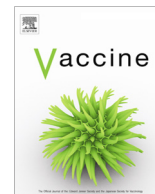


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## Global alignment of immunization safety assessment in pregnancy – The GAIA project



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### ABSTRACT

Immunization in pregnancy provides a promising contribution to globally reducing neonatal and under-five childhood mortality and morbidity. Thorough assessment of benefits and risks for the primarily healthy pregnant women and their unborn babies is required. The GAIA project was formed in response to the call of the World Health Organization for a globally concerted approach to actively monitor the safety of vaccines and immunization in pregnancy programs. GAIA aims to improve the quality of outcome data from clinical vaccine trials in pregnant women with a specific focus on the needs and requirements for safety monitoring in LMIC.

In the first year of the project, a large and functional network of experts was created. The first outputs include a guidance document for clinical trials of immunization in pregnancy, a basic data collection guide, ten case definitions of key obstetric and neonatal health outcomes, an ontology of key terms and a map of pertinent disease codes.

The GAIA Network is designed as an open and growing forum for professionals sharing the GAIA vision and aim. Based on the initial achievements, tools and services are developed to support investigators and strengthen immunization in pregnancy programs with specific focus on LMIC.

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### 1. Introduction

Reducing neonatal and under-five childhood mortality and morbidity is a target of the Health Sustainable Development Goal [1]. Immunization in pregnancy provides a promising contribution

to achieving this goal [2]. Whilst immunizing pregnant women against tetanus has been practiced for decades, new strategies such as antenatal influenza and pertussis vaccination are now being systematically evaluated and are recommended by WHO [3–5]. Additional promising vaccines are in development for global use in pregnancy such as group B streptococcal (GBS) and respiratory syncytial virus (RSV) vaccines [6–8].

Introduction of these vaccines comes with tremendous potential benefit, specifically for women and children living in low and middle income countries (LMIC) due to the higher perinatal and

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infant mortality rates in this setting. However, there is much at stake when it comes to immunization of pregnant women. The safety of any product given to primarily healthy mothers and their unborn babies receives intense professional and public scrutiny. First, this is because two lives can be directly affected during a time of vulnerability, yet both are also likely to benefit from the prevention of serious infections. Second, safety concerns are not exclusive to maternal vaccination programs alone since similar concerns are raised with the use of the same vaccines in routine childhood and adult immunization programs (e.g., influenza and pertussis vaccines). In turn, a vaccine found to be safe for pregnant women and neonates would likely be well accepted by the general public for other target groups. Thus, the potential beneficial and harmful effects of immunization in pregnancy and its ethical implications are augmented by the ramifications on routine pediatric and adult immunization programs. Therefore, thorough assessment of the safety of vaccines during pregnancy is required given the potential for numerous confounding events associated with pregnancy itself in women and the fetus, and in the neonatal period.

Particularly challenging for monitoring and communicating the benefits and risks of immunization programs in pregnancy is that several common health outcomes may be perceived as both a measure of benefit and risk and this assessment may change over time. For example, immunization may decrease the stillbirth rate if a vaccine decreases infections that lead to stillbirth. However, stillbirths will still occur in pregnancies and may also be perceived and reported as adverse events following immunization. Particularly early during program introduction, the impact of reducing mortality due to immunization may not be detectable on the population level while pregnancy complications, such as stillbirth, are registered. This makes early benefit-risk analyses challenging and may compromise the viability of an immunization program independently of any causal relationship between the complication and immunization.

Therefore, product or program specific safety issues need to be identified to appropriately assess the benefit-risk profile of these vaccines and their implementation programs and to protect the target population from unintended harm. On the other hand, unfounded public or professional concerns can jeopardize beneficial vaccine programs and need to be rapidly refuted based on rigorous and credible science and globally coordinated decision-making and communication.

Addressing these issues requires more than communication strategies. It requires active monitoring and research to enable confident communication with high quality data. As important safety concerns tend to be serious but rare health events, their investigation requires a harmonized approach and needs to be based on large sample sizes to provide satisfactory statistical confidence of risk estimates and to enable comparison of multiple populations and programs. This is best addressed by close global collaboration based on a harmonized approach [9–11].

The general need for a globally concerted approach to actively monitor the safety of vaccines and programs of immunization is recognized by the WHO Global Vaccine Safety Blueprint, the strategic plan of the Global Vaccine Safety Initiative [12]. A recent WHO consultation specifically identified the currently fragmented research, the current lack of data comparability as well as the need to improve the quality of safety data to inform decision making and system strengthening [13].

## 2. The GAIA project

### 2.1. Aim and objectives and first outcomes

The GAIA project aims to improve the outcome data quality from clinical vaccine trials in pregnant women with a specific focus

on the needs and requirements for safety monitoring in LMIC. GAIA addresses three main objectives to achieving this aim. First, to improve comparability of safety data across products, programs, and populations for effective and efficient strengthening of immunization programs in pregnant women. Second, to optimize the value of local investigations by global harmonization of methods. Third, to promote scientific progress by increasing analytic power and options through globally concerted approaches.

In a first step, the GAIA project has established an open and dynamic network of professionals concerned with monitoring the safety of immunization in pregnancy. Together, compiling a shared terminology and developing case definitions for selected obstetric and neonatal outcomes create a common understanding of the outcomes monitored. Consensus guidance is developed for harmonized safety monitoring in clinical trials, and tools are created for effective and efficient data collection, synthesis and pooling, with a focus on LMIC needs and requirements.

### 2.2. Network

The development of a global standard requires the engagement of a large number of stakeholders (e.g. regulatory agencies, public health organizations, academic institutions and health care providers) and experts who will collaborate on a voluntary basis on the development, review and validation of the standards and tools through an iterative process in the framework of multiple streamlined working groups with a specified task. The GAIA Network is designed as an open and growing forum for professionals sharing the GAIA vision and aim. In the first year of the project (January to December 2015), the forum of partners, participants and stakeholders has grown to 412 individual professionals. This was achieved by identifying and inviting professionals active in the field and calling for participation via pertinent professional organizations and mailing lists. Table 1 shows their country of origin and the distribution across WHO regions.

The formation and coordination of the network and the creation and guidance of the working groups and activities requires a dedicated small group of partners driving progress. In the GAIA project, experts from 13 organizations (The US National Institutes of Health, Brighton Collaboration Foundation, World Health Organization, Global Healthcare Consulting, University of Washington, Baylor College of Medicine, Hudson Institute of Medical Research, Erasmus Medical Center, Cincinnati Children's Hospital, St George's, University of London, Public Health Agency Canada, Synapse Research Management Partners and International Alliance for Biological Standardization) collaborate in a carefully designed governance structure to coordinate and guide the activities of the network partners [14].

The GAIA project leverages the unique accrual of expertise in its project partners and the wider network and is designed to achieve its aim by capitalizing on existing methods and infrastructures. In the following sections, we outline the methods and first outcomes of the GAIA project.

### 2.3. Standardized case definitions for key outcomes

WHO and the Brighton Collaboration (BC) held a consultancy of key stakeholders in July 24–25, 2014 in Geneva to review current practice and advice on a strategic direction towards a harmonized approach for monitoring immunization in pregnancy programs [13]. This meeting highlighted the current lack of harmonization and the missed opportunity of giving added value to individual studies by overcoming fragmented research and diverse approaches through consensus formation and harmonization. For example, there is limited consensus and harmonization across studies and analyses on even the most fundamental terms and

**Table 1**  
GAIA Network by World Health Organization region and country.

Region	Country	Count	Percentage	Region	Country	Count	Percentage	
AFRO	South Africa	8	7.5%	EURO	UK	17	19%	
	Uganda	5			Netherlands	9		
	Burkina Faso	2			Sweden	7		
	Congo DR	2			Denmark	5		
	The Gambia	2			Germany	5		
	Ghana	2			Italy	5		
	Kenya	2			Spain	5		
	Burundi	1			United Kingdom	4		
	Cameroon	1			Greece	3		
	Ethiopia	1			Switzerland	3		
	Lebanon	1			France	2		
	Moçambique	1			Hungary	2		
	Nigeria	1			Latvia	2		
	Sudan	1			Albania	1		
	Togo	1			Austria	1		
	EMRO	Egypt			1	Belgium		1
		Iran			1	Croatia		1
Morocco		1	Poland	1				
United Arab Emirates		1	Israel	1				
PAHO	USA	131	Portugal	1				
	Uruguay	1	Russia	1				
	Colombia	1	Serbia	1				
	Canada	27	Slovenia	1				
	Brazil	7	WPRO	Taiwan	1			
	Bolivia	1		Philippines	4			
	Argentina	5		New Zealand	2			
SEARO	India	26	Lao	1				
	Pakistan	5	Korea Rep.	1				
	Bangladesh	2	Japan	1				
	Sri Lanka	1	Cambodia	1				
	Nepal	1	Australia	12				
	Indonesia	1	INT <sup>a</sup>	Int. Organizations	64 (15%)			
	Bhutan	1						
	Thailand	1						

<sup>a</sup> This category is not a WHO Region, but comprises organizations with primarily international or global scope (e. g. international vaccine manufacturers, public health organizations).

concepts such as stillbirth or accurate assessment of gestational age [15]. Such differences can significantly impact interpretation and meaningful data comparisons.

The GAIA consortium is developing standardized case definitions of key outcomes according to the Brighton Collaboration standard process [16]. Case definition development is prioritized based on the recommendations of the global consultative process held at the World Health Organization in 2014 and by the ad hoc need for monitoring emerging safety concerns [17]. To achieve the need of developing many definitions in a short timeframe, the Brighton Collaboration standard process was expanded to enable “batch production” of definitions. Two task forces comprising expertise from public health institutes, regulatory authorities,

academic and patient care organizations and vaccine manufacturers were created, to simultaneously develop ten neonatal and ten obstetric outcome definitions, respectively, in dedicated working groups. These groups are primarily comprised of neonatologists and/or obstetricians while a few coordinating and advising professionals contribute vaccine safety expertise and guided the groups on the Brighton Collaboration standard method of case definition development. Case definitions are developed specifically to incorporate clinical assessment methods commonly used in LMIC to optimize inclusion of cases from all settings. The draft case definitions are developed based on literature review and consensus formation within the respective working groups. These documents are submitted for peer review by a reference group comprising the GAIA Network of professionals concerned with immunization in pregnancy, the Brighton Collaboration Network of professionals concerned with vaccine safety and additional organizations or professional societies with expertise in the respective outcome. Overall case definition development was coordinated by Global Health Consulting, the neonatal task force by Baylor College of Medicine and the obstetric task force by University of Washington. Together with the other partners in the Coordination Team, they were guiding the simultaneous activities of over 200 volunteering professionals in the ten working groups, each led by a subject matter expert driving the respective manuscript development. The first 10 case definitions (Table 2) establishing the proof of principle of this modified approach are published in this special issue of Vaccine [18–27]. A subsequent set of 10 prioritized case definitions is in development (Table 2). Demonstrating the flexibility, efficiency and effectiveness of this established process, an additional working group was formed to develop a case definition of microcephaly on fast track in response to the Zika virus epidemic and in preparation of related vaccine development efforts.

2.4. Guidelines and data collection matrix

The WHO and the Brighton Collaboration (BC) consultancy also recognized the need for guidance on basic data collection, analysis and presentation of vaccine safety data. This is specifically, because no such global consensus guidelines exist to meet the need of concerted safety monitoring throughout the life cycle of vaccines or for global access in rapidly emerging immunization in pregnancy programs.

The GAIA project develops guidelines for harmonized data collection, analysis and presentation according to the Brighton Collaboration standard process [16]. Based on existing Brighton Collaboration guidance documents, St George’s, University of London coordinated the development of the first GAIA guideline on vaccine safety monitoring in clinical trials, which was finalized following wide peer review and feedback from investigators of ongoing studies and parallel projects. It is published in this special issue of Vaccine [28].

**Table 2**  
Standardized case definitions developed for the first 21 obstetric and neonatal outcomes.

	Obstetric outcomes	Neonatal outcomes	Enabling terms
First set of 10 case definitions	<ul style="list-style-type: none"> <li>• Hypertensive disorders of pregnancy</li> <li>• Non-reassuring fetal status</li> <li>• Postpartum hemorrhage</li> <li>• Pathways to premature birth</li> <li>• Maternal death</li> </ul>	<ul style="list-style-type: none"> <li>• Stillbirth</li> <li>• Preterm birth</li> <li>• Congenital anomalies</li> <li>• Neonatal infections</li> <li>• Neonatal death</li> </ul>	<ul style="list-style-type: none"> <li>• Assessment of Gestational Age</li> <li>• Live birth</li> </ul>
Second set of 10 case definitions	<ul style="list-style-type: none"> <li>• Abortion</li> <li>• Antenatal bleeding</li> <li>• Gestational diabetes</li> <li>• Dysfunctional labor</li> <li>• Intra uterine growth retardation</li> </ul>	<ul style="list-style-type: none"> <li>• Low birth weight</li> <li>• Small for gestational age</li> <li>• Neonatal encephalopathy</li> <li>• Respiratory distress in the newborn</li> <li>• Failure to thrive</li> </ul>	
Additional case definition		<ul style="list-style-type: none"> <li>• Microcephaly</li> </ul>	

St George's, University of London also coordinated the development of a data collection matrix outlining key variables to be collected in different safety monitoring settings during the vaccine and program life cycle. Based on the review of case report forms (CRF) from previous immunization in pregnancy trials and the new case definitions and guidance document a tailored subset was compiled to facilitate harmonized collection of data in CRFs in clinical vaccine trials involving pregnant women where safety is an outcome. It was finalized following wide peer review and feedback from investigators of ongoing studies and parallel projects and is also published in this special issue of *Vaccine* [29].

### 2.5. Tools

To further promote a common understanding and shared language, a list of over 3000 terms comprising obstetric and neonatal outcomes (e.g. stillbirth) and enabling terms (e.g. prematurity) is structured in an ontology catalog demonstrating their hierarchical and conceptual dependencies enriched by synonyms and disease concept descriptions. This is of particular use for the development of multilingual data collection forms. This effort builds on the existing products and expertise at the Enterprise Vocabulary Services at the National Cancer Institute also in collaboration with the National Children's Study and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development at NIH and will be made available as an dedicated, user friendly, searchable database on the NIH website.

The case definitions with the glossary and ontology of terms have enabled creation of a map of disease codes that can be used for retrieval of data on specific outcomes from electronic health care databases (e.g., ICD9, ICD10, MedDRA, WHOArt, and READ). The mapped disease codes will be made available via the same GAIA terminology database described above. A systematic literature search on existing observational studies around pertussis and influenza maternal immunization safety was coordinated by Erasmus Medical Center and will reflect disease codes and algorithms that have been used to extract data from electronic health care databases and prepares for further expansion of the GAIA work into observational settings.

The existing Automated Brighton Collaboration Case Classification tool (ABC tool) will be expanded to include the newly developed set of case definitions for automated classification of reported events into their level of diagnostic certainty. The rule based tool classifies the information and also prompts the investigator to the type of information that should be collected (on follow-up) for a given case to meet the highest possible level of diagnostic certainty [30]. All tools will be described in more detail in an upcoming special issue of *Vaccine*.

## 3. Dissemination

The GAIA project aims to serve different stakeholders in the field of immunization in pregnancy. To achieve this aim, GAIA is promoting review, use and recommendation of its outcomes by key stakeholders in the field of global vaccine safety research and monitoring including national and international public health and regulatory organizations as well as vaccine manufacturers. Similarly, the wider scientific community and health care professionals are invited to review outcomes early in the process, provide comments and utilize the shared network, standards and tools. This effort is facilitated by engagement and dialogue with stakeholder organizations, presentations and workshops at scientific conferences, regular newsletters and publication in the scientific literature.

All outputs are made available through the GAIA website [31]. Immunization in pregnancy is an evolving field, and adaptation

of standards and tools to specific vaccines, protocols, populations, geographic regions, and other factors is necessary when evaluating the safety of vaccines in pregnancy. The Brighton Collaboration is addressing this continuing need and makes available an inventory of GAIA standards and related work as part of its online vaccine safety resources for professionals concerned with vaccine safety [32].

Standards and tools should ultimately be applied in clinical trials as well as in signal verification and hypothesis testing studies and enable and accelerate multinational collaborative research on immunization in pregnancy. To this end, GAIA inspired an International Consensus Conference on Harmonized Safety Monitoring of Immunization in Pregnancy in March 2016 at the National Institute of Health (NIH) in Bethesda, MD, U. S. A. The conference brought together 142 registered participants from regulatory authorities, public health institutes, academia and industry to discuss new safety data from immunization in pregnancy studies, to identify converging stakeholder needs and requirements for high quality data, to review GAIA standards and tools for safety monitoring and to build consensus on the best practice guidance for monitoring vaccine safety in pregnancy in the light of current experience with a focus on LMIC.

### 3.1. Summary and next steps

The GAIA project has established a large and functional network of experts and a purpose infrastructure around first outputs, which may serve as a platform for continued collaborative improvement of the quality of data generated for strengthening programs of immunization in pregnancy with specific focus on LMIC. The immediate next outputs will be the next set of eleven case definitions and the finalized online services and tools.

Capitalizing on the initial achievements of the GAIA project and following the recommendations of the consensus conference, GAIA could also be effectively utilized as a platform for capacity building in LMIC, specifically for monitoring the safety of immunization in pregnancy. Such capacity building could include the development of specific training modules for data safety monitoring boards (DSMBs) and National Immunization Technical Advisory Groups (NITAGs). Investing in a globally concerted approach will give added value to the individual studies/investments and strengthen a multinational platform for immunization in pregnancy.

With increasing implementation of immunization in pregnancy programs and research in LMIC, innovative approaches to validate the implementation of classic research methods as well as novel study designs and benefit-risk monitoring frameworks will be needed as critical next elements of a global active safety monitoring infrastructure, which will ultimately allow rapid evaluation and response to safety signals or concerns related to products and programs for maternal immunization.

### Conflict of interest disclosure

UH is a member of the "Global Pertussis Initiative" which receives unrestricted educational grants from Sanofi Pasteur, USA. FM is investigator in the Novavax clinical trials of RSV vaccines for pregnant women and Baylor College of Medicine receives the funds for the conduct of these studies. PTH is an investigator for clinical trials done on behalf of St George's, University of London, UK, sponsored by vaccine manufacturers including Novavax, Pfizer and GSK. He has been a consultant to Novartis and Pfizer on group B streptococcus vaccines and Novavax on RSV vaccines but receives no funding for this. The other authors do not have a conflict of interest to declare.



## Disclaimer

The findings, opinions and assertions contained in this consensus document are those of the individual authors. They do not necessarily represent the official positions of each author's organization (e.g., government, university, or corporation).

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