAIA definitions, and there are cross-walks between ICD-9, ICD-10 and MedDRA. Work is under way to identify and validate ICD-10 coding for PRISM maternal vaccine safety studies. It was noted that the FDA provides funding to the research project aiming to assess the applicability of GAIA case definitions in LMICs.

Dr Corinne de Vries

Nineteen European registries provide information on vaccines and medicines during pregnancy. There are currently three scenarios for the use of medicines during pregnancy – unintended pregnancies of persons using medicines, intended pregnancies of a mother under treatment for a disorder (e.g. diabetes), and intended use specifically to protect the newborn (e.g. RSV vaccine, folic acid). Many women also use over-the-counter (OTC) products. Other than in exceptional circumstances, pregnant women are currently excluded from clinical trials since experimenting of pregnant women is considered unethical and in any case a large number of subjects would be needed to yield useful data.

Eudravigilance is the European Medicines Agency’s pharmacovigilance database. The agency is carrying out an inventory in all the European Union’s 28 Member States. Natural pregnancy “wastage” is high; of lost pregnancies, 60% are lost in the first few weeks, those occurring in the next few weeks (10%) are miscarriages, and 30% are live births. Methodological considerations for European regulators include short-term versus chronic use of a medicine, nationally authorized versus centralized products, OTC products versus prescribed medicines, lumping or splitting exposures and pregnancy outcomes, competing endpoints, the natural history of disease, and how long follow-up should last.

Discussion:
Thanks were expressed for the regulatory contribution to the discussions. A range of issues were raised, including how much data can be shared by the present systems, and how much information can be obtained, as well as the need for validation of ICD. A question was raised as to whether pregnancy registries in Europe on specific products could be used in developing countries, and whether the European databases could consider gathering data from developing countries and pharmaceutical companies. For data in registries, it was noted that the FDA relies on the sponsor of the registry, and there are limited data from spontaneous reporting. The EMA gives advice to non-European countries on the balance of risk and benefit of a product supplied to a developing country, but if a product cannot be marketed in Europe it is not supplied to other areas. If a product requires specific information to be provided, in Europe it is up to the recipient country to decide what information to provide.

Needs for pregnancy vigilance in the International Programme for Drug Monitoring
Dr Marie Lindquist

In 1968 after the thalidomide crisis, countries agreed to share data from post-marketing surveillance systems. The Uppsala Monitoring Centre (UMC) was set up 10 years later to administer WHO’s International Programme for Drug Monitoring. UMC functions as a WHO collaborating centre and has more than 120 countries contributing data to its database, including AEFI (though in varied amounts). In many countries a majority of the data originates from pharmaceutical companies. Patients may also report suspected adverse reactions.

New risk scenarios continue to arise. For instance, as new medicines are developed they are not all tested on the affected populations. Also, in a situation of emergency, there is pressure to release
vaccines as quickly as possible. Other risk scenarios include mass vaccinations campaigns, the increased use of combination vaccines, and the use of live vaccines (which could potentially damage the fetus if given to a pregnant woman). Agile pharmacovigilance methods are needed, with full cooperation, communication, and recognition of harm when it occurs.

A number of lessons have been learned over the years, such as the fact that it is difficult to prove causality. Adverse events are rare, thus giving low statistical power to studies. Some might propose that a different standard for evidence should be accepted. And while 1 adverse event in 10,000 vaccinees may be negligible, it is not negligible for the affected person.

Discussion:
The speaker was thanked for the longstanding contribution of the UMC. Several participants raised the issue of anti-vaccine arguments. It was felt that it is not always simple to counter these arguments even if they are obviously wrong. The provision of evidence is part of the answer to these arguments, but some people take rumours or inflammatory reports of harm as evidence. One can only be open and honest. This issue relates to the wider question as to what truth is and how it is perceived. In Europe when there is an adverse case, WHO tries to work both with companies and with regulators to align their responses.

Harmonizing data for decision-making and progress tracking – the approach of the Health Data Collaborative

Dr K Viswanathan

The Health Data Collaborative (HDC) is a global network of 35 partners including governments, UN agencies, foundations, academics, private enterprises, civil society organizations and development partners that are implementing a better approach to strengthening national health information systems and capacity to track progress towards national health priorities and health-related sustainable development goals through:
- Financial and technical support better aligned with country priorities
- Harmonization of data tools and global standards for all countries

The HDC approach aims to achieve:
- Reduction in fragmentation of health data systems in favour of one nationally owned system
- Increase efficiencies of investments in health information systems by coordinating donor support and avoiding duplication
- Development of a technical package of harmonized health information system tools and global standards to be adopted by countries
- Sharing lessons and best practices
- Promoting use of data for policy and accountability

Country investments
As the world transitions to the SDGs, with the vast scope of country data required to monitor progress across health and other sectors, there is a need for smarter, more efficient investments in country data systems and capacities in order to foster development of scaled and sustainable national systems. This requires a much more concerted, integrated approach to measurement and use of evidence, including harnessing of innovations provided by the digital and data revolution, and greater alignment of both domestic and external investments to ensure well-resourced and effective country systems.

There are a small number of countries that are part of a joint learning agenda with HDC partners. The aim of the learning agenda is to demonstrate what works best in terms of effective and efficient approaches to investing in and reforming health information system in different settings.
The initial 3 exemplar countries are: Kenya, Malawi and Tanzania (with others joining in the near future).

Global standards and tools
Collective action of the HDC partners also includes coordination in the development and harmonization of global public goods. The partners will work together to harmonize across a set of global tools, standards and innovation and fragmentation and duplication. One such effort is the development of international standards for health data (based on health program requirements) with application for DHIS 2.0 (software currently used in many countries as their health management information system).

Discussion:
Participants expressed interest in this new development, requesting further information and asking for further reports as the HDC progresses. In response to requests for further information, the speakers explained that Kenya, Malawi and Tanzania were the initial countries that were assisted by the HDC. Kenya, for instance, wished to strengthen its use of data. The HDC provides one system that aims to present data on a range of issues from a range of sources. It offers one source that everyone can use, ensuring that all obtain the same data. The project was said to be indicative of WHO’s core role of standard setting. A module to set standards for data on maternal, newborn, child and adolescent health is being developed. The HDC is an effort to align different data systems in one routine system.

Next steps towards harmonized approaches
Participants agreed that maternal vaccination would be a positive step forward for the health of mothers and babies, especially if delivered in the context of routine maternal and newborn health care. However, it is essential that there should be an effective system of monitoring in place to identify any adverse events that could be associated with maternal immunization. This is not only in the best interests of mothers but is also wanted by the companies that produce vaccines and by the regulators who require it for licensing to go ahead.

Monitoring of pregnancy outcomes for women and their offspring should take the best advantage of all available data sources. Participants urged that terminologies and definitions used in pharmacovigilance for maternal vaccines should be harmonized. They also agreed that the different coding systems used in the delivery of health care should be effectively mapped so that persons doing the reporting of diseases and conditions should not have to do the harmonization themselves. The important factor would be to leverage the different systems to obtain the public health data needed. It was also agreed that the GAIA definitions represented the most promising and appropriate framework to underlie work in this area. It was reported that vaccine companies also indicated their interest in using the GAIA definitions.

For most vaccines, rare untoward effects are not identified during clinical trials, so post-marketing studies carried out by the maternal and child health services will be needed. Clinical trials will provide information about more frequent effects to allow early licensing of important products. Public health surveillance is also used for spontaneous reporting but, in order to interpret the data, knowledge of background rates of the conditions of interest is needed. It was concluded that monitoring should be done in the context of routine service provision rather than surveillance. It would also be important to use electronic medical records where possible. It was proposed that any study on the topic of maternal immunization should include the stages of pregnancy, birth and the postnatal period.
There was general appreciation that the meeting had brought together many different programmes, many different perspectives and many different systems. It would be important to conduct a mapping of existing systems so that countries can work jointly to increase their ability to monitor the most important health outcomes. There was a common desire for a simple system that collects the data that is required. The HIV programme, for example, has considerable experience of studying the effects of medicines in pregnant women and if vaccine studies go ahead it would be beneficial to use the same definitions across programmes. The various types of data required could be derived from a single efficient data system, so that the data gathered are not just vaccine-related data but include all data that can protect the health and well-being of mothers and babies. Participants urged that the need for training must be considered, and it was proposed to make the discussion of GAIA definitions and vaccinations a more formal part of MNCH activities in WHO.

The Chair said that the meeting highlighted many important activities related to safety monitoring of maternal immunization and that there was a need to share information and experience. She said there had been a call to establish a more formal group in order to move forward with efforts to gather more data on maternal immunization, which would require more consistency in data-gathering. The establishment of a more formal long-term group could be a recommendation to the next meeting of the Global Advisory Committee on Vaccine Safety.

The Chair thanked all participants for their contributions to the progress made at the meeting and thanked the WHO staff for making it possible. A one-page meeting summary on “Harmonizing pregnancy vigilance: the way forward” (Annex 3) would be submitted to the meeting of the Global Advisory Committee on Vaccine Safety in early December 2017.
Annexes

Annex 1. Agenda of the meeting

Stakeholders meeting on Maternal Interventions Vigilance: Safety Monitoring and Surveillance in Vaccine and other Research Settings

Domaine de Penthes, Geneva, Switzerland, 20-21 November 2017

Agenda

Background

Maternal immunization has the potential of improving health outcomes for mothers and their babies. Several promising vaccines are in the development pipeline. Safety monitoring of vaccines administered during pregnancy will require enhanced vigilance mechanisms and standardized case definitions of key events in pregnant women and newborns. Immunization, however, is only one of many medical interventions during pregnancy and early childhood. Adequate vigilance requires that harmonization of methods be compatible with the work of other stakeholders including several WHO programmes.

Meeting objectives

This meeting is convened in collaboration between Vaccines, Essential Medicines, Reproductive, and Maternal, Newborn, Child and Adolescent Health departments from WHO. Its preparation benefited from advice of six additional departments. The objectives of the meeting are to:

• review current methods or methodologies to monitor outcomes of maternal immunization and other interventions, with a particular focus on pharmacovigilance;
• assess these vigilance methodologies and identify where harmonization is needed;
• assess their global applicability for maternal immunization and other interventions;
• propose coordination mechanisms and a roadmap to support their harmonization across programmes and partners working on improving pregnancy and early childhood health events.

Expected outcomes

• A report from the meeting will be published by WHO and findings submitted to the December 2017 GACVS meeting.
• Subsequently, it is proposed that the coordination mechanisms that will emerge from this meeting will be further developed by all WHO programmes working on pregnancy interventions to ensure adoption of harmonized methodologies for vigilance and outcome monitoring.
### Day 1 - Monday, 20 November 2017

#### 08:30 Opening session

- Welcoming remarks; participants introduction; adoption of agenda; open question time to Chair and Secretariat (30 min)  
  L. Mason / P. Zuber
- Need for harmonized vigilance approaches for pregnancy interventions and recent initiatives - A partner’s perspective (20 min + 10 min questions)  
  S. Kochhar
- Maternal immunization safety monitoring in low- and middle-income countries: A roadmap for programme development (20 min + 10 min questions)  
  E. Lackritz

#### 10:00 Coffee break

#### 10:30 Monitoring of maternal and early childhood outcomes

**Purpose of the session**
- Review approaches used by WHO programmes and others
- Illustrate current challenges

- WHO landscape for monitoring outcomes of pregnancy (20 min + 10 min questions)  
  A. Moran
- Pregnancy and early childhood outcomes monitoring through health and demographic surveillance systems (20 min + 10 min questions)  
  P. Waiswa (WebEx)
- Discussion (30 min)

#### 12:00 Lunch
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<thead>
<tr>
<th>Time</th>
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<tr>
<td>13:30</td>
<td>Maternal Immunization safety in the context of MNCH interventions (20 min + 10 min questions)</td>
<td>A. Sobanjo-ter Meulen</td>
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<td>14:00</td>
<td><strong>Maternal and early childhood outcomes terminologies</strong></td>
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<td><strong>Purpose of the session</strong></td>
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<td></td>
<td>• Overview of three existing systems</td>
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<td>• Present GACVS advice on vaccine safety during pregnancy</td>
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<td>- ICD 11 definitions of pregnancy outcomes (20 min + 10 min questions)</td>
<td>R. Jakob / D. Chou</td>
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<td>- MedDRA terminology for pregnancy (20 min + 10 min questions)</td>
<td>J. Harrison (WebEx)</td>
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<td>- The GAIA project - Standardized case definitions of adverse events following maternal immunization (20 min + 10 min questions)</td>
<td>J. Bonhoeffer</td>
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<td>- GACVS reviews of the safety of vaccines in pregnancy (20 min + 10 min questions)</td>
<td>M. Gruber (WebEx)</td>
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<td>16:00</td>
<td><strong>Coffee break</strong></td>
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<td>16:30</td>
<td><strong>Breakout – Applicability of existing terminologies</strong></td>
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<td><strong>Purpose of the session</strong></td>
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<td>• Examine 4 maternal or early childhood health outcomes and assess their applicability</td>
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<td>• Compare corresponding terminology systems</td>
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<td></td>
<td>Work groups on abortion, pre-term birth, stillbirth and congenital anomalies</td>
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<tr>
<td>18:00</td>
<td><strong>Adjourn</strong></td>
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Chair: Elizabeth Mason  
Rapporteur: David Bramley

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<td><strong>Report from work groups</strong></td>
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<td>Discussion (20 min)</td>
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<td>09:30</td>
<td><strong>Assessing case definitions</strong></td>
<td>Present ongoing projects</td>
<td>T. Verstraeten</td>
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<td>- Multicenter assessment of definitions to measure early childhood morbid conditions (20 min + 10 min questions)</td>
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<td>- Assessment of definitions for pregnancy and early childhood morbid conditions in industrialized countries</td>
<td>M. Sturkenboom</td>
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<td></td>
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<td>(20 min + 10 min questions)</td>
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<td>10:30</td>
<td><strong>Coffee break</strong></td>
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| 11:00  | **Maternal and early childhood outcomes surveillance systems** | Describe existing pregnancy registries  
Discussion methodological aspects of congenital defect surveillance | C. Moore                            |
|        |                                | - Global systems for monitoring congenital anomalies (20 min + 10 min questions)                           |                                     |
|        |                                | - Attempts at harmonizing reporting on pregnancy outcomes (20 min + 10 min questions)                    | K. Khan                             |
|        |                                | - Use of public health registries in assessing pregnancy interventions (20 min + 10 min questions)       | A. Labrique (WebEx)                 |
| 12:30  | **Lunch**                      |                                                                                                           |                                     |
### 14:00  Evolving needs for assessing pregnancy interventions

**Purpose of the session**
- Discuss approaches and processes for harmonizing public health outcomes monitoring

- A regulator’s perspective to harmonization needs for pregnancy interventions (20 min + 10 min questions)  
  S. Anderson / C. de Vries
- Needs for pregnancy vigilance in the International Programme for Drug Monitoring (20 min + 10 min questions)  
  M. Lindquist
- Harmonizing data for decision making and progress tracking – the Health Data Collaborative Approach (10 min)  
  K. Viswanathan
- Discussion (20 min)

### 15:30  Coffee break

### 16:00  Next steps towards harmonized approaches

**Purpose of the session**
- Moderated discussion

### 17:00  Adjourn
Annex 2. List of participants

**PARTICIPANTS**

<table>
<thead>
<tr>
<th><strong>PARTICIPANTS</strong></th>
<th><strong>T****el.:</strong></th>
<th><strong>E-mail:</strong></th>
</tr>
</thead>
</table>
| **Dr Steve Anderson**  
Director  
Office of Biostatistics and Epidemiology  
Center for Biologics Evaluation and Research  
U.S. Food and Drug Administration  
10903 New Hampshire Ave.  
Bldg 71, Room 1216  
Silver Spring, MD 20993  
United States of America | +1 240 402 8577 | Steven.Anderson@fda.hhs.gov |
| **Ms Sharan Apoorva**  
Programme Officer, Vaccine Safety Division  
International Clinical Epidemiology Network (INCLEN)  
F1/5, Phase 1 Okhla Industrial Area  
New Delhi 110020  
India | +41 77 963 8196 | apoorva@inclentrust.org |
| **Dr Martina Lukong Baye**  
Coordinator  
National Multisector Program to Combat Maternal, Newborn and Child Mortality (PLMI)  
Ministry of Public Health  
Yaoundé  
Cameroon | +237 2222 19065 | tinabayel@yahoo.fr |
| **Dr Jan Bonhoeffer**  
President  
Brighton Collaboration Foundation  
Spitalstr. 33  
CH - 4056 - Basel  
Switzerland | +41 764 191 890 | j.bonhoeffer@brightoncollaboration.org |
| **Pr Corinne de Vries**  
European Medicines Agency (EMA)  
Canary Wharf  
30 Churchill Place  
London, E14 5EU  
United Kingdom | +44 20 36607248 | corinne.devries@ema.europa.eu |
<table>
<thead>
<tr>
<th>Name</th>
<th>Title/Role</th>
<th>Address</th>
<th>Telephone</th>
<th>Email</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr Linda Eckert</td>
<td>Professor, Obstetrics &amp; Gynecology Adjunct Professor, Global Health</td>
<td>University of Washington 325 9th Ave Box 359865 Seattle, WA 98104 USA</td>
<td>+1 206-744-3977</td>
<td><a href="mailto:Eckert@uw.edu">Eckert@uw.edu</a></td>
</tr>
<tr>
<td>Dr Marie-Hélène Grillet</td>
<td>Representative International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) Sanofi Pasteur Pharmacovigilance Campus Sanofi Lyon 14, Espace Henry Vallée 69007 Lyon France</td>
<td></td>
<td>+33 437 669 840</td>
<td><a href="mailto:marie-helene.grillet@sanofi.com">marie-helene.grillet@sanofi.com</a></td>
</tr>
<tr>
<td>Dr Marion Gruber (by WebEx)</td>
<td>Director Office of Vaccines Research and Review (OVRR) Center for Biologics Evaluation and Research (CBER) Food and Drug Administration 1401 Rockville Pike Rockville, MD 20852 United States of America</td>
<td></td>
<td>+1 301 796 2630</td>
<td><a href="mailto:marion.Gruber@fda.hhs.gov">marion.Gruber@fda.hhs.gov</a></td>
</tr>
<tr>
<td>Dr Judy Harrison (by WebEx)</td>
<td>Chief Medical Officer MedDRA Maintenance and Support Services Organization (MSSO) 133 Stallings Island St. Bluffton, SC 29910 United States of America</td>
<td></td>
<td>+1 908 437 8534</td>
<td><a href="mailto:judy.harrison@meddra.org">judy.harrison@meddra.org</a></td>
</tr>
<tr>
<td>Pr Khalid Khan</td>
<td>BJOG Editor-in-Chief The CoRe Outcomes in Women’s and Newborn health Initiative (CROWN) Women's Health Research Unit Centre for Primary Care and Public Health Blizard Institute Barts and The London School of Medicine and Dentistry Yvonne Carter Building 58 Turner Street London E1 2AB United Kingdom</td>
<td></td>
<td>+44 7977 559415</td>
<td><a href="mailto:k.s.khan@qmul.ac.uk">k.s.khan@qmul.ac.uk</a></td>
</tr>
<tr>
<td>Dr Sonali Kochhar</td>
<td>Medical Director, Global Healthcare Consulting E-16 A, Defence Colony New Delhi-110024 India</td>
<td></td>
<td>+91-9810848944</td>
<td><a href="mailto:sonalikochhar@yahoo.co.in">sonalikochhar@yahoo.co.in</a></td>
</tr>
<tr>
<td>Name</td>
<td>Position</td>
<td>Institution</td>
<td>Address</td>
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<tr>
<td>Dr Sushena Krishnaswamy</td>
<td>Infectious Diseases Physician</td>
<td>Monash Infectious Diseases</td>
<td>Monash Health</td>
<td>+61 3 9594 4564</td>
</tr>
<tr>
<td>Dr Alain Labrique (by Webex)</td>
<td>Director</td>
<td>Johns Hopkins University Global mHealth Initiative</td>
<td>615 N. Wolfe St.</td>
<td>+1 443 287-4744</td>
</tr>
<tr>
<td>Dr David J. Lewis</td>
<td>Representative</td>
<td>International Federation of Pharmaceutical Manufacturers and Associations (IFPMA)</td>
<td>Novartis Campus</td>
<td>+41 61 324 3589</td>
</tr>
<tr>
<td>Dr Marie Lindquist</td>
<td>Director</td>
<td>Uppsala Monitoring Centre (UMC) WHO Collaborating Centre for International Drug Monitoring</td>
<td>751 40 Uppsala</td>
<td>+46 18 65 60 60</td>
</tr>
<tr>
<td>Dr Punam Mangtani</td>
<td>Associate Professor of Epidemiology (Clinical) Programme Director MSc Epidemiology Faculty of Epidemiology and Population Health</td>
<td>London School of Hygiene and Tropical Medicine Keppel Street London WC1E 7 HT</td>
<td></td>
<td>+44 20 7 927 2057</td>
</tr>
<tr>
<td>Dr Elizabeth Mason</td>
<td>Consultant</td>
<td>Global Public Health Sàrl</td>
<td>CH – 1218 Le Grand-Saconnex</td>
<td>+44 7539584181 (UK)  +41 788988262 (Swiss)</td>
</tr>
</tbody>
</table>
| **Pr Matthews Mathai**  
| Chair in Maternal and Newborn Health  
| Centre for Maternal and Newborn Health  
| Liverpool School of Tropical Medicine  
| Liverpool  
| United Kingdom | **tel.: +44 151 705 3396**  
| **e-mail:** Matthews.Mathai@lstmed.ac.uk |
| **Dr Ushma Mehta**  
| Senior Researcher  
| Centre for Infectious Disease Epidemiology and Research  
| School of Public Health and Family Medicine  
| University of Cape Town  
| Observatory 7925  
| South Africa | **tel.:**  
| **e-mail:** ushmaza@gmail.com |
| **Dr Olga Menang**  
| Pharmacovigilance Senior Officer  
| Foundation for Appropriate Technologies in Health (PATH)  
| Rue de Varembé 7  
| 1202 Geneva  
| Switzerland | **tel.: +41 22 747 1083**  
| **e-mail:** omenang@path.org |
| **Dr Cynthia Moore**  
| Director  
| Division of Birth Defects and Developmental Disabilities  
| National Center on Birth Defects and Developmental Disabilities  
| Centers for Disease Control and Prevention  
| 4770 Buford Highway, Mail-Stop E-86  
| Atlanta, GA 30341  
| United States of America | **tel.: +1 404 498 3927**  
| **e-mail:** cam0@cdc.gov |
| **Dr Flor Muñoz Rivas**  
| Associate Professor of Pediatrics, Section of Infectious Diseases  
| Molecular Virology and Microbiology  
| Baylor College of Medicine  
| Transplant Infectious Diseases  
| Texas Children’s Hospital  
| One Baylor Plaza, BCM/280  
| Houston, Texas 77030  
| United States of America | **tel.: +1 832 824 4371**  
<p>| <strong>e-mail:</strong> <a href="mailto:florm@bcm.edu">florm@bcm.edu</a> |</p>
<table>
<thead>
<tr>
<th>Name</th>
<th>Title and Affiliation</th>
<th>Contact Information</th>
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<tbody>
<tr>
<td>Pr Pieter Neels</td>
<td>Human Vaccine Committee Chair International Alliance for Biological Standardization (IABS) Vaccine-Advice BVBA Associate Professor University of Namur</td>
<td>tel.: +32 33 84 16 93 e-mail: <a href="mailto:Pieter.Neels@vaccine-advice.be">Pieter.Neels@vaccine-advice.be</a></td>
</tr>
<tr>
<td></td>
<td>St. Antoniusbaan 281 2980 Zoersel Belgium</td>
<td></td>
</tr>
<tr>
<td>Dr Sonia Pagliusi</td>
<td>Executive Secretary Developing Countries Vaccine Manufacturers Network (DCVMN)</td>
<td>tel.: +41 22 595 1393 e-mail: <a href="mailto:s.pagliusi@dcvmn.org">s.pagliusi@dcvmn.org</a></td>
</tr>
<tr>
<td></td>
<td>Route de Crassier 7 1262 Nyon Switzerland</td>
<td></td>
</tr>
<tr>
<td>Dr Alexander Precioso</td>
<td>Vice-President Developing Countries Vaccine Manufacturers Network (DCVMN) Butantan Sao Paulo Brazil</td>
<td>tel.: +55 11 3723-2121 e-mail: <a href="mailto:alexander.precioso@butantan.gov.br">alexander.precioso@butantan.gov.br</a></td>
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<tr>
<td></td>
<td>Butantan Sao Paulo Brazil</td>
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</tr>
<tr>
<td>Dr Ajoke Sobanjo-ter Meulen</td>
<td>Senior Program Officer Bill and Melinda Gates Foundation 1432 Elliott Ave. West Seattle, WA 98119 United States of America</td>
<td>tel.: +1 206-709-3100 e-mail: <a href="mailto:Ajoke.Sobanjo-TerMeulen@gatesfoundation.org">Ajoke.Sobanjo-TerMeulen@gatesfoundation.org</a></td>
</tr>
<tr>
<td></td>
<td>1432 Elliott Ave. West Seattle, WA 98119 United States of America</td>
<td></td>
</tr>
<tr>
<td>Pr Andy Stergachis</td>
<td>Professor of Pharmacy &amp; Global Health Associate Dean, School of Pharmacy Director, Global Medicines Program University of Washington H-362B Box 357631 Seattle, WA 98195-7631 United States of America</td>
<td>tel.: +1 206 221 0703 e-mail: <a href="mailto:stergach@uw.edu">stergach@uw.edu</a></td>
</tr>
<tr>
<td></td>
<td>University of Washington</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Seattle, WA 98195-7631 United States of America</td>
<td></td>
</tr>
<tr>
<td>Pr Miriam Sturkenboom</td>
<td>President of VACCINE.GRID Foundation Department of Global Health Julius Center Utrecht University Medical Center Utrecht The Netherlands</td>
<td>tel.: +31 107044126 e-mail: <a href="mailto:mcjm.sturkenboom@gmail.com">mcjm.sturkenboom@gmail.com</a></td>
</tr>
<tr>
<td></td>
<td>Julius Center Utrecht University Medical Center Utrecht The Netherlands</td>
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</tr>
<tr>
<td>Dr Thomas Verstraeten</td>
<td>Managing Director P-95</td>
<td>Koning Leopold III laan 1 3001 Heverlee Belgium tel.: +32 474 534868 e-mail: <a href="mailto:thomas.verstraeten@p-95.com">thomas.verstraeten@p-95.com</a></td>
</tr>
<tr>
<td>Dr Peter Waiswa (by WebEx)</td>
<td>Associate Professor</td>
<td>Department of Health Policy, Planning and Management Makere University School of Public Health INDEPTH Network Maternal and Newborn Health Research Kampala Uganda tel.: +256 414534258 e-mail: <a href="mailto:pwaiswa@musph.ac.ug">pwaiswa@musph.ac.ug</a></td>
</tr>
<tr>
<td>Mr David Bramley</td>
<td></td>
<td>Chemin des Vergers 13 1197 Prangins Switzerland tel.: +41 22 362 0327 e-mail: <a href="mailto:david@bramley.ch">david@bramley.ch</a></td>
</tr>
<tr>
<td>Ms Alba Maria Ropero</td>
<td>Regional Advisor Immunization Unit</td>
<td>Department of Family, Gender and Life course WHO Regional Office for the Americas 525, 23rd Street, N.W. Washington, D.C. 20037 United States of America tel.: +1 202 974 3706 e-mail: <a href="mailto:roperoal@paho.org">roperoal@paho.org</a></td>
</tr>
<tr>
<td>Dr Houda Langar</td>
<td>Regional Adviser Vaccines Regulation and Production (VRP)</td>
<td>Department of Health System Development (HSD) WHO Regional Office for the Eastern Mediterranean Abdul Razzak Al Sanhouri Street Nasr City/Cairo Egypt tel.: +202 227 65690 e-mail: <a href="mailto:langarh@who.int">langarh@who.int</a></td>
</tr>
<tr>
<td>Mr Oleg Benes</td>
<td>Technical Officer Vaccine-preventable Diseases and Immunization (VPI)</td>
<td>Communicable Diseases and Health Security (DCH) WHO Regional Office for Europe UN City, Marmorvej 51 2100 Copenhagen Denmark tel.: +45 45337052 e-mail: <a href="mailto:beneso@who.int">beneso@who.int</a></td>
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**WHO HEADQUARTERS**

<table>
<thead>
<tr>
<th>Name</th>
<th>Position</th>
<th>Telephone Number</th>
<th>Email Address</th>
</tr>
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<tbody>
<tr>
<td>Dr Madhav Balakrishnan</td>
<td>Medical Officer</td>
<td>+41 22 791 3786</td>
<td><a href="mailto:balakrishnanm@who.int">balakrishnanm@who.int</a></td>
</tr>
<tr>
<td><strong>Safety and Vigilance</strong></td>
<td>Regulation of Medicines and other Health Technologies Essential Medicines and Health Products Health Systems and Innovation</td>
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<tr>
<td><strong>World Health Organization</strong></td>
<td>Avenue Appia 20</td>
<td>1211 Geneva 27</td>
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<td></td>
<td><strong>Switzerland</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dr Doris Chou</td>
<td>Medical Officer</td>
<td>+41 22 791 5030</td>
<td><a href="mailto:choud@who.int">choud@who.int</a></td>
</tr>
<tr>
<td><strong>Adolescents and at-Risk Populations</strong></td>
<td>Reproductive Health and Research Family, Women’s and Children’s Health</td>
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<td><strong>World Health Organization</strong></td>
<td>Avenue Appia 20</td>
<td>1211 Geneva 27</td>
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<td></td>
<td><strong>Switzerland</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dr Christine Guillard Maure</td>
<td>Technical Officer</td>
<td>+41 22 791 1532</td>
<td><a href="mailto:maurec@who.int">maurec@who.int</a></td>
</tr>
<tr>
<td><strong>Safety and Vigilance</strong></td>
<td>Regulation of Medicines and other Health Technologies Essential Medicines and Health Products Health Systems and Innovation</td>
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</tr>
<tr>
<td><strong>World Health Organization</strong></td>
<td>Avenue Appia 20</td>
<td>1211 Geneva 27</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Switzerland</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dr Christine Halleux</td>
<td>Scientist</td>
<td>+41 22 791 2559</td>
<td><a href="mailto:halleuxc@who.int">halleuxc@who.int</a></td>
</tr>
<tr>
<td><strong>Intervention and Implementation Research</strong></td>
<td>Special Programme for Research and Training in Tropical Diseases HIV/AIDS, TB and Neglected Tropical Diseases</td>
<td></td>
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<tr>
<td><strong>World Health Organization</strong></td>
<td>Avenue Appia 20</td>
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<td></td>
<td><strong>Switzerland</strong></td>
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<td></td>
</tr>
<tr>
<td>Dr Robert Jakob</td>
<td>Medical Officer</td>
<td>+41 22 791 5877</td>
<td><a href="mailto:jakobr@who.int">jakobr@who.int</a></td>
</tr>
<tr>
<td><strong>Data Standards and Informatics</strong></td>
<td>Information, Evidence and Research Health Systems and Innovation</td>
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<td>Name</td>
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</tr>
<tr>
<td>Dr Eve Lackritz</td>
<td>Medical Officer</td>
<td>High Threat Pathogens, Infectious Hazard Management, WHO Health Emergencies Programme</td>
<td>tel.: +41 22 791 3494, e-mail: <a href="mailto:lackritze@who.int">lackritze@who.int</a></td>
</tr>
<tr>
<td>Dr Smaragda Lamprianou</td>
<td>Consultant</td>
<td>Safety and Vigilance, Regulation of Medicines and other Health Technologies, Essential Medicines and Health Products, Health Systems and Innovation</td>
<td>e-mail: <a href="mailto:lamprianous@who.int">lamprianous@who.int</a></td>
</tr>
<tr>
<td>Dr Viola Macolic Sarinic</td>
<td>Technical Officer</td>
<td>Safety and Vigilance, Regulation of Medicines and other Health Technologies, Essential Medicines and Health Products, Health Systems and Innovation</td>
<td>tel.: +41 22 791 1069, e-mail: <a href="mailto:macolicv@who.int">macolicv@who.int</a></td>
</tr>
<tr>
<td>Dr Garrett Mehl</td>
<td>Scientist</td>
<td>Adolescents and at-Risk Populations, Reproductive Health and Research, Family, Women’s and Children’s Health</td>
<td>tel.: +41 22 791 4915, e-mail: <a href="mailto:mehlg@who.int">mehlg@who.int</a></td>
</tr>
<tr>
<td>Dr Allisyn Moran</td>
<td>Scientist</td>
<td>Epidemiology, Monitoring and Evaluation, Maternal, Newborn, Child and Adolescent Health, Family, Women’s and Children’s Health</td>
<td>tel.: +41 22 791 1956, e-mail: <a href="mailto:morana@who.int">morana@who.int</a></td>
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<tr>
<td>Dr Clive Ondari</td>
<td>Coordinator</td>
<td>Safety and Vigilance</td>
<td>World Health Organization</td>
</tr>
<tr>
<td>Dr Kavitha Viswanathan</td>
<td>Technical Officer</td>
<td>Global Platform for Measurement and Accountability</td>
<td>World Health Organization</td>
</tr>
<tr>
<td>Dr Shanthi Pal</td>
<td>Group Lead, Medicines Safety</td>
<td>Safety and Vigilance</td>
<td>World Health Organization</td>
</tr>
<tr>
<td>Dr Juan Pablo Peña-Rosas</td>
<td>Coordinator</td>
<td>Evidence and Programme Guidance</td>
<td>World Health Organization</td>
</tr>
<tr>
<td>Mrs Francoise Renaud</td>
<td>Technical Officer</td>
<td>Strategic Information and Planning</td>
<td>World Health Organization</td>
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<tr>
<td>Dr Nathalie Roos</td>
<td>Technical Officer</td>
<td>Epidemiology, Monitoring and Evaluation</td>
<td>Maternal, Newborn, Child and Adolescent Health Family, Women’s and Children’s Health World Health Organization Avenue Appia 20 1211 Geneva 27 Switzerland</td>
</tr>
<tr>
<td>Dr Joshua Vogel</td>
<td>Technical Officer</td>
<td>Maternal Perinatal Health, Prevent Unsafe Abortion</td>
<td>Reproductive Health and Research Family, Women’s and Children’s Health World Health Organization Avenue Appia 20 1211 Geneva 27 Switzerland</td>
</tr>
<tr>
<td>Dr Patrick Zuber</td>
<td>Group Lead, Vaccine Safety</td>
<td>Safety and Vigilance</td>
<td>Regulation of Medicines and other Health Technologies Essential Medicines and Health Products Health Systems and Innovation World Health Organization Avenue Appia 20 1211 Geneva 27 Switzerland</td>
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Annex 3. Harmonizing pregnancy vigilance: the way forward

Maternal immunization has the potential to improve health outcomes for women and their babies. The stakeholder meeting gathered technical experts from academia, technical and regulatory agencies. It highlighted considerable efforts ongoing in several public health communities to generate the data necessary to measure progress and minimize risks. It also confirmed that many existing programmes are complementary and can potentially build a stronger joint system. Improved pregnancy vigilance will benefit from enhanced collaboration and can provide quality data needed by all stakeholders, including several WHO programmes.

During the meeting, examples of current terminologies and systems for monitoring maternal, fetal and early childhood outcomes were reviewed and assessed. Subsequently, examples of surveillance and research settings where those terminologies are being used were reviewed. Harmonized monitoring of health outcomes for pregnancy interventions\(^1\) will benefit from a broad agreement on a minimal set of components that should be common to study in order to detect important health adverse outcomes and allow comparison across study sites and countries.

Discussions addressed global applicability of vigilance methodologies for maternal health interventions during pregnancy. Several situations were highlighted that will affect the quantity and quality of data available. For example, during clinical research, there is a higher possibility for specific diagnosis, as compared to public health surveillance where diagnoses may be based on minimal requirements. Likewise, weak civil registration systems can even prevent the identification of vital events. It has therefore been proposed to develop harmonized sets of minimal data to be collected for all studies and evaluations of pregnant women according to study characteristics, ranging from minimal to optimal infrastructure and clinical conditions. The following elements will be considered in combination:

- health-care infrastructure and information system capacity (minimal-, intermediate- and high-income setting);
- availability of civil registration and vital statistics (CVSR) and/or pregnancy registries;
- type of study (clinical trial, observational study, public health surveillance);
- outcome of interest (maternal, fetal/newborn/child);
- stage of pregnancy during which interventions\(^2\) are being studied (first, second or third trimester [define cut-offs], first two, last two, any trimester with consideration to pre-pregnancy and lactation).

Following the meeting, WHO’s Global Advisory Committee on Vaccine Safety (GACVS) plans to review findings and recommendations at its 6–7 December 2017 meeting and to assess progress against recommendations made in June 2016 when it examined guidelines developed by the Global Alignment of Immunization safety Assessment in pregnancy (GAIA) project. As the GACVS focus is vaccine-specific, participants’ views will also be sought on other important WHO processes. This includes, in particular, presentation to WHO programmes on maternal and child health and on reproductive health, and to the International Classification of Diseases Medical and Scientific Advisory Committee, to examine recent tools such as GAIA definitions and their mapping to ICD and

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\(^1\) Any intervention in pregnant women such as medical treatment, diagnostic procedure or preventive intervention such as nutritional supplement or vaccination.

\(^2\) This is the period in which the interventions are given that are being studied – the outcomes observed will also include the newborn and child.
MedDRA terms. The establishment of an interdepartmental task force to address harmonization between data systems will be proposed within WHO. Once established, the task force will reach out to multiple stakeholders through the WHO network of regional and country offices and propose collaborative mechanisms to synergize expertise and optimize data access.