Maternal Immunization Safety Monitoring in Low- and Middle-Income Countries:

A Roadmap for Program Development

Building an approach that is practical, affordable, and sustainable

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Abbreviations and Acronyms

ACIP	United States Advisory Committee on Immunization Practices
ADR	adverse drug reaction
AE	adverse event
AEFI	adverse event(s) following immunization
ANC	antenatal care
AVAREF	African Vaccine Regulatory Forum
CIOMS	Council for International Organizations of Medical Sciences
CDC	Centers for Disease Control and Prevention
CHAMPS	Child Health and Mortality Prevention Surveillance
CHW	community health worker
CRVS	Civil Registration and Vital Statistics
DCVRN	Developing Country Vaccine Regulators Network
DHIS2	District Health Information Software, Version 2
DHS	Demographic and Health Surveys
DSA	Demographic Surveillance Area
DTaP	diphtheria, tetanus, and acellular pertussis, (vaccine)
DTP	diphtheria, tetanus, and pertussis (vaccine)
EMA	European Medicines Agency
EPI	Expanded Program on Immunization
EU	European Union
EUROCAT	European Surveillance of Congenital Anomalies
FDA	United States Food and Drug Administration
GAIA	Global Alignment on Immunization Safety Assessment in Pregnancy
GACVS	Global Advisory Committee for Vaccine Safety, World Health Organization
GAPPS	Global Alignment to Prevent Prematurity and Stillbirth
Gavi	Gavi, The Vaccine Alliance (formerly the Global Alliance for Vaccines and Immunization)
GBS	group B streptococcus
GIVS	Global Immunization Vision and Strategy
GSK	GlaxoSmithKline
HDSS	Health and Demographic Surveillance Sites
HIC	high-income country
HIS/HMIS	Health Information System/Health Management and Information System
HISP	Health Information Systems Program
ICBDSR	International Clearinghouse for Birth Defects Monitoring Systems
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICSR	individual case safety report
IgG	immunoglobulin G
INDEPTH	International Network for the Demographic Evaluation of Populations and Their Health
IPV	inactivated poliovirus vaccine
LMIC	low- and middle-income country
MDGs	Millennium Development Goals
MI	maternal immunization
MICS	Multiple Indicator Cluster Survey
MNCH	maternal, newborn, and child health
NGO	non-governmental organization
NITAG	National Immunization Technical Advisory Group
NRA	National Regulatory Authority
PAHO	Pan American Health Organization, WHO Regional Office for the Americas
PASS	Post-Authorization Safety Studies
PBRER	Periodic Benefit-Risk Evaluation Reports
PREVENT	Program for Enhancing Vaccine Epidemiology Networks and Training
PV	pharmacovigilance
RCORE	Regional Centres of Regulatory Excellence
RHS	Reproductive Health Surveys
RSV	respiratory syncytial virus
SAGE	Strategic Advisory Group of Experts (on Immunization), World Health Organization
SEARO	South-East Asia Regional Office, World Health Organization
Tdap	tetanus diphtheria and pertussis, (vaccine)
UK	United Kingdom
UMC	Uppsala Monitoring Centre
UNICEF	United Nations Children's Fund
USAID	United States Agency for International Development
WHO	World Health Organization
WHO-PQ	World Health Organization Pre-Qualification

Executive Summary

Immunizations have served as a cornerstone of public health, a clear success story in the prevention of mortality and severe morbidity worldwide. Maternal immunization holds the promise of further reducing morbidity and mortality among pregnant women and infants, particularly in low- and middle-income countries (LMICs) where there is the greatest burden of vaccine-preventable disease and the most limited access to basic health services. Global efforts are underway to develop, evaluate, and implement new vaccines targeted specifically for use in pregnant women in LMICs. As these efforts go forward, it is a critical time to formulate an organized and comprehensive approach to monitoring safety of maternal immunizations in LMICs and thereby track safety and effectiveness to ensure program success and public confidence.

The development of systems to monitor safety of maternal immunizations in LMICs presents a number of unique challenges. Vital registries and health reporting systems for pregnant women and infants are often inadequate, and most existing population-based health surveillance systems lack the sensitivity and accuracy needed to track complications of pregnancy and adverse birth outcomes. Even serious adverse events, such as fetal loss, stillbirth, neonatal death, and congenital malformations, are often not counted, reported, or investigated. Pharmacovigilance systems that identify, evaluate, and respond to potential adverse events following immunization (AEFI) are often rudimentary in LMICs. Successful safety monitoring programs will require an integrated approach supporting the needs of program managers, researchers, industry, regulatory agencies, healthcare providers, public health agencies, governmental and nongovernmental organizations, and civil society as part of an overall effort to improve the health of women and children worldwide.

This report, developed with support from the Bill & Melinda Gates Foundation and input from a large, multidisciplinary group of experts, summarizes existing programs in pharmacovigilance and maternal, newborn, and child health (MNCH) surveillance in LMICs, identifies gaps and needs, and outlines a roadmap for program development and implementation for monitoring the safety of maternal immunizations in LMICs.

Current pharmacovigilance systems in LMICs

Pharmacovigilance systems consist of the systems, structures, and stakeholders needed to ensure the safety and effectiveness of drugs and vaccines and protect public health. In this context, pharmacovigilance includes the detection, reporting, evaluation, corrective action, education, and communication of events throughout the lifecycle of a vaccine from pre-licensure through post-licensure. The field of vaccine pharmacovigilance has expanded, but to date has had limited application to maternal immunization. Most clinical trials and pre-approval studies typically exclude pregnant women from participation; no vaccines are currently labelled for use in pregnant women. Systems that monitor maternal immunization safety require unique methodologies that allow tracking, in a linked fashion, exposures to vaccines, maternal morbidities, and outcomes of both pregnant women and their offspring over time. Maternal

immunization safety monitoring in LMICs is further challenged by the general lack of pharmacovigilance training, capacity, structures, and resources for national and regional pharmacovigilance and Expanded Program on Immunization (EPI) programs.

Multiple international, regional, and national entities have demonstrated interest and investment in strengthening and development of pharmacovigilance systems that can serve as a basis for development of functional maternal immunization pharmacovigilance programs. These include ministries of health through their clinical, regulatory, and public health programs, EPI, national regulatory agencies, national pharmacovigilance centers, the World Health Organization (WHO), UNICEF, the Gavi Alliance, U.S. and European regulatory agencies (FDA, EMA), the Council for International Organizations of Medical Science (CIOMS), academic researchers, and industry. The African Vaccine Regulatory Forum (AVAREF) has advanced model regulatory procedures and support for regulatory capacity. The Global Alliance on Immunization Safety Assessment in Pregnancy (GAIA), as part of the Brighton Collaboration, has developed standardized case definitions and reporting systems specific to maternal immunization. Increased investment and coordination of these efforts, specifically related to adverse events in pregnant women and infants, serve as the foundation for future safety monitoring of maternal immunization in LMICs. Capacity building at the country level will be essential for program development, across the full spectrum of training and education of healthcare providers in detection and reporting of AEFI, education and sensitization of the general public, data management systems, and pharmacovigilance programs that review and respond to AEFI. Given the rudimentary nature of data systems for MNCH in many LMICs, introduction of new vaccines for use in pregnancy will need to develop prospective, active surveillance systems of women vaccinated in pregnancy. Passive surveillance would be unlikely to be of sufficient utility to evaluate safety and effectiveness in most low-resource settings.

Current MNCH surveillance and survey systems in LMICs: a foundation for maternal immunization safety monitoring

A number of surveillance and survey systems have been established in LMICs where civil registration and vital statistics are often lacking or inadequate. Population-based sentinel surveillance sites, such as the Health and Demographic Surveillance Systems (HDSS) monitor all the births, deaths, migration, and key health indicators of the entire population living within a defined geographic area. Households are visited on a regular basis and may serve as a good platform for building systems to monitor pregnant women and their infants prospectively over time. Pregnancy registries can monitor the safety of vaccines and other medications administered during pregnancy, but have had limited application to date in LMICs. health information systems (HIS) provide data on patients who access health facilities. However, HIS can be biased and lack standardized diagnoses, laboratory assessment, and case definitions, and have incomplete data for quantification of vaccine safety and effectiveness at the population level. Population-based household surveys utilize a sampling framework that is representative of the general population, but capture self-reported information retrospectively that would not be sufficiently sensitive or medically-validated to accurately monitor key adverse events of interest. Building on existing platforms for MNCH surveillance will strengthen these systems and improve efficiencies for new program efforts. Integration and coordination of maternal immunization with existing MNCH services and surveillance will serve to strengthen existing programs, leverage infrastructure, and minimize disruption of routine MNCH services.

Recommendations

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 focused and coherent strategy could have a major impact on the success of maternal immunization pharmacovigilance programs. The overall goal must be to develop a cohesive approach that is practical, affordable, and builds on existing infrastructure and investments. A number of key priority areas were identified for program development.

Improved data for detection and assessment of AEFIs

Collection of important data on pregnancy and newborn outcomes in LMICs has traditionally been weak in several critical areas, including gestational age assessment, fetal loss, stillbirth, congenital malformations, and maternal morbidity. Strengthening prospective data systems, standardized case definitions and procedures, active surveillance methods, and measurement of priority

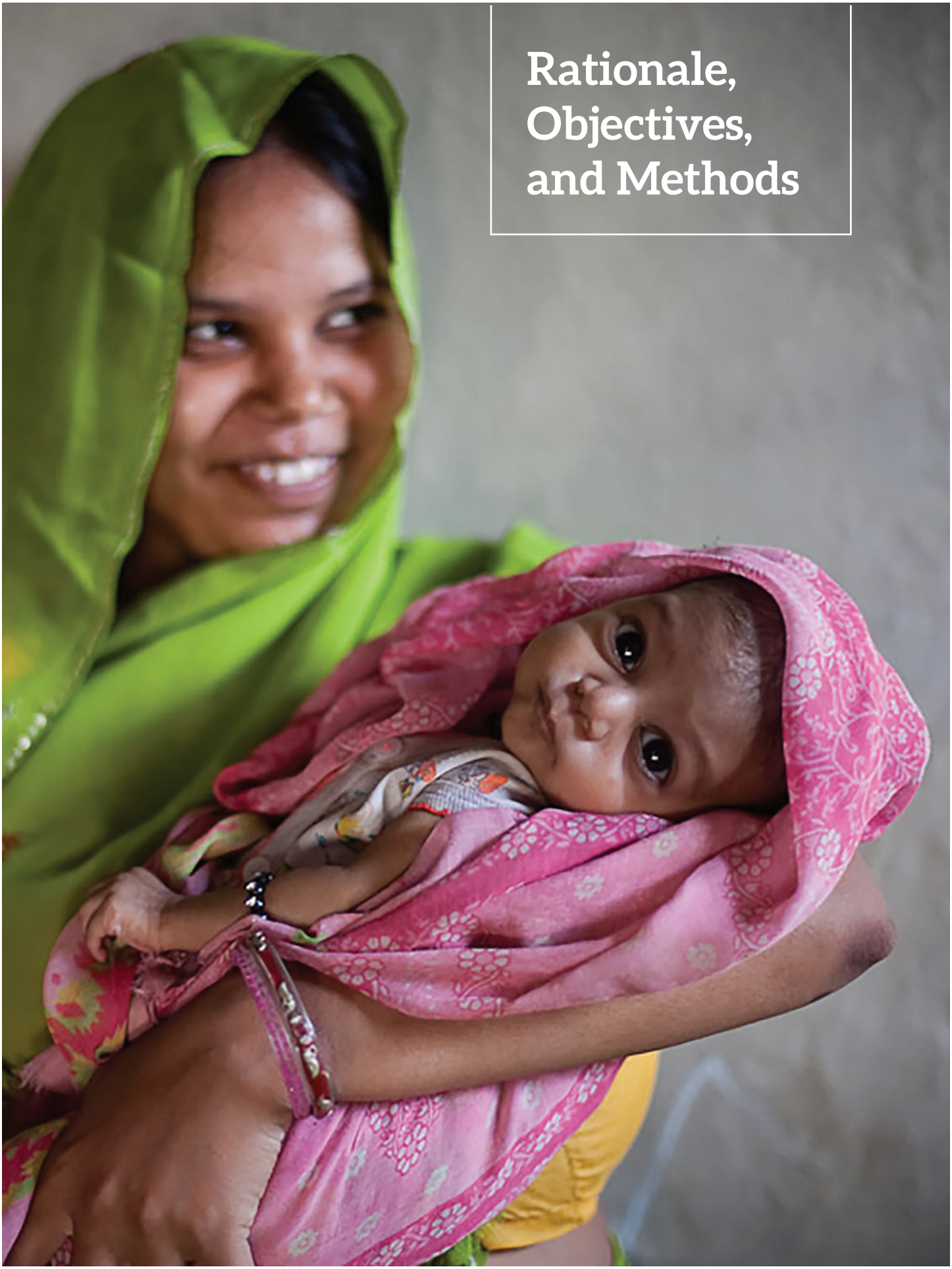
adverse events are needed to track vaccine safety. Data on the rates of adverse events among vaccinated and unvaccinated populations, controlling for other variables, and on the incidence of vaccine-preventable infections, will be needed to evaluate the risks and benefits of newly-introduced vaccines. Attention to improved data quality and standardization across sites will allow comparability and pooling of data for evaluation of rare events. Maternal immunization safety monitoring will need to be built through coordination with other MNCH programs, health surveillance systems, and immunization efforts to leverage current investments, increase efficiencies, reduce costs, improve sustainability, and reduce the burden on providers and patients.

Strengthened pharmacovigilance systems for maternal immunization

Existing pharmacovigilance programs will need to be adapted at both the international and country levels to address the unique events specific to maternal immunization. Important actions include the development of guidelines for detecting, reviewing, and responding to events related to the health of pregnant women and their offspring; the establishment of better linkages among pharmacovigilance systems and stakeholders; enhanced training of personnel; and the creation of models for data sharing and communication. **A targeted, comprehensive landscape analysis of key stakeholders and existing activities** would serve as the starting point to develop a functional platform for program development. This analysis should encompass industry, regulatory agencies, public health agencies, vaccine programs, aid organizations, country government leaders, policy makers, epidemiologists, clinical researchers, and healthcare organizations working in vaccines, MNCH, pharmacovigilance, and related fields. Mapping exercises will identify the availability of essential program elements, gaps that need to be addressed, feasibility, and the current investments, political will, and opportunities for coordination across key program areas. Reviews would help identify sentinel sites and build a structure for stepwise program implementation, operation, and capacity building. **Coordination of stakeholders** will be needed to strengthen maternal immunization pharmacovigilance programs throughout the lifecycle of vaccine development and implementation. Important actions include improving linkages between national pharmacovigilance centers and EPI programs, sharing best practices and lessons learned, and engaging the regulatory community and the pharmaceutical industry. These efforts need to be fully integrated with ongoing global efforts for strengthening pharmacovigilance for all medications and vaccines.

Implementation Plan

The process of developing this landscape analysis was in and of itself a catalytic process, demonstrating the breadth of efforts in this area and bringing together an array of organizations and thought leaders who normally have not had the opportunity to interact. The roadmap for program development outlines a cohesive strategy, building on existing systems and leveraging existing investments and technical expertise. This strategy will be best implemented in countries with sufficient existing infrastructure and then built out in a step-wise fashion to larger populations and more challenging conditions. Leadership, at both the international and country levels, will be needed to bring the multiple entities together to create a common direction and program plan. On the international level, strong leadership and coordination will be needed to convene strategic stakeholders and implement an actionable agenda. Leadership and coordination will also be essential at the country level, with a specific focus on strengthening pharmacovigilance systems, healthcare delivery, training and capacity building, and public health surveillance of health outcomes of pregnant women and their children. Successful implementation of maternal immunization pharmacovigilance programs will require political will and the mobilization of financial and human resources at both the national and international levels. Going forward, continued leadership, coordination, communication, and advocacy will be needed to ensure that the introduction of new maternal immunizations is accompanied by the political and financial support to track safety, and thereby protect public trust and program success.



Rationale, Objectives, and Methods

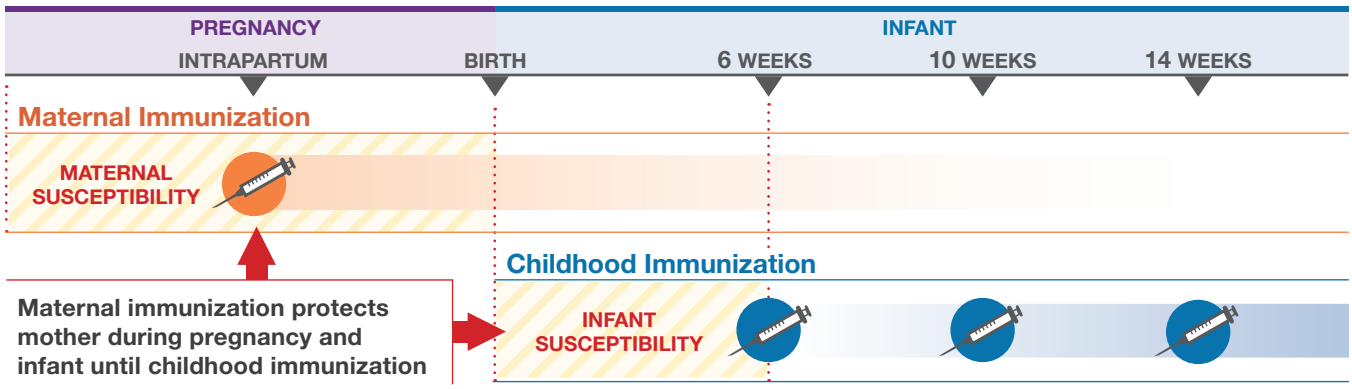
Primum non nocere – "first do no harm" – is a fundamental principle of medical care and bioethics. Medical interventions, both therapeutic and preventive, are built on the premise of advancing health and minimizing the risk of adverse or unintended consequences. Adhering to these most basic principles of medical practice, the risk of disease must be greater than the risk of the intervention. Advancing new interventions to protect health must therefore be accompanied by programs that monitor both the benefits and risks of those interventions. When preventing or treating a disease that is fatal or carries a high risk of morbidity to the patient, the tolerance of risk of an intervention may be relatively high. In the case of vaccines, where the intervention is given to a healthy population to prevent disease, the risks associated with the vaccine must be extremely low, especially in a population at relatively low risk of acquiring disease. Even if adverse events are extremely rare, when multiplied by millions of people who receive vaccines, the numbers of persons affected by an adverse event can become appreciable. Actual or perceived harm associated with vaccines can also damage confidence in vaccination programs and lead to low vaccine uptake by the population.

Immunizations are a cornerstone of public health, a clear success story in the prevention of mortality and severe morbidity worldwide. Maternal immunization holds the promise of further reducing morbidity and mortality among pregnant women and infants. This is particularly true in low- and middle-income countries (LMICs), where there is the greatest burden of vaccine-preventable diseases and access to basic health services is most limited. Women are at increased risk of severe infections during pregnancy, and many vaccine-preventable causes of severe disease and death in infants occur in the first months of life, before protection can be conferred by childhood immunizations. To address these vulnerable periods of pregnancy and infancy, global efforts are underway to develop, evaluate, and implement vaccines specifically targeted for use in pregnant women in LMICs. These maternal immunizations would establish protective immunity in pregnant women that then would be transferred via passive antibody to the fetus before birth. As these efforts move forward, systems are needed in LMICs that can monitor the effectiveness of vaccines and accurately and promptly identify, evaluate, and respond to potential adverse events following immunization (AEFIs) among pregnant women and their offspring.

Effective pharmacovigilance systems will be an essential component for advancing maternal immunization programs. By rapidly and effectively identifying and assessing safety issues, pharmacovigilance systems can help gain the confidence of providers, pregnant women, and the general population. However, such systems can be difficult to implement in LMICs, where basic health surveillance and functional regulatory systems for medical products are often rudimentary or generally lacking.

The development of pharmacovigilance systems for maternal immunization in LMICs presents a number of unique challenges. Vital registries and health reporting systems for pregnant women and infants are often inadequate, and most of the existing population-based health surveys lack sensitivity and accuracy for monitoring complications of pregnancy and birth outcomes. Even serious adverse events, such as fetal loss, stillbirth,

Figure 1 | The role of maternal immunization in protecting pregnant women and young infants.



Modified from: Sobanjo-Ter Meulen A, Abramson J, Mason E, et al. Path to impact: a report from the Bill and Melinda Gates Foundation convening on maternal immunization in resource-limited settings; Berlin - January 29-30, 2015. *Vaccine* 2015;33:1873-2518.

neonatal death, and congenital malformations, are often not counted, reported, or investigated. Monitoring outcomes of pregnancy and infancy is further complicated by the need to track, in a linked manner, both the mother and her offspring for months or even years after vaccination in areas where access to medical care, facility deliveries, and maintenance of medical records are sporadic. Case definitions of key events in pregnant women and newborns lack standardization; clinical settings often lack the diagnostic tools and trained healthcare workers required for accurate detection and diagnosis of medical complications; and healthcare providers in antenatal care settings are likely to have less experience and training in detecting and reporting AEFIs. Investigating whether an adverse event is causally related to a vaccine given in pregnancy is complicated by the relatively frequent occurrence of complications of pregnancy independent of vaccination. Results of pre-licensure animal studies may have poor predictive value for human pregnancy and fetal health, and pre-approval clinical trials typically exclude pregnant women from participation in both LMICs and high-income countries.

Robust methods for maternal immunization safety monitoring, reporting, evaluation and response in LMICs are needed to advance research, implementation, and post-marketing surveillance. These methods need to encompass immunization programs, researchers, industry, regulatory agencies, advocacy groups, and governmental and nongovernmental organizations as part of an overall effort to improve the health of women and infants worldwide.

This report outlines a roadmap for the development of essential maternal immunization pharmacovigilance systems in LMICs. It summarizes current vaccine pharmacovigilance systems, identifies gaps, and outlines system needs in LMICs specifically designed for monitoring the safety of maternal immunization. Although focused on maternal vaccines for respiratory syncytial virus (RSV), group B streptococcus (GBS), and pertussis, the report has broad implications for the introduction of new vaccines and medications used by pregnant women worldwide.

The report has five major sections:

1. **A summary of the vaccines currently used and being studied for use** in pregnant women in LMICs.
2. **A review of current pharmacovigilance systems and organizations** for monitoring vaccine and drug safety in LMICs.
3. **A review of existing maternal, newborn, and child health (MNCH) surveillance systems** that can be used as platforms for monitoring the safety of maternal immunizations.
4. **Recommendations** for building and strengthening systems to monitor the safety of maternal immunization, leveraging existing infrastructure and activities of key organizations.
5. **An implementation plan** that identifies key activities, organizations, and investments needed to operationalize maternal immunization pharmacovigilance programs for new and existing vaccines in LMICs.

The project was supported by a grant of the Bill & Melinda Gates Foundation and was guided by a Core Advisory Group of technical experts. A group of co-authors wrote the report based on literature reviews, telephone interviews, and expert input from over 70 contributors and stakeholder who attended a 2-day meeting in Seattle, Washington, in January 2017 and helped to shape the contents of the report. The report is not intended to serve as official recommendations or to represent a consensus statement of the participating individuals or their organizations. Rather, the report outlines a strategic framework for program development based on the collaborative networks and investments of the multiple stakeholders and country programs involved in maternal immunization safety monitoring in LMICs.

SECTION

1

Vaccines targeted for use in pregnancy

Vaccines targeted for use in pregnancy

Immunizations have been targeted for use in pregnant women since the introduction of tetanus toxoid vaccine over 50 years ago. Vaccines are administered to pregnant women to protect the woman during pregnancy, protect the newborn through passive antibody transfer to the fetus, and decrease the risk of maternal disease soon after delivery, and thereby the risk that a mother will transmit infection to the newborn.[2] Some infections are more severe in pregnant women owing to immunologic and physiologic changes of pregnancy. A recent review by the World Health Organization (WHO) found no evidence of increased risk to the fetus with use of inactivated viral and bacterial vaccines and toxoids administered during pregnancy.[3] In addition, transplacental transfer of antibodies has been found to be a safe, effective, and cost-effective method of enhancing antibody levels in infants.[4]

Tetanus toxoid

WHO and national organizations recommend use of tetanus toxoid for all pregnant women at risk for tetanus worldwide, as well as combination tetanus toxoid-acellular pertussis vaccines. This practice was based on studies conducted in the 1960s in developing countries where rates of both maternal and neonatal tetanus mortality were known to reach up to 30%. Currently, WHO recommends two doses of tetanus toxoid in the first pregnancy, and one dose in each subsequent pregnancy, not to exceed a maximum of five doses. This recommendation specifically pertains to settings without routine childhood DTaP (diphtheria, tetanus, acellular pertussis) or DTP (diphtheria, tetanus, and poliomyelitis) immunization.

The administration of tetanus toxoid to millions of pregnant women worldwide has reduced rates of neonatal tetanus with minimal to no risk to the mother and fetus.[5,6] Worldwide, tetanus toxoid is estimated to be administered in 80% of pregnancies, and its administration has been cited as a model for how maternal immunization can be built into the infrastructure of antenatal care in resource-limited settings.[7]

Influenza

Both seasonal and pandemic influenza infections are associated with increased risk of severe morbidity and mortality among pregnant women and young infants less than six month of age, and increased risk of adverse birth outcomes including preterm birth, stillbirth, and congenital malformations.[8] The importance of influenza disease and vaccination during pregnancy was highlighted during the 2009 influenza A/H1N1 pandemic, when pregnant women had a higher rate of severe infections and hospitalization than non-pregnant women, with the risk increasing each trimester.[9,10,11]

Influenza vaccine has been recommended for pregnant women in the United States since the 1960s.[12] Inactivated influenza vaccine and acellular pertussis vaccines are recommended in many middle- and high-income countries but are not yet used in most low-income settings. Inactivated influenza vaccine has demonstrated good immunogenicity in pregnant women compared with non-pregnant women, and it provides increased antibody concentrations in infant cord blood.[4,9,10]

In May 2012, the WHO Strategic Advisory Group of Experts (SAGE) identified pregnant women as a priority group for inactivated seasonal influenza vaccination. This recommendation was based on evidence of severe disease during pregnancy, the vaccine's safety and effectiveness, and its ability to protect both the mother and infant.[13,14] In November 2012, WHO advised that vaccination of pregnant women against influenza could occur at any time during pregnancy.[14] Multiple prospective controlled studies of trivalent inactivated influenza vaccine have been conducted in LMICs, including Bangladesh, South Africa, Mali, and Nepal, and have demonstrated the vaccine's safety in pregnant women and their infants.[15,16,17,18] Large studies of influenza and pertussis vaccines in pregnant women have been conducted or are being planned in LMICs and will provide further data for these areas.[10,4,19,1]

Pertussis

Although pertussis infection in pregnant women can result in serious morbidity, young infants less than 2 months of age are at greatest risk of fatal disease and serious morbidity.[20,21,22,23,24] The worldwide burden of pertussis remains high, with an estimated 16 million cases per year, 95% of which occur in LMICs.[25] The acellular pertussis vaccine is recommended for pregnant women, primarily to prevent severe disease and death in young infants. Vaccine coverage, however, remains low in many LMICs.[20]

Beginning in 2000, pertussis outbreaks in the United States resulted in increased deaths among young infants, which led to recommendations for the immunization of pregnant women.[26] In 2011, the United States Advisory Committee on Immunization Practices (ACIP) expanded acellular pertussis vaccine recommendations from

a "cocoon" strategy (vaccination of adults and care providers around the infant) to include pregnant women who had not yet received a vaccine against pertussis, preferably during their late second or third trimester.[27] Given low vaccination rates among pregnant women and evidence that maternal anti-pertussis antibodies are short lived, ACIP updated its recommendations in 2012 to include vaccination of all pregnant women starting at 20 weeks gestation regardless of prior vaccination.[28] Several observational studies and one randomized controlled trial have assessed the safety of pertussis vaccine during pregnancy in the United States and found no increased risk of adverse maternal or neonatal outcomes.[29,30]

In 2011-2012, the United Kingdom experienced an increase in pertussis disease, most notably among young infants. After introduction of the TDaP/IPV vaccine (tetanus, diphtheria, acellular pertussis, and inactivated polio vaccine) for pregnant women, pertussis rates fell in all age groups, with the greatest decrease in infants younger than three months with an estimated vaccine efficacy of 92% based on 82 confirmed cases in infants younger than 3 months at onset (95% CI: 84-95%). In the UK, TDaP/IPV is currently routinely given to pregnant women, while TDaP is administered in the United States.[31,32] Administration of pertussis vaccine earlier in pregnancy has been shown to confer greater antibody transfer to infants.[33] Investigators in the UK and United States have confirmed that pertussis vaccination during pregnancy is significantly more effective in preventing pertussis disease in infants than vaccination postpartum. The most recent of these studies found that maternal TDaP vaccination confers significant protection against pertussis over the entire first year of life.[30,34,35,36]

Vaccines in the development pipeline for use in pregnancy

Promising new vaccines for group B streptococcus (GBS) and respiratory syncytial virus (RSV) are under development and are entering clinical trials. Both are targeted for use in pregnant women in high-, middle-, and low-income countries.

Group B streptococcus

Group B streptococcus (GBS) is one of the most common pathogens responsible for mortality and severe morbidity due to sepsis and meningitis during the first weeks of life, particularly in sub-Saharan Africa and other regions where routine screening and treatment late in pregnancy is not feasible. In sub-Saharan Africa, neonatal sepsis is one of the leading causes of neonatal deaths, accounting for an estimated 3.1 deaths per 1,000 live births.[38] GBS is one of the leading etiologic agents of neonatal sepsis and is the leading cause of neonatal meningitis. The majority of GBS cases present as early-onset disease, occurring during the first few days or even hours of life, which makes diagnosis difficult in LMICs.[39] A meta-analysis of early-onset GBS, using data from sub-Saharan Africa in studies published between 1990 and 2014,[40] showed an incidence of 1.3 per 1,000 births (95% CI: 0.81, 1.9), and incidence of late-onset GBS disease of 0.73 per 1,000 births (95% CI: 0.48, 1.0). The prevalence of GBS and GBS serotypes varies worldwide and within continents.[41] An estimate based on 17 studies found a 22% GBS colonization rate in African countries, with an estimated vaccine efficacy of 92% (95% CI: 84-95%), based on 82 confirmed cases in infants less than 3 months of age at onset.[42,39,30] A recent prospective observational study using appropriate microbiological methods in tertiary hospitals in Latin America and Asia revealed a varying incidence of neonatal GBS cases, ranging from 2.35 per 1,000 live births in the Dominican Republic, to 0.76 in Hong Kong, to no cases in Bangladesh.[43] These data suggest that GBS is commonly undiagnosed and unrecognized in many parts of the world. In countries in Africa and Latin America, GBS incidence is similar to that of North America prior to implementation of intrapartum antibiotic prophylaxis.[44]

GBS is responsible for substantial maternal morbidity and mortality both during pregnancy and postpartum.[37,45,46,47,48] High-income countries have significantly reduced GBS-related morbidity and mortality in mothers with antibiotic therapy and in neonates with prenatal maternal screening programs and targeted antibiotic prophylaxis. However, this approach has not proven effective at preventing late-onset disease in infants (at 7 to 89 days of life) and is logistically difficult to implement in LMICs. Prophylaxis is also not effective in preventing disease in women. Maternal immunization for GBS is estimated to be a more effective and cost-effective strategy for prevention of neonatal infection (30-54%) than prophylaxis (10%).[49] As a result of these challenges and the significant burden of disease in the first 48 hours of life, GBS vaccines are uniquely suited for use in pregnant women in LMICs.

The development of polyvalent conjugate vaccines to enhance immunogenicity to multiple GBS serotypes has been ongoing for several decades, with several vaccine candidates now under development. A trial evaluating the safety and immunogenicity of a multivalent conjugate GBS vaccine was conducted in non-pregnant women in South Africa and subsequently among pregnant women in South Africa and Malawi.[50] This vaccine included GBS types Ia, Ib, and III conjugated to CRM_{197}, a mutant diphtheria

CASE STUDY

Influenza and Pertussis Maternal Immunization in Argentina

Argentina is an upper-middle-income country that adopted strong public health vaccine policies, including transitioning its focus from child vaccination to family vaccination, including pregnant women. All inhabitants of the country are guaranteed access to vaccinations covered under the National Immunization Schedule free of charge through primary care facilities. Since 2011, Argentina has added both influenza and pertussis vaccination for all pregnant women to the National Immunization Schedule to strengthen prevention and improve maternal and child health. Influenza was added to the schedule in 2011, and vaccine coverage reached 88% by 2014. Pertussis vaccination for pregnant women, as part of the TDaP vaccine, was incorporated into the National Immunization Schedule in 2014, and vaccination coverage reached 67% by 2014. Argentina was the first country in Latin America to have a comprehensive vaccination strategy against pertussis for pregnant women.

Vaccine safety outcomes were monitored for both influenza and pertussis, and AEFIs were reported from 2011 to 2014 with oversight by the country's Ministry of Health and Expanded Program on Immunization (EPI). A total of 10 AEFIs were reported for those who received influenza vaccine (for a rate of 0.7 cases per 100,000 doses) of which 4 were mild events associated with the vaccine and 5 were program errors. No serious adverse events related to vaccination were reported. A total of 20 AEFIs were reported for the TDaP vaccine, 7 of which were mild and related to the vaccine. No serious or fatal events were reported. In 2014, Argentina recorded the lowest number of deaths due to pertussis in the last 40 years, providing strong support for including this vaccine as part of the National Immunization Schedule.[37]

toxin, and was administered to women with and without HIV infection at 24 to 35 weeks of gestation.[51] These studies demonstrated that the vaccine was safe and immunogenic, although less immunogenic in women with HIV. Efficacy studies have yet to be conducted, and additional antigens will need to be included to cover the range of strains associated with invasive disease. The high prevalence of HIV in LMICs, particularly in parts of sub-Saharan Africa, may be a challenge in the development of a GBS vaccine for use in pregnancy and may require alternate dosing schedules to achieve optimal transplacental antibody transfer.[52]

Respiratory syncytial virus

Respiratory syncytial virus (RSV) is the most common pathogen associated with respiratory disease requiring medical treatment and hospitalization in young infants worldwide.[53,54] Infection with RSV is particularly severe in the first 6 months of life and is an important cause of child death due to pneumonia. In high-income countries, hospitalization rates for RSV are as high as 20 per 1,000 infants under 6 months of age; however, 99% of RSV-related deaths occur among children in LMICs (Hall et al., 2009). Worldwide, RSV causes an estimated 3.08 million cases of acute lower respiratory tract infection and 66,000 to 199,000 deaths in children under 5 years of age.[55,56,57] Since the risk of severe RSV infection is highest among young and/or preterm infants, the main strategy of maternal vaccination in high-, middle-, and low-income countries is to prevent infection in infants younger than 4 to 6 months of age who have less mature lungs and smaller airways.[58] Estimates suggest that maternal immunization could provide protection for infants through 6 months and reduce 31% of infant infections and an even higher percentage of hospitalizations.[55,59,60]

Although a number of promising candidate vaccines have been developed, RSV vaccine development has been hindered by a lack of understanding of the molecular characteristics related to viral infection and the immune response in humans needed to confer protection, as well as the lack of an easily manipulated animal model. Testing of a formalin-inactivated RSV vaccine in the 1960s resulted in several deaths as well as morbidity in children vaccinated as infants who were subsequently naturally exposed to RSV.[61,62] These outcomes led to substantial concerns regarding the administration of any RSV vaccine to infants or young children not previously infected with RSV, which in turn increased interest in the development of vaccines for use in pregnant women.

Multiple RSV vaccines are currently in development.[63] Small studies of RSV vaccines have demonstrated safety, good immunogenicity in pregnant women, lack of reactogenicity, efficient RSV-specific IgG transfer from mothers to neonates, and protective effects of maternal antibodies for infant RSV infection.[64,65] Vaccines intended for use in pregnant women typically contain a part of the F or fusion protein of RSV, with the goal of producing protective antibodies similar to those currently obtained from the licensed monoclonal antibody palivizumab, which is given intramuscularly in many high-income countries to protect preterm or high-risk infants from RSV disease.[66] Clinical trials of the post-fusion F nanoparticle vaccine by Novavax (Gaithersburg, MD) have progressed the furthest, with a large international Phase 3 clinical trial currently underway.[64] Other vaccine candidates, including pre-fusion F vaccines, are under development by GlaxoSmithKline and others, with the goal of developing even more immunogenic vaccines.[67]

Table 1 | GBS and RSV vaccines in the development pipeline for use in pregnant women[38,44,62,68,69,70]

ORGANIZATION	DEVELOPMENT PHASE	VACCINE
Group B streptococcus (GBS)		
GlaxoSmithKline/Novartis	Phase II and POC trial in pregnant women	CRM197-CPS conjugate vaccine: multivalent
PATH/Biovac	Preclinical	Polyvalent conjugate vaccine
Pfizer/BMGF	Preclinical	Polyvalent vaccine
MinervaX	Phase Ia completed; Phase Ib	N-terminal domains of the Rib and AlphaC surface proteins
GlaxoSmithKline	Preclinical	Pilus proteins
Respiratory syncytial virus (RSV)*		
NIH/NIAID/VRC	Phase I	RSV F Protein
GlaxoSmithKline	Phase II	RSV F Protein
Novavax	Phase III	RSV F Nanoparticle

*Other RSV vaccines under development, including live attenuated vaccine, viral vector vaccines, and long-acting monoclonal antibody passive prophylaxis, are not included in this table (See PATH 2016 Vaccine Snapshot).

SECTION

2

Current state of global vaccine pharmacovigilance systems:

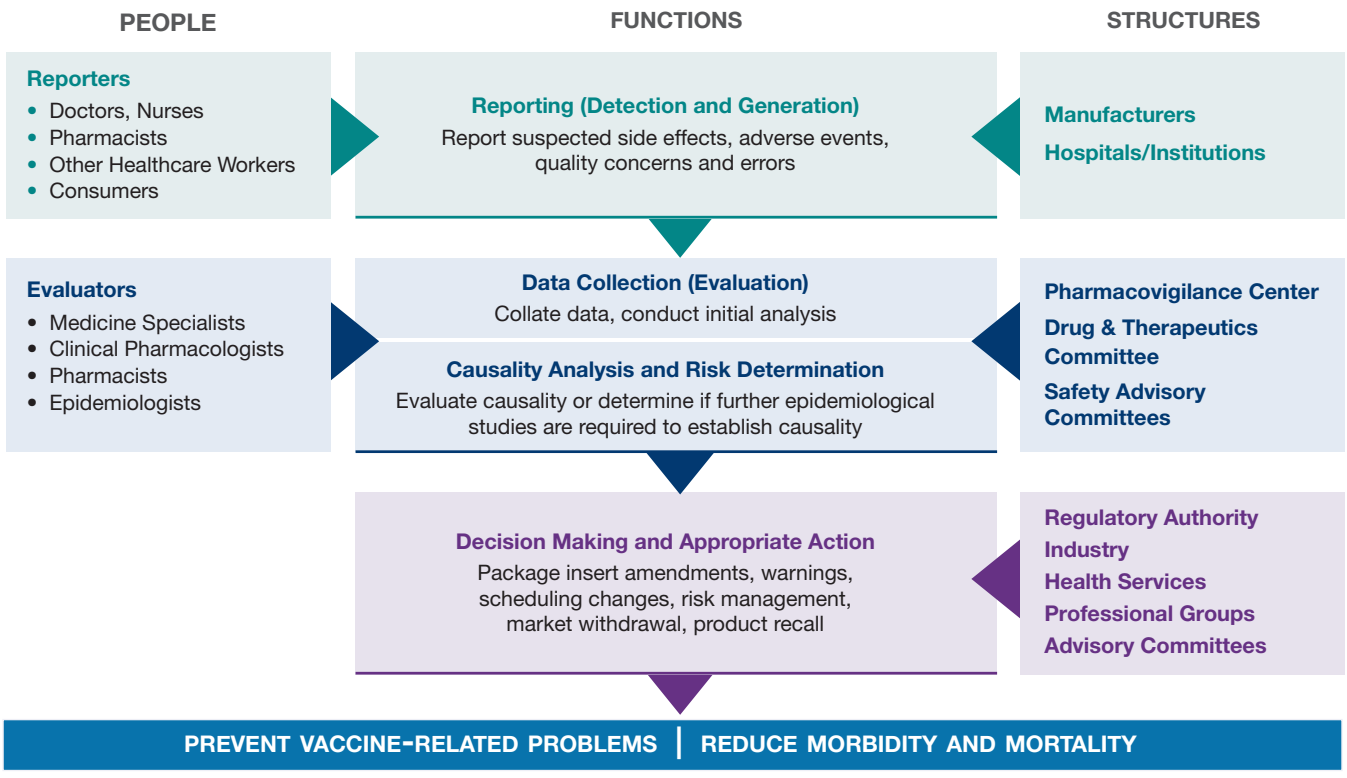
existing capacity and opportunities for maternal immunizations in LMICs

As new maternal immunizations become available in LMICs for diseases of global importance, there is an increasing need for effective pharmacovigilance throughout the life-cycle of vaccines, from pre-licensure through post-licensure phases.[71] Vaccine pharmacovigilance is defined as the science and activities related to the detection, assessment, understanding, and communication of AEFIs and other vaccine-related issues and the prevention of untoward effects of vaccines.[72] AEFIs are any untoward medical occurrences that follow immunization, which do not necessarily have a causal relationship with the usage of the vaccine.[73] An adverse event is any unfavorable or unintended sign, abnormal laboratory finding, symptom, or disease. While most AEFIs are mild, some adverse events are a potential cause for concern and need to be investigated.[74] If not responded to promptly, serious AEFIs may pose a continued health risk, erode public confidence in vaccine safety, and result in declines in immunization coverage.

Pharmacovigilance systems are comprised of the systems, structures, and stakeholders necessary to ensure the safety and effectiveness of drugs and vaccines and protect public health (Figure 2). The successful implementation of maternal immunization pharmacovigilance systems in LMICs involves multiple stakeholders – including regulators, pharmaceutical companies, healthcare providers, patients, and donors – and requires good practices, including appropriate methods for surveillance, risk assessment, risk management, communication, and benefit-risk assessment. Functional pharmacovigilance systems broadly identify people, structures, and functions that support decision making and actions to prevent or mitigate problems related to drugs and vaccines. They also generate the data needed to evaluate the risks and benefits of a vaccine throughout its lifecycle.

The field of vaccine pharmacovigilance has expanded, but has had limited application to maternal immunization programs. Here, pharmacovigilance programs require different surveillance methods in different settings and a high level of safety vigilance to minimize the risks to women and their offspring. They require signal detection methods for the occurrence of adverse events of interest related to pregnancy and the evaluation and elucidation of causation for events that may be temporally associated with adverse pregnancy outcomes such as miscarriage, fetal death, congenital anomalies, or neonatal death, which are not routinely monitored in most pharmacovigilance systems. Other immunization-

Figure 2 | The pharmacovigilance framework



Modified from: *Strengthening Pharmaceutical Systems (SPS). Supporting pharmacovigilance in developing countries: the systems perspective*. Submitted to the U.S. Agency for International Development by the SPS Program. Arlington, VA: Management Sciences for Health, 2009."

related issues also need to be identified during the post-licensure phase of maternal immunization, such as vaccination administration errors, poor product quality, or contamination.

Overview: How vaccines are administered to pregnant women in LMICs

The three means by which women in LMICs most often receive immunizations during pregnancy are (1) antenatal care (ANC) clinics, (2) primary care clinics, or (3) community outreach or immunization campaigns. In most settings, maternal immunizations are mainly administered in antenatal care settings. In settings with low coverage for MNCH care, community health workers work in tandem with facility-based health staff to reach those in greatest need through home visits and other community-based outreach.[75] Additionally, women of childbearing age may receive vaccines through mass vaccination outreach campaigns.

Routine care of pregnant women and their children provides an infrastructure for the delivery of maternal immunization in LMICs. MNCH platforms are often funded primarily through national health services, often augmented through specific health initiatives or other donor support. In contrast, most immunization programs are funded through the Expanded Program on Immunization (EPI), which tends to be administratively distinct. This separation contributes to programmatic complexities and a lack of accountability, including in the area of safety reporting. Maternal immunization efforts will likely be most successful and sustainable if they are integrated with existing MNCH services, thereby leveraging existing infrastructure and avoiding the disruption of routine MNCH services.

Antenatal care programs face multiple operational challenges in providing maternal healthcare. These include shortages of qualified nurses, midwives, and physicians; insufficient outreach and access to the most vulnerable populations; lack of access to health information systems for monitoring and planning purposes; weaknesses in maintaining cold chain; and wide variations in the availability and quality of essential services, including clinical expertise, laboratory capacity, and access to essential drugs and vaccines. Women in LMICs may face multiple barriers to accessing care, including geographic, cultural, and economic barriers, which can limit vaccine coverage and follow-up of women during antenatal care and their infants postpartum. Another challenge is that antenatal care services, where maternal immunizations would be provided, may occur in different venues from the care of the infant, making it difficult to link the data on vaccination of women with potential later adverse events in their offspring. Furthermore, in most LMICs, health records, including those of pregnant women and infants, are incompletely maintained. Records are generally recorded manually, may be maintained in log books rather than by individual patient records, and may stay with the patient rather than the health facility. Medical records may not be maintained in a complete or standardized manner, and electronic health records tend to be unavailable, thereby limiting the ability to link records between mothers and children.

In-country systems for identifying, reporting, and reviewing potential adverse health events in LMICs

Detection and reporting of adverse events at the local level

Recognizing and reporting of potential adverse health events post-vaccination are important for identifying new safety signals that can guide appropriate actions by healthcare providers, ministries of health, vaccine manufacturers, program managers, and others. Once a potential AEFI occurs, the patient may present for care to the healthcare setting where the vaccine was administered, to another healthcare setting, or not at all. Healthcare workers are responsible for identifying and acting on an AEFI, including reporting it as soon as possible through appropriate mechanisms. However, the identification and reporting of AEFIs at the level of patient care are highly variable and depend on many factors, including the patient's and clinician's ability to recognize adverse events, identify a potential association with the vaccine, be willing to report an event, and have knowledge of the systems by which they are reported. Since serious AEFIs are likely to be relatively rare, the ability to interpret and detect a true signal above a known baseline rate is likely to be limited in LMICs without external assistance, enhancement, and special studies. Underreporting and incomplete reporting of AEFIs in such spontaneous or passive surveillance systems are major challenges globally, and particularly in LMICs.

A lack of experience and knowledge among patients and providers on the reporting of AEFIs further challenges the introduction of vaccines for pregnant women. The success of systems for spontaneous reporting of AEFIs is influenced by many factors, including perceptions of

disease, expectations of treatment, perceived linkages to vaccination, and motivations for reporting by patients and health workers (Table 2). Education and training materials need to be developed, for providers and for patients, to improve understanding of the benefits of maternal immunization, potential AEFIs, and reporting processes. These materials will need to be adapted and field tested for use in different languages and different cultural contexts. Monitoring maternal immunization safety will require systems that prospectively collect and link data from AEFIs and from vaccinations administered for women and infants over time and across data sources. Systems with the capacity to link records are therefore needed to successfully implement sustainable vaccine safety monitoring systems in LMICs. Efforts are underway to explore novel technologies, such as the use of mHealth and mobile devices, to advance data collection in countries with limited infrastructure in health information systems, such as with PATH's Better Immunization Data (BID) initiative.[76] Currently, vaccine safety record linkage studies in LMIC's are generally in pilot stages.[77,78]

Vaccine safety monitoring at the national level

Ministries of health, through their national regulatory authorities (NRAs) and national immunization programs such as EPI have responsibility for developing and maintaining a national AEFI surveillance system. Additionally, most LMICs have a national pharmacovigilance center that is typically situated within their ministry of health, most commonly within their national regulatory authority. However, the monitoring, reporting, and analysis of AEFIs are usually performed by EPI, often with insufficient linkages with national pharmacovigilance centers that primarily focus on drugs.[79] Despite the widespread use of vaccines, many LMICs lack even basic pharmacovigilance systems to

Table 2 | Challenges in reporting suspected adverse drug reactions (ADR) or adverse events following immunization (AEFI) in low- and middle-income countries by patients and healthcare providers.

Patient Challenges	Healthcare Provider Challenges
1. Patient may not receive or follow instructions for appropriate use of medicine, or may receive medicine from an unofficial source or provider.	1. Unexpected AEs may go unrecognized as ADRs or AEFIs.
2. Patient may not recognize that s/he is experiencing an ADR or AEFI.	2. May not appropriately ask about, monitor and/or manage AEs.
3. Patient may perceive that some adverse events (AEs) are actually indicators of drug efficacy, rather than side-effects.	3. May not advise patient on possible AEs, including drug interactions and signs of ADRs or AEFIs.
4. Patient does not seek medical attention for a potential ADR or AEFI.	4. A culture of reporting of AEs may be lacking. May fear reporting AEs (e.g., concerned about losing credibility or perceived as causing harm to the patient, fear of litigation).
5. AE reports by patients are not accepted by some national pharmacovigilance centers.	5. May not be aware of AE reporting system or may not know how to report a suspected AE.
6. Varying degrees of patient literacy.	6. May not be aware of which AEs are the highest priority for reporting.
	7. AE reporting forms not available in all health care facilities.
	8. AE reporting form may be viewed as burdensome.
	9. Completed forms may not be forwarded to national Pharmacovigilance centers or EPI program.
	10. AE reporting forms may be incomplete.
	11. Lack of feedback when AEs are reported to the national pharmacovigilance center or EPI program.

ensure post-approval vaccine safety. All components of these pharmacovigilance systems and the interactions and collaboration between pharmacovigilance centers, NRAs, EPIs, and MNCH programs need to be strengthened. The introduction of new maternal vaccines will further increase the need for strengthening pharmacovigilance systems in general, as well as the specific need to build capacity for monitoring the safety of women and newborns.

Investigation of adverse events and causality assessment

A core structure for vaccine pharmacovigilance at the national level is the AEFI review committee. Functional AEFI committees review individual serious and unusual AEFIs, monitor reported AEFI data for potential signals of previously unrecognized vaccine-related adverse events, perform causality assessment, and provide recommendations for further investigation, education, corrective action, and communication. Causality assessment is the systematic review of data about an AEFI case to determine the likelihood of a causal association between the adverse event and the vaccine received. Causality assessment of AEFIs can be performed in three situations: (1) at the level of the individual AEFI case report, to determine from previous evidence and logical deduction if an AEFI in a specific individual is causally related to use of the vaccine; (2) at the population level, to test if there is a causal association between use of a vaccine and a particular AEFI; and (3) in the context of safety signal investigations. Evaluations of AEFIs involve a clinical investigation of the case, including assessment of the presence of risk factors, comorbidities, other medications and exposures, and potential clinical errors. Causality assessment may also include investigation of potential upstream events, including errors in manufacturing, transport, storage, or administration of the vaccine. AEFI review committees need to compare adverse events in vaccine recipients to local background rates to evaluate safety. If a vaccine is implicated in an AEFI case or cluster, it may be necessary to test the vaccine quality. Investigations may require access to a national laboratory or a regional reference laboratory to aid in confirmatory testing. In countries that produce their own vaccines, vaccine manufacturers and national control laboratories may need to be part of the national AEFI surveillance system.

Currently, the majority of LMICs do not have the basic elements of minimal vaccine safety capacity in place. Many LMICs lack processes to review and assess immunization interventions and strategies, including causality assessment. A 2014 WHO South-East Asia and Western Pacific region's intercountry workshop involving 10 countries identified several challenges with causality assessment of AEFIs at the country and regional level.[80] Among these were poor quality of data, high staff turnover rates, and deficits in AEFI investigation training and timely investigation. Inadequate data, including the general lack of an autopsy following a maternal death or the death of an infant or child after immunization, often lead to causality assessments being categorized as "unclassifiable." Lack of adequate financial support from countries for AEFI committees and investigation teams further constrains these efforts.

These reviews underscore the importance of pharmacovigilance systems as efforts move forward to build systems to monitor maternal immunization safety. When applied to maternal immunization safety monitoring, causality assessment tools will be limited by the lack of quality data on maternal exposures and birth outcomes, as well as by a lack of technical expertise and experience in evaluating AEFIs among pregnant women and their offspring. Assessments of AEFIs in LMICs are challenged by relatively high baseline rates of pregnancy complications and adverse birth outcomes that may be temporally-associated but not related to vaccination, such as fetal loss, stillbirth, maternal hemorrhage, preeclampsia, congenital malformations, and spontaneous preterm birth. Knowledge of an adverse event in the mother, fetus, or infant, its temporal association with product administration, and background rates of adverse pregnancy outcomes in the general population is critical to evaluating a safety signal, its potential causal relationship with a vaccine, and the risk-benefit profile of the vaccine.

In-country vaccine pharmacovigilance-related regulatory agencies and public health programs in LMICs

National regulatory agencies and national pharmacovigilance centers in LMICs

Pharmacovigilance in LMICs is conducted by national pharmacovigilance centers administratively situated within or in collaboration with NRAs. NRAs have a legal basis that defines their mandate and enforcement powers and core functions related to vaccines, such as issuing vaccine marketing authorizations, licensing vaccine production and vaccine distribution facilities, and ensuring that post-marketing surveillance is conducted, taking into

account assessments of risks and benefits. National pharmacovigilance centers are expected to collaborate with their national immunization programs in developing and maintaining national AEFI surveillance systems.

An analysis by WHO of the NRAs in over 100 countries showed that most LMICs still need to strengthen their vaccine safety functions.[81,82] This survey of regulators found a need for a coordinated system, supported by sufficient infrastructure and resources, to standardize and communicate AEFI data to all relevant vaccine safety stakeholders in LMICs.[83] Regulators identified a particular need for standardized and readily accessible AEFI reporting forms, improved spontaneous and active surveillance mechanisms, adequate vaccine safety expertise and training, coordinated exchanges of vaccine safety information between NRAs and public health agencies, shared access to vaccine safety data, and the political will to establish, sustain, and support regulatory authorities. In addition, a 2008 analysis of 55 LMICs identified many challenges and barriers to promoting pharmacovigilance in these settings, including the lack of staff trained in pharmacovigilance, little or no budget for pharmacovigilance, and lack of a sufficient legal mandate to compel adverse event reporting by marketing authorization holders.[84] Less than half of the 55 LMICs responding to a survey had budget support for pharmacovigilance; 13% had no pharmacovigilance system at all. Other assessments of pharmacovigilance systems have identified LMICs with few functional pharmacovigilance systems.[85]

A landscape analysis conducted by WHO examined several dimensions related to global vaccine pharmacovigilance systems, including stakeholder surveys of vaccine safety experts, vaccine manufacturers, and regulators; systems analyses of existing international vaccine safety initiatives and vaccine pharmacovigilance infrastructure in a sample of 11 LMICs; and a financial analysis to assess the cost of implementing strategies of the Global Vaccine Safety Blueprint.[80] The landscape analysis reported that vaccine manufacturers emphasized the need for harmonization in signal detection, reporting, and evaluation of AEFIs. Specific areas requiring harmonization include data collection, AEFI definitions, terminology for reported events and vaccine safety, medical review and report management, vaccination history, and causality assessment. The establishment of sentinel sites or centers for monitoring and coordinating professional activities was proposed as a possible approach for improving vaccine safety surveillance.

Initiatives such as the Developing Country Vaccine Regulators' Network (DCVRN), which was launched by WHO in 2006, and the WHO-African Vaccine Regulatory Forums (AVAREF), established by WHO in 2006, may help bridge some of the identified gaps. In particular, maternal immunization initiatives could build upon these systems.[86] To do so, increased expertise in obstetric complications is required.

CHALLENGES NATIONAL PHARMACOVIGILANCE SYSTEMS

- **Vaccine safety functions need to be strengthened in most LMICs, including coordination with EPIs, standardization, and communication of AEFI data to all relevant vaccine safety stakeholders.**
- **NRAs in LMICs lack a sufficient number of staff trained in pharmacovigilance, have little or no budget for pharmacovigilance, and may lack a sufficient legal mandate to compel adverse event reporting by marketing authorization holders.**
- **NRAs in LMICs need technical assistance to ensure vaccines meet good manufacturing practice and other global standards.**
- **New systems, resources, and engagement of the MNCH field are needed to develop the infrastructure and technical knowledge needed for monitoring vaccine safety in pregnant women and their children.**

Expanded Program on Immunization (EPI)

While vaccine regulation typically falls under the oversight of a country's drug regulatory authority, the programmatic aspects of immunization programs - including monitoring, reporting, and analysis of AEFIs - are usually separate from a country's national pharmacovigilance center. These activities are typically carried out by a country's public health program, such as its EPI, often with insufficient linkages with national pharmacovigilance centers that primarily focus on drugs (Figure 3). In many countries, AEFIs detected and reported by EPI are not commonly shared with national pharmacovigilance centers.[78] In addition, coordination and communication between drug and vaccine authorities responsible for safety can be limited.[87]

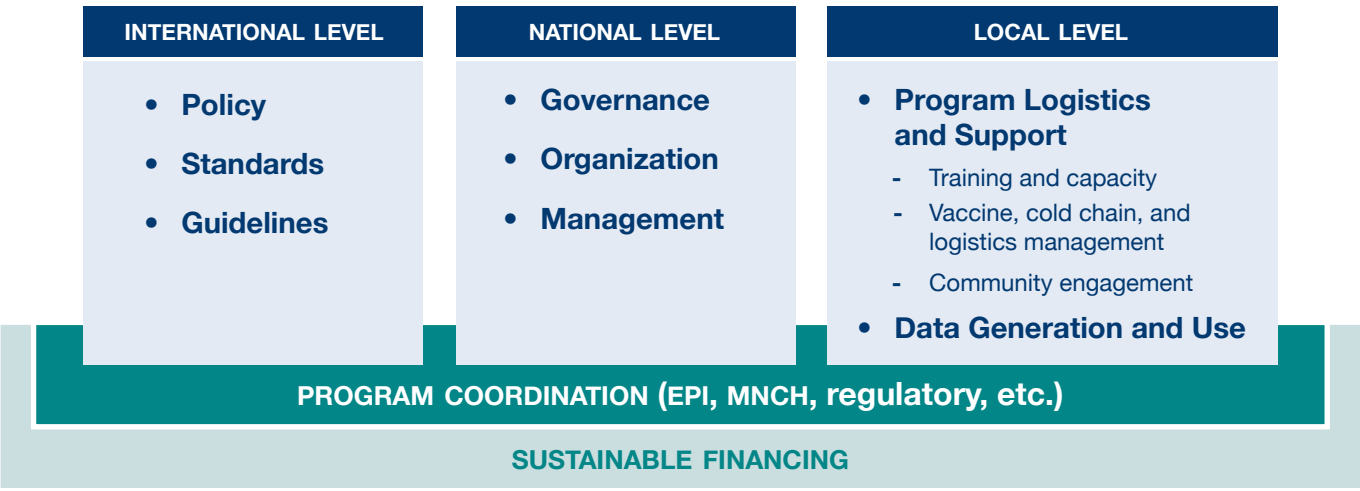
The role of each country's EPI is guided by principles set out in the Global Vaccine Action Plan, a global framework designed to achieve the Decade of Vaccines vision of delivering universal access to immunization by 2020 and beyond.[78] Each country's EPI conducts vaccination and strengthens routine immunization programs to meet coverage targets and to accelerate control of vaccine-preventable diseases. Yet the majority of LMICs do not have the elements of minimal vaccine safety capacity in place for established vaccines included in EPI, including a pharmacovigilance unit or focal point with dedicated budget for safety surveillance and systems to monitor and collect AEFI.85,86 WHO encourages EPIs to collect immunization systems data on issues such as vaccine coverage, planning, financing, surveillance, human resources, logistics management, outreach activities, and vaccine safety. Introduction of maternal immunization in antenatal care settings adds increased complexity to the system, requiring additional training in vaccine administration and pharmacovigilance and stronger linkages between EPIs and MNCH programs.

CHALLENGES	COUNTRY PROGRAMS

- Antenatal care settings face operational challenges for the integration of maternal immunization and pharmacovigilance strategies, including shortages of qualified staff.
- Health workers administering vaccinations, particularly those in antenatal and postpartum care settings, may lack the necessary training on detecting, reporting, and responding to AEFIs.
- Prenatal care, the provision of vaccines to pregnant woman, and follow-up of infants commonly occur in different venues, making it difficult to link information on vaccination of the mother and health outcomes in offspring.
- Limitations of current approaches to causality assessment for vaccines are exacerbated in LMICs by a lack of quality data on maternal exposures and infant outcomes, as well as by limitations in the expertise and experience of those performing causality classifications.
- Causality assessment of AEFIs in LMICs is challenged by relatively high baseline rates of pregnancy complications and adverse birth outcomes, such as spontaneous abortion, stillbirth, maternal hemorrhage, preeclampsia, congenital malformations, and spontaneous preterm birth.
- Knowledge of background rates of pregnancy outcomes and relevant maternal and infant medical conditions occurring in LMICs is lacking.
- Most LMICs lack information sharing and collaboration between the EPI, regulatory authority, MNCH programs, and the national pharmacovigilance center.

Modified from: Shen AK, Fields R, McQuestion M. The future of routine immunization in the developing world: challenges and opportunities. *Glob Health Sci Pact* 2014;2:381-394."

Figure 3 | Critical elements for quality and reliability in routine immunization programs



Modified from: Shen AK, Fields R, McQuestion M. The future of routine immunization in the developing world: challenges and opportunities. *Glob Health Sci Pact*. 2014;2(4):381-394. http://dx.doi.org/10.9745/GHSP-D-14-00137.

Currently available approaches to maternal immunization pharmacovigilance in LMICs

Most of the common side effects of a vaccine are identified in studies before the vaccine is licensed. However, less common events may not be detected in these studies. Therefore, pharmacovigilance systems are needed to continuously monitor for possible side effects after a vaccine is licensed, including monitoring of large populations for detection of rare events. If a link is identified between a possible side effect and a vaccine, health officials need to take appropriate action, weighing the benefits of the vaccine against its risks to determine if recommendations for using the vaccine should change.

The evaluation of vaccine safety in pregnant women requires special consideration of events unique to both the fetus and woman during pregnancy. For example, vaccines in pregnancy may raise concerns over the potential risk of teratogenicity, fetal loss, and preterm birth as a result of an inflammatory response.[88] Other adverse pregnancy outcomes potentially associated with maternal immunization include spontaneous abortions, stillbirth, low birthweight, preterm birth, and neurologic impairment in the offspring.

Immunization in the first trimester is usually avoided as the risks to fetal development are highest in this period. However, accurate assessment of gestational age in LMICs is challenging, generally ascertained by fundal height or reported last menstrual period (LMP), both of which often yield inaccurate results. In recent years, some countries have trained personnel to perform ultrasound for gestational age, thereby improving the accuracy of gestational age dating.[82,90]

Pre-licensure pharmacovigilance

In high- and low-resource settings, clinical trials for maternal immunization rely on good clinical practices and on regulations and standards established by regulatory agencies such as the U.S. Food and Drug Administration (FDA) or the European Medicines Agency (EMA).[91] In clinical trials, data are systematically collected on efficacy and adverse events under controlled conditions where patients are followed for defined periods of time post-vaccination. Results are reported to regulatory agencies where the trial is conducted via expedited and routine reporting and through annual development safety update reports. Clinical trials generally have relatively short durations of study, relatively small sample sizes, and limited diversity among participating patients and providers. These limitations make it essential to continue monitoring medical products, including vaccines, for safety and effectiveness after approval, when the product is more widely used in the general population.

A spectrum of approaches is employed in LMICs to ensure that essential MNCH outcomes are consistently captured in clinical trials. At one end of the spectrum, the research team conducts real-time monitoring and management of all pregnant women enrolled in the trial as well as the infants born to those pregnancies. At the other end of the spectrum, the research program strengthens the established framework for the routine

collection of safety data through local, national, or regional systems. The appropriateness of the approach taken, which has significant implications for the trial design and budget, will depend on numerous factors, including the strength and completeness of the existing MNCH data capture systems in country, the phase of the trial, the safety endpoints to be captured, and the sample size of pregnant women and infants that need to be recruited and followed. Each approach has distinct advantages and disadvantages and will be appropriate to different settings. However, in all cases, the need to consistently capture safety data within a clinical trial should not be viewed in isolation. Rather, every opportunity should be taken to enhance routine local and national safety data collection and to facilitate good practice and audit in line with established WHO recommendations.[92,93]

During the clinical development of most vaccines and drugs, pregnant women are actively excluded from trials. If pregnancy does occur during the trial, the usual procedure is to discontinue treatment and drop the patient from the study, although her pregnancy is typically followed to term. Consequently, product-specific information regarding the safety and effectiveness of vaccines in pregnant women is rarely available. The majority of vaccines are not targeted for use in pregnancy during their development. In fact, all vaccines currently recommended for use in pregnant women by WHO, ACIP, and others are used off-label—that is, in a manner not specified in the official approved labeling. Unless a vaccine is specifically indicated for use in pregnancy, no studies are conducted prior to product licensure to determine the vaccine's safety in pregnant women.

Fortunately, clinical trials of vaccines specifically targeting pregnant women have been increasing in number, with the primary objective of reducing morbidity and mortality in pregnant women and their infants.[2,94] Standardized case definitions for key obstetric and neonatal events following maternal immunization have been developed by the Global Alignment of Immunization Safety Assessment in Pregnancy (GAIA) project, coordinated by the Brighton Collaboration Foundation. This project has also established case definition algorithms, a searchable database of terms, and mapping of disease codes across coding terminologies, including MedDRA and ICD. This will help in the development of standardized data that can be merged and compared across sites and countries. Sites participating in pre-licensure clinical trials need to provide obstetric, perinatal, and infant care as well as document pregnancy outcomes using standard tools.[95,96] Sites with the capacity for short- and long-term follow-up of children are preferred for clinical trials, and strategies for linking data from both mother and infant, collected from potentially different venues, need careful consideration.

A variety of challenges to monitoring safety in clinical vaccine trials in LMICs, including those focused on maternal immunization, have been described.[97,98,99,100,102] Obstacles for clinical studies of maternal vaccines during pregnancy include issues related to the specific geographical sites, such as local customs, concomitant complications of pregnancy, malnutrition, infectious diseases, and the availability and completeness of medical records at local sites. Long-term follow-up of both mothers and infants participating in maternal immunization clinical trials may differ in terms of duration and intensity of follow-up. Timing of other vaccines given in pregnancy may also affect results.[103] Some complications of pregnancy, such as preeclampsia and severe malaria, may occur at higher rates during the first pregnancy, requiring the evaluation of complications and potential adverse events in vaccine recipients versus controls based on factors other than treatment group. Finally, congenital anomalies occur naturally, and the presence of both major and minor congenital anomalies must be evaluated for the biological plausibility of their being related to a vaccine.

CHALLENGES PRE-LICENSURE PHARMACOVIGILANCE

- **Adverse effects are not necessarily predictable based on pre-licensure studies alone due to inherent limitations of these studies.**
- **Pre-approval vaccine studies typically exclude pregnant women unless use in pregnancy is sought as an indication.**
- **Findings from vaccine clinical trials conducted in high-income countries may not answer priority safety questions of relevance to LMICs.**

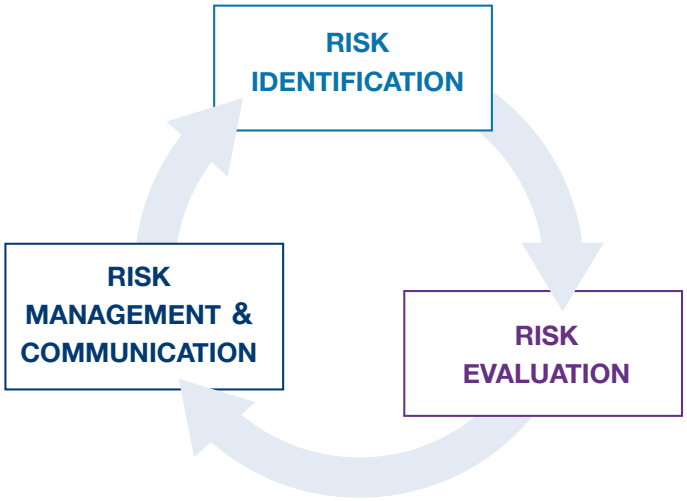
Approaches to post-licensure vaccine pharmacovigilance

Post-licensure vaccine pharmacovigilance is essential because much remains unknown about the risks and benefits of a vaccine at the time of approval. This is particularly the case under real-world, resource-poor conditions, where the incidence, pattern, and severity of adverse events may be different due to local environmental and host factors. To better understand the safety profile of maternal vaccines, surveillance systems need to systematically collect information on vaccines and other medicinal products taken by pregnant women, pregnancy outcomes, infant health, and the presence of potentially confounding factors such as comorbidities, maternal age, and gravidity.

Figure 4 illustrates three essential steps in the pharmacovigilance process—risk identification, risk evaluation, and risk management and communication. **Risk identification** involves the use of information from spontaneous and active surveillance systems and from other sources to identify key adverse events of interest related to pregnancy (in mothers and infants), their temporal association with product administration, and any country-specific or site-specific background prevalence rates of adverse pregnancy outcomes. In practice, this signal detection process is limited in LMICs by lack of resources and capacity constraints. **Risk evaluation** involves activities designed to assess potential safety signals. These activities include qualitative assessments of AEFIs by review committees through standardized case definitions and causality assessment to determine whether there is a reasonable possibility that the vaccine is etiologically related to the adverse event. Additionally, risk evaluation often involves the use of epidemiological methods, such as active surveillance and formal epidemiological investigations (for example, cohort and case-control studies) to confirm and quantify the relationship between the vaccine and the adverse event. **Risk management and communication** involves an iterative process for evaluating and taking steps to ensure that a medical product's benefit-risk balance remains favorable and to communicate those benefits and risks. Key requirements for pharmaceutical companies within the area of risk management and communication are the preparation of Risk Management Plans, Risk Evaluation and Mitigation Strategies, Periodic Safety Update Reports, Periodic Benefit-Risk Evaluation Reports, and development safety update reports.

Building systems for pharmacovigilance of maternal immunization will require adaptation, training, guidelines, and capacity building for this entire system of risk identification, risk evaluation, and risk management and communication. These systems will need to be modified to take into account the health complexities unique to pregnancy, assessing events in the context of existing background rates, tracking both mothers and infant dyads over time, and building the expertise to evaluate obstetric, perinatal, and neonatal complications.

Figure 4 | Essential steps in the pharmacovigilance process



Spontaneous surveillance systems

The mainstay of post-licensure vaccine pharmacovigilance in LMICs is spontaneous or passive adverse event reporting. In a spontaneous reporting surveillance system, any healthcare provider, pharmaceutical company, and patient can report a suspected adverse event to a public health or governmental organization via various mechanisms, including phone, internet, or postal systems. Spontaneous reporting systems are relatively easy and inexpensive to run and play a vital role in detecting potential new safety signals.

For a variety of reasons, spontaneous surveillance systems have limited utility as a platform for maternal immunization pharmacovigilance in LMIC settings. A major limitation of spontaneous surveillance systems in LMICs is the extremely low reporting of AEFIs by healthcare providers. As of September 2016, the Uppsala Monitoring Centre database of individual case safety reports (ICSRs), known as VigiBase®, contained more than 14 million reports.[104] However, only 54,278 cases of adverse events have been reported with any vaccine from LMICs to date. Of those ICSRs, just 13,442 were among females aged 12 to 44 years and only 130 describe adverse events following maternal immunizations.[105] Spontaneous surveillance systems have other limitations in monitoring adverse events

during pregnancy and pregnancy outcomes. Importantly, lack of a well-defined population denominator precludes measurement of incidence. Spontaneous reporting systems can be time consuming for already overburdened health professionals, reflect biases by both subjects and healthcare professionals, and are known to significantly underreport adverse events. Patients and providers in LMICs may not have sufficient training, empowerment, or mechanisms for understanding and reporting events, particularly those working in obstetrics and antenatal care. **For these reasons, spontaneous surveillance systems cannot and should not be relied on by themselves to identify post-market safety concerns with novel and newly introduced vaccines in LMICs.**

CHALLENGES SPONTANEOUS SURVEILLANCE SYSTEMS

- Limitations of spontaneous reporting include the lack of denominator data, poor infrastructure, low reporting, reporting biases (including a general bias toward reporting more severe outcomes), incomplete reports, lack of causality assessment, insufficient training and sensitization, limited data on background population rates, and lack of comparison groups. These issues are particularly common for maternal health and perinatal outcomes.
- AEFIs from EPI programs are not commonly shared with national pharmacovigilance centers and therefore are not forwarded to the Uppsala Monitoring Centre for signal analysis.
- Passive mechanisms of spontaneous reporting of adverse drug effects are generally inadequate to detect drug-induced fetal risks or the lack of such risks.

Active Surveillance Systems

Spontaneous surveillance systems for maternal immunization need to be supplemented with active surveillance pharmacovigilance systems that involve follow-up of patients and dedicated studies of individual problems and concerns. Active surveillance aims to detect adverse events on an ongoing basis within a defined group of people. It involves the systematic collection, analysis, and interpretation of data and is especially useful in conjunction with safety surveillance following the introduction of new vaccines. Cohort event monitoring, which is especially useful in LMICs, enrolls a group of people taking a drug or vaccine in a prospective cohort study and then systematically records data on all adverse events that occur in those patients. Sentinel surveillance programs based on a few select sites can also provide substantial, high-quality data from a smaller population with the added benefit of logistical ease. Examples in LMICs include cohort studies of AEFIs associated with the administration of a pentavalent DTP-hepatitis B vaccine/Hib vaccine conducted in Ghana, Guatemala, and India.[106,107,108]

FDA and the EMA recommend active surveillance, such as pregnancy registries, for medical products on the market that are likely to be used during pregnancy or by women of childbearing age.[109,110] Pregnancy registries use a prospective study design in which women are enrolled at their first antenatal care visit (or earlier when possible) and then followed through and beyond birth prior to any knowledge of a complication of pregnancy or adverse outcomes. Additional requirements involve the inclusion of comparison groups and sample size considerations.

Sentinel sites are one approach to overcoming some of the logistical challenges of active surveillance. Initially, the focus might be building on existing infrastructure and capacity so that AEFIs can be reliably identified. Therefore, the identification and evaluation of existing longitudinal demographic, health, and vaccination data collection systems are crucial. These include (1) demographic surveillance systems (to generate reliable population denominators and socioeconomic data), (2) morbidity and health outcome registries (to collect potential AEFIs and monitor incidence rates of events of interest in vaccinated and unvaccinated persons), and (3) vaccination registries (to relate potential adverse events to exposure and to monitor vaccination administration).The utility of these systems for vaccine

safety assessment purposes can be evaluated by trying to replicate already known positive adverse event associations, such as febrile seizures following measles vaccination. A proof of concept for this approach was recently completed in 16 countries, nearly all of which were LMICs, showing that global collaboration and sentinel based studies are possible in LMICs.[107] Active surveillance systems for vaccine safety monitoring need to be well integrated into national health systems.

CHALLENGES ACTIVE SURVEILLANCE SYSTEMS

- There are few examples of active surveillance systems for vaccine pharmacovigilance in LMICs. Those that do exist are most often donor funded or are supported by industry.
- Active surveillance pharmacovigilance requires careful planning and is more complex and costly to implement than spontaneous surveillance pharmacovigilance. This approach requires leadership, clearly identified responsibilities for organizations, and commitments to investment.

Phase IV Studies

Phase IV refers to studies conducted in the post-marketing period when the real-world effectiveness of a drug or a vaccine is evaluated, typically in field settings. Data from Phase IV studies complement the efficacy and safety data from pre-marketing studies. The EMA refers to these as post-authorization studies (PASS). Medicine regulators often require some type of Phase IV studies to clarify issues that were not resolved during a medical product's pre-licensure period. The size and designs of such studies can vary, sometimes consisting of a formal epidemiological study, an interventional clinical trial, or studies involving large populations using databases or registries of treated patients. Phase IV studies are performed in addition to conducting routine pharmacovigilance surveillance.

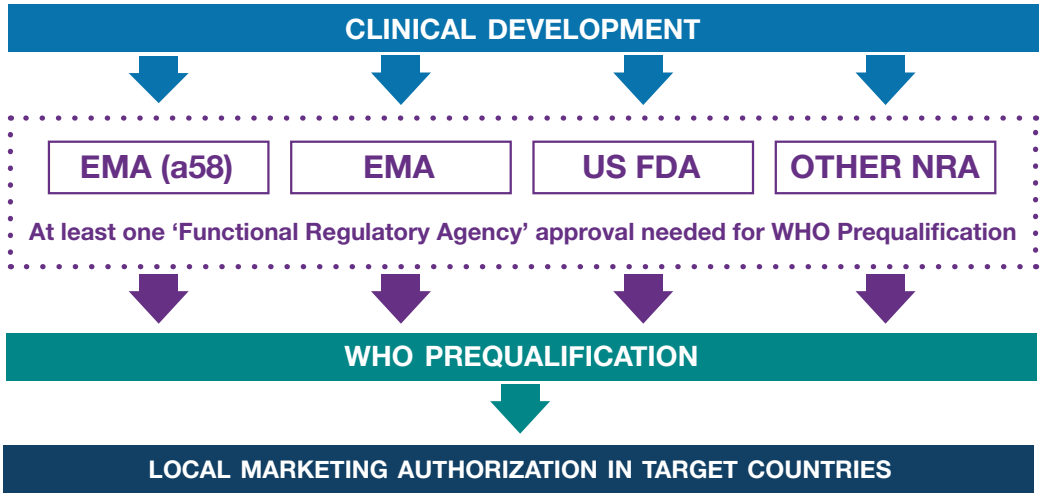
The role of international organizations in strengthening pharmacovigilance systems in LMICs

A broad range of international organizations work to strengthen pharmacovigilance systems in LMICs, including WHO, the Uppsala Monitoring Centre, FDA, the EMA, the Brighton Collaboration, regulatory agencies, and academia. Funding mechanisms are beginning to be available to LMICs for strengthening their pharmacovigilance systems (such as those provided through the Global Fund to Fight AIDS, Tuberculosis and Malaria and the Bill & Melinda Gates Foundation), and some are specific for strengthening vaccine pharmacovigilance systems (e.g., Gavi). Additionally, regional initiatives are engaged in the safety of vaccines, such as the African Medicines Regulatory Harmonization initiative, the African Vaccine Regulatory Forum, and the Developing Country Vaccine Regulators Network.[111] Many of these efforts are already focused on the unique issues related to safety monitoring among pregnant women and their offspring, but additional attention is needed for issues specific to maternal immunization pharmacovigilance. Increased coordination of efforts by these international organizations will be critical to leverage limited resources to effectively address programmatic needs for maternal immunization safety monitoring in LMICs.

Stringent regulatory agencies

Stringent regulatory agencies, such as FDA and the EMA (through Article 58), have established procedures exclusively for LMICs to support their medicines and vaccine regulatory systems (Figure 5). However, there is a lack of harmonization and minimal guidance for safety monitoring for maternal immunization among the FDA, EMA, and International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).[95] Only general guidance is available in the FDA and ICH guidelines, although specific requirements and guidance are now emerging.[112] The EMA has outlined specific requirements for evaluating vaccines in pregnant women, including criteria to select medicinal products for which active surveillance in pregnancy is necessary, guidance on how to monitor accidental or intended exposure to medicinal products during pregnancy, and specific requirements for reporting and presenting data on adverse outcomes of exposure during pregnancy.[109]

Figure 5 | Stringent regulatory agencies, such as the U.S. FDA and EMA (through Article 58), have established procedures exclusively for LMICs to support their medicines and vaccine regulatory systems.



EMA: European Medicines Agency;
U.S. FDA: United States Food and Drug Administration;
NRA: National Regulatory Authority;

EMA a58: EMA Article 58, Assessment of quality, safety and efficacy of a medicine or vaccine intended for use only outside the European Union

Modified from: Sobanjo-Ter Meulen A, Abramson J, Mason E, et al. Path to impact: a report from the Bill and Melinda Gates Foundation convening on maternal immunization in resource-limited settings; Berlin - January 29-30, 2015. *Vaccine* 2015;33:1873-2518.

African Vaccine Regulatory Initiatives

In 2005, WHO identified gaps in the functioning of many African regulatory systems pertaining to vaccines, such as the lack of legal frameworks, regulatory standards and guidance, and the training, recruitment, and retention of regulatory experts and professionals to oversee clinical trials.[113] As a result, the African Vaccine Regulatory Forum (AVAREF) was established to provide critical expertise on clinical trials regulation.[114] To date, AVAREF has enhanced communication between regulators, encouraged the adoption of model regulatory procedures, and spurred several countries to adopt good clinical practice inspections. It also has fostered the development of a regional strategy and the formation of NGOs dedicated to supporting the development of regulatory capacity. Other organizations have also helped to bridge gaps. For example, the South African Development Countries started a joint regulatory dossier evaluation forum in 2014 between Zambia, Zimbabwe, Botswana, and Namibia. In May 2014, the African Medicines Regulatory Harmonization (AMRH) of the African Union designated the University of Ghana and the Pharmacy and Poisons Board of Kenya as Regional Centres of Regulatory Excellence (RCOREs) in pharmacovigilance. These RCOREs are expected to provide leadership in capacity building, methods development and strengthening of pharmacovigilance in Africa for all medical products including medicines, vaccines and medical devices. When the African Medicines Agency is established in 2018, the RCOREs are expected to continue their roles in building capacity and improving pharmacovigilance in Africa.[115]

World Health Organization (WHO)

WHO has implemented its Blueprint strategy for strengthening vaccine pharmacovigilance in LMICs through the Global Vaccine Safety Initiative (Table 3). Internationally, WHO, through its collaboration with the Uppsala Monitoring Centre (UMC), created a global network to share data and information about the benefits and risks of medical products. Since 1978, UMC has managed the major aspects of the worldwide pharmacovigilance network known as the WHO Programme for International Drug Monitoring. This expanding network of more than 130 countries shares a common database to which participating members contribute medicinal safety data, such as individual case safety reports (ICSRs). However, as previously noted, few ICSRs associated with vaccines from LMICs are contained in the UMC database. Additionally, the WHO Pre-Qualification (WHO-PQ) scheme prequalifies medicines and vaccines from manufacturers in several

LMICs for use in LMICs through the United Nations and donor-funded medicine and vaccine procurement. The process of WHO-PQ includes an assessment of a manufacturer's safety surveillance system for gathering and critically reviewing AEFI reports. Within its Maternal Influenza Immunization Project, WHO specifically developed guidance to inform the introduction of influenza vaccine targeting pregnant women in countries, providing specific advice on AEFI surveillance for this vulnerable target group.

The Global Advisory Committee on Vaccine Safety (GACVS), which is an independent expert clinical and scientific advisory body, provides WHO with scientifically rigorous advice on vaccine safety issues of potential global importance. GACVS activities include assessing causal relationships between vaccines and their components and adverse events based on AEFI reports, evaluating procedures for causality assessment, and providing scientific recommendations to assist WHO, WHO's Strategic Advisory Group of Experts (SAGE), national governments, and international organizations in formulating policies regarding vaccine safety issues, with particular attention to problems affecting developing countries.

Council for International Organizations of Medical Science

The Council for International Organizations of Medical Science (CIOMS) provides guidance on drug safety-related topics through its working groups. CIOMS

Table 3 | The WHO Vaccine Safety Blueprint outlines requirements for minimal capacity for vaccine pharmacovigilance

Structural Elements
• A national dedicated vaccine pharmacovigilance capacity, with designated staff for this purpose, stable basic funding, clear mandates, well-defined structures and roles, collaborating with the WHO Programme for International Drug Monitoring.
• Healthcare workers and others encouraged to report vaccine safety issues.
• A reporting form for individual case safety reports (i.e., a national reporting form for AEFIs).
• A national AEFI database or system for collating, managing and retrieving AEFI reports.
• A national AEFI expert review committee (ARC) that is able to provide technical assistance on causality assessment of serious AEFIs and clusters of AEFIs so that unwanted risk can be managed.
• A clear strategy for risk communication that identifies risks and benefits to prepare health professionals, caregivers, and the public for possible vaccine reactions, explaining possible coincidental events, encouraging the monitoring of AEFIs by all concerned, and with preparedness plans in place to address vaccine safety crises (risk communication is dynamic and needs a feedback loop to all relevant stakeholders).
• Harmonized methods and tools for the monitoring and investigation of AEFI implemented.
Managerial Elements
• A regulatory framework is in place that defines the provisions for monitoring and management of AEFIs.
• Clear lines of accountability have been identified for the conduct of vaccine safety work.
• An institutional development plan is in place for implementation of performance indicators.
• The institutional development plan is periodically evaluated and revised to ensure continuous quality improvement in the conduct of national vaccine safety activities.
• There is a commitment to sharing information on vaccine safety with other countries.

Modified From: *WHO Vaccine Safety Blueprint*. Geneva, Switzerland: WHO; 2012

has a Vaccine Pharmacovigilance Working Group composed of representatives from the pharmaceutical industry, regulatory agencies, governmental institutions, and academia, including representatives from LMICs and from international organizations. CIOMS recently published the CIOMS Guide to Active Vaccine Safety Surveillance.[116]

The Brighton Collaboration, including the Global Alliance on Immunization Safety Assessment in Pregnancy (GAIA)

The Brighton Collaboration is an independent professional network with the mission of enhancing the science of vaccine research by providing standardized, validated, and objective methods for monitoring safety profiles and the benefit-risk ratios of vaccines. One of its key activities is development of standardized case definitions of AEFIs.[117] The GAIA project aims to provide standards and tools to establish a globally shared understanding of outcomes and approaches to monitoring, with a specific focus on the needs of LMICs.[118]

Gavi Alliance

The Gavi Alliance (Gavi) is the most important nongovernmental donor for vaccines. Among its goals are addressing vaccine inequity, leveraging economies of scale, supporting long-term funding, shaping vaccine markets, accelerating access to vaccines, strengthening vaccine delivery platforms, and sustaining immunization. Gavi's support to strengthen health systems encompasses vaccine supply chains, service delivery, the health workforce, communities and partners, health information systems, and health management.[119]

UNICEF

UNICEF is the world's leading supplier of vaccines to developing countries, supplying vaccines to over 40% of the world's children. It is a key partner in global public-private immunization partnerships, including the Initiative to Eliminate Maternal and Neonatal Tetanus. UNICEF has facilitated the introduction of new vaccines in LMICs and works with partners to gain and maintain support for immunization from governments and local leaders.[120]

Vaccine manufacturers and other vaccine developers

Vaccine manufacturers and vaccine developers have critical roles in the pre- and post-licensure safety monitoring of new vaccines. The development and manufacture of safe, effective, and quality vaccines and biologicals must comply with ICH and international and national regulatory requirements. Throughout the lifecycle of a vaccine—from product development and clinical trials to post-licensure safety monitoring—manufacturers and developers generate information for the investigator's brochure, summarize product characteristics, and provide periodic safety updates as well as risk-benefit assessment reports, including Periodic Benefit-Risk Evaluation Reports (PBRERs). PBRERs are submitted to NRAs as part of the new biological or medicine application for licensure, in compliance with the Common Technical Document professional plan and, where applicable, the risk management plan for the product. PBRERs may be required as justification for an application for a labeling amendment of Summary of Product Characteristics, a package insert, a change of indication, a new safety alert, or as supporting application information for registration of a dossier. Although pharmaceutical companies – particularly multi-national pharmaceutical companies - generally have a functional safety surveillance system in place that works worldwide, adverse events reported spontaneously following vaccination in LMICs are rare. In fact, considering the number of vaccine doses distributed to low- and middle-income countries, the results are striking. The low reporting rate of AEFIs from LMICs is consistent for multiple pharmaceutical industries, suggesting that the majority of LMICs do not have the elements of minimal vaccine safety capacity in place. The case study below illustrates an example of a vaccine manufacturer's efforts to strengthen professional capacity in LMICs.

Interactions among international organizations

Close collaboration, coordination, and communication among organizations can promote high quality safety data collection, reporting, analysis, and information exchange as well as targeted investments to strengthen safety surveillance of not only immunization programs but other in-country pharmacovigilance activities. But more needs to be done to systematically support maternal immunization vaccine pharmacovigilance in resource-limited settings. New vaccines for use in pregnant women in LMICs further heighten the need for functional systems, new approaches, and expanded investments and coordination by all the organizations focused on strengthening vaccine safety in LMICs.

CASE STUDY

Industry Engagement in Strengthening Pharmacovigilance in LMICs

In response to the need for functional pharmacovigilance systems in LMICs for assessment of malaria vaccine, GlaxoSmithKline (GSK) formed a pharmacovigilance working group in January 2015 to review and endorse a strategy for strengthening pharmacovigilance in sub-Saharan Africa. The program was developed to align with each country's pharmacovigilance needs and priorities for long-term sustainability, with country ownership, empowerment, and a culture of improved adverse event reporting. This project was not linked to introduction of any specific drug or vaccine, but rather was intended to benefit safety surveillance for existing, newly-approved and future vaccines and drugs as part of GSK's strategic plan to strengthen capacity in sub-Saharan Africa and expand access to essential drugs and vaccines. The objectives of this enhanced pharmacovigilance project were to improve local reporting of adverse events in the region and to monitor the safety of vaccines and medicines by facilitating dedicated pharmacovigilance personnel in healthcare facilities, providing the required technical support, performing pharmacovigilance training and mentoring of healthcare workers, and conducting site performance evaluations. The pilot projects were led by the ministries of health and involved key national stakeholders. GSK partnered with PATH for the pharmacovigilance training and mentorship of healthcare workers and to provide financial support defined in a collaboration agreement, which (including salaries of dedicated pharmacovigilance and data management personnel, logistics, and material for the pharmacovigilance centers). The project, which started in the fourth quarter of 2016 and is planned to continue until the fourth quarter of 2018, will be conducted in three selected countries: Malawi, Côte d'Ivoire, and the Democratic Republic of Congo. In general, the strategy in each selected country follows three steps:

1. A diagnostic step or gap analysis is performed in collaboration with the local GSK representatives to identify the gaps in the chain of detection and reporting of the safety information.
2. Joint meetings with national health authorities are held to obtain endorsements of the project, define the pharmacovigilance tools and basic interventions adapted to the local situation to improve country pharmacovigilance systems, and select key performance indicators.
3. The project is implemented with pharmacovigilance training and mentoring performed every 6 weeks.

This pharmacovigilance enhancement project is product independent. By increasing awareness among healthcare workers, it should benefit safety surveillance for existing, newly approved, and future vaccines and drugs in the region. It could also be adapted specifically for maternal immunization programs. This project in the sub-Saharan Africa region aims to leverage existing platforms and expertise, especially the WHO Program for International Drug Monitoring. It uses current pharmacovigilance standards developed by CIOMS and ICH with the hope of engaging additional partners to roll out the initiative on a broad scale. Discussions are being organized with national vaccine stakeholders such as ministry of health representatives, EPIs, national regulatory agencies, the National Malaria Control Program, and national pharmacovigilance centers to optimize pharmacovigilance systems in accordance with the WHO safety blueprint for LMICs.

CHALLENGES INTERNATIONAL ORGANIZATIONS

- There is a lack of harmonization and minimal guidance available for safety monitoring for maternal immunizations among regulatory agencies and others, including FDA, the EMA, and ICH.
- Greater coordination is needed among the many international stakeholders who are supporting LMICs to strengthen their vaccine pharmacovigilance systems, particularly with a new focus on maternal immunization pharmacovigilance.
- Guidance documents and harmonization tools from the GAIA have not been field tested in LMICs to assess practicality, utility, and impacts on improving data quality.
- Countries often lack the capacity to harness resources to strengthen health systems and capacity building for surveillance, investigation, and management of AEFIs, including establishment of AEFI surveillance systems and development of tools, guidelines, and AEFI training and other resources that might be available from Gavi and others.[121]
- While UNICEF and WHO activities include ensuring capacity for surveillance and monitoring in the Global Immunization Vision and Strategy (GIVS) for the decade 2006 to 2015, there is little evidence of support for strengthening vaccine pharmacovigilance systems or maternal immunization pharmacovigilance systems in particular.
- Although pharmaceutical companies have pharmacovigilance systems in place that function worldwide, the spontaneous reporting of adverse events following vaccination from LMICs is scarce or sometimes nonexistent.
- Although not necessarily required, risk management plans could be submitted to national regulatory authorities in LMICs to better ensure the safety of medicines globally.

SECTION

3

Current MNCH surveillance systems in LMICs:

defining a foundation for maternal immunization safety monitoring

In high-income countries, MNCH outcomes are tracked through vital registration and data from medical records and other national health reporting systems. In LMICs, however, these data are generally not available. Births, deaths, and clinical events often occur outside of medical facilities; vital registration systems are lacking; and medical records are incomplete or poorly maintained. However, a number of survey and surveillance systems are in place that could provide information on maternal and infant health in low-resource settings. To identify existing capacity that could be developed to monitor the safety of vaccines used in pregnancy, this section summarizes some of the key systems that could be used for collecting health data on pregnant women and their children.

Civil registration and vital statistics (CRVS)

In high-income countries, MNCH surveillance systems are structured to provide timely and accurate tracking of births and maternal, neonatal, and child morbidity and mortality, including ascertainment of cause of death. Civil registration and vital statistics (CRVS) reporting systems capture all births and deaths and are a cornerstone of MNCH data collection.[122] In the United States, for example, birth certificates collect data on congenital malformations, newborn complications, birthweight, gestational age, plurality, maternal risk factors in pregnancy, maternal infections, obstetric procedures, method of delivery, maternal morbidity, antenatal care visits, and demographic information.[123] EU countries have similarly rigorous CRVS systems in place.[124] These systems track important indicators on the entire population of live births and allow linkages with death certificate data. CRVS systems, however, are still largely lacking or nonexistent outside of high-income settings.[125,126,127] Although only about one-third of the world's population has a functional civil registration system, efforts are underway to strengthen CRVS systems in LMICs.[128,129] Given these challenges, a number of surveillance systems and surveys have been implemented in LMICs to monitor standardized MNCH indicators. These systems are outlined below, with the intent of providing an overview of available systems that can serve as platforms for post-licensure surveillance of maternal immunization safety in LMIC.

MNCH sentinel surveillance and surveys

Health and Demographic Surveillance Systems

Health and Demographic Surveillance Systems (HDSS) are sentinel surveillance sites that monitor all births, deaths, migration, and key health indicators of the entire population living in a defined geographic area [the demographic surveillance area (DSA)], with all households mapped and enumerated. HDSS data are collected via face-to-face household interviews in which household residents are asked about events that occurred since the prior survey. HDSS household visits occur at regular intervals, usually two to four times per year, to collect population-based longitudinal data. Sampling frequency can be dictated by the availability of financial resources; additional resources for special studies can augment the DSA size, visit frequency, and data collected. Data collection is organized at the household and individual levels, thereby making it possible to link information on mothers and children longitudinally over time. Because HDSS captures standardized data on all residents of a particular area, it provides denominator data and therefore the capacity to calculate rates. HDSS sites vary in size but have the distinct advantage of monitoring populations with a relatively large sample size, although the samples are not nationally representative.[132,133]

Many HDSS sites are coordinated by the International Network for the Demographic Evaluation of Populations and their Health (INDEPTH), which is made up of 46 member sites in 20 countries, mostly based in Africa and Asia where civil registration systems have been historically lacking. Surveillance of pregnancy and pregnancy outcomes is coordinated by the INDEPTH MNCH Working Group. All INDEPTH sites collect a core set of standard indicators, but data collection is flexible and is modified according to country and program needs. The standardized indicators allow for data to be compared, although to date many sites do not strictly adhere to standardized definitions or measures.[95,124]

Pregnancy outcomes are categorized as live birth, abortion, miscarriage, or stillbirth.[130,131] All deaths, including maternal, neonatal, and child deaths, are reported, and verbal autopsies are conducted for all reported deaths. Investigations of pregnancy loss or stillbirth are not conducted at most sites. Self-reported data regarding details of recent pregnancy, antenatal care, labor and delivery, maternal and neonatal health outcomes, and postpartum complications are also

collected. The primary strength of the HDSS sites is the ability to collect standardized data on the entire population, providing a platform for special studies and monitoring vaccine safety over time. Data collected at the household level could be linked to individual clinical records. Although not currently done in most sites, such linkage could strengthen the quality of reported health events. Maternal and child records are linked over time, which provides crucial information for monitoring AEFIs following maternal immunization.

HDSS systems have a number of limitations. Health information is self-reported and can be severely affected by limitations in the informant's medical knowledge, recall bias, lack of validation by medical records, and lack of awareness of asymptomatic events. Underreporting of these events can be exacerbated in sites where household visits are less frequent (e.g., every 6 to 12 months). The information captured in interviews may be imprecise or subjective, making ascertainment of true AEFIs difficult. Pregnancies, pregnancy loss, and other adverse events may be underreported due to cultural sensitivities. Self-reported medical complications, even if confirmed with linkages to clinical records, are generally non-standardized and not confirmed by laboratory investigation. Fetal losses (both spontaneous and elective) are underreported, as are early neonatal deaths. Due to the nonspecific symptoms of many early neonatal deaths, cause of death is difficult to ascertain by clinical assessment or verbal autopsy. Underlying factors related to stillbirth are not investigated or reported. Important information related to pregnancy health and newborn outcomes, such as gestational age and non-visible congenital malformations, are generally not accurately measured, detected, or reported. Data summaries and reports are conducted inconsistently across sites; data transfer may be delayed or reported irregularly. Population size may be limited, and results may not be generalizable to other national or regional populations.

Despite these limitations, HDSS and other sentinel population cohorts could provide a platform for adding information relevant for monitoring MNCH health and disease and standard reporting for AEFIs. Some HDSS sites have integrated electronic data collection from health facilities that are linked to the household interviews.[132,133] With additional resources, the frequency of household visits could be increased and additional data and laboratory, ultrasound, and radiologic investigations could be added. HDSS sites have already been used for pharmacovigilance projects in pregnancy.[134,135] A pilot project called PREVENT (PRogram Enhancing Vaccine Epidemiology Networks and Training) is underway to evaluate detection of signals for fever and seizures using the INDEPTH infrastructure for post-licensure vaccine safety monitoring.[136] Proof of concept and evaluations are underway in Mozambique (Manhiça), Kenya (Kisumu), and Ghana (Navrongo), exploring the capacity of local data systems for medical record linkage, vaccination records, data validity, and capacity for risk-benefit assessments of maternal immunization. These sites have already been used for systematically assessing pregnancy outcomes associated with maternal antimalarial use.[82,137] Taken together, HDSS hold the potential to be important platforms for post-licensure surveillance of maternal immunization safety.

Pregnancy registries

In many high-income countries, pregnancy registries (also known as pregnancy exposure registries) are used throughout the post-marketing phase to monitor the safety of medications used during pregnancy. Pregnancy registries use a prospective design, i.e., enrolling women at their first ANC visit, before the outcome of pregnancy is known, and following outcomes of women and their children. Pregnancy outcomes are systematically recorded in these registries, including miscarriage, elective terminations, fetal death/stillbirth, live birth, anthropometric measurements, and visible congenital malformations. Efforts are made to capture information on deliveries that occur in health facilities and at home.[82,89,137] Pregnancy registries have numerous advantages. By enrolling women before outcomes are known, the prospective approach of pregnancy registries avoids recall and reporting biases of both patients and providers, allows for the systematic recording of concomitant diseases and medications, and uses standardized methods to assess outcomes[89,108] The availability of both numerator and denominator data allows calculations of baseline rates of events, AEFIs, and disease incidence in vaccinated and unvaccinated populations.[82]

Pregnancy registries also have some limitations. Because reporting for some pregnancy registries is generally voluntary, prospectively reported pregnancies may lead to reporting bias toward high-risk pregnancies; abnormal outcomes are more likely to be reported than normal outcomes. Enrollment of women who attend antenatal care may bias results and diminish the generalizability of findings. Late disclosure of pregnancy and late initiation of antenatal care limit information regarding the first trimester of pregnancy, gestational age dating, and early pregnancy loss. Without close attention to quality, data quality can be poor and non-standardized, including

data on drug and vaccine exposures, pregnancy complications, and detection of adverse pregnancy outcomes. This limits the precision of whether and when a drug exposure or an adverse pregnancy outcome might have occurred. Home births and migration increase the potential for loss to follow-up, which may bias results.[88] Pregnancy registries are not typically powered to exclude increases in the rates of specific birth defects. Finally, women who consent to take part in a study may have different characteristics from those who do not consent, introducing selection bias.[89,82] WHO has established a protocol for pregnancy registries adapted for resource-limited settings, aimed at providing evidence for the safety of medicines used in pregnancy.[89]

Pregnancy registries have been used infrequently in LMICs, but studies have been implemented using practical methods and the resources available primarily at antenatal care clinics. Building on clinic infrastructure, staff are trained to better record visits, with a particular focus on disorders of pregnancy, medications and vaccines used, and improved ascertainment of pregnancy outcomes.[82,89] A recent successful example of a pregnancy registry in LMICs is the Assessment of the Safety of Antimalarials used during Pregnancy (ASAP) study that took place in Kenya, Mozambique, and Burkina Faso.[83] Conducted through the Malaria in Pregnancy Consortium, the researchers performed a meta-analysis of ASAP and other prospective observational studies and found no difference in the risk of miscarriage, stillbirth, or major congenital anomalies associated with artemisinins used during the first trimester compared with the use of quinine during the same gestational period.[137]

CHALLENGES PREGNANCY REGISTRIES

- There are few examples of pregnancy registries conducted in LMICs.
- Even fewer pregnancy registries follow the health of children beyond the newborn period.
- Since some adverse reproductive outcomes are relatively rare, pooling of data from pregnancy registries is needed to allow for systematic reviews and meta-analysis.

While pregnancy registries in high-income countries tend to be supported by pharmaceutical companies, those conducted in LMIC settings are generally one-time studies that are supported by donor organizations or research funding. Pregnancy exposure registries have had some success in providing reassurance that certain drugs or vaccines are overall not major teratogens; examples include the Antiretroviral Pregnancy Registry and Lamotrigine Pregnancy Registry.[138] Pregnancy registries have also had success in generating signals of potential teratogenicity that require further investigation.

Health information systems

Health information systems (HIS) collect information from health facilities and provide aggregated routine data on healthcare delivery. Data collected by HIS address health outcomes (mortality, disease incidence), health system performance, provision of care, and health infrastructure.[126] Several resources exist to assist countries in the design and maintenance of HIS, including the WHO Health Metrics Network's framework for country health information systems and the Health Information Systems Program (HISP). WHO guidance is the first attempt at a unifying framework to HIS development and outlines essential global health statistics that should be integrated into country HIS.[139] HISP is a South Africa-based global network of individuals, entities, and organizations that designs, implements, and sustains district health Information systems in Africa and Asia, established by the Department of Informatics at the University of Oslo. HISP manages the open-source web-based DHIS2 software that is currently used by 13 sub-Saharan African countries, Bangladesh, 7 states in India; 12 countries have adopted program or partial national roll-out using this software, and 18 are in the pilot phase of early roll-out.[140]

HIS data have the advantage of being facility based, with clinicians reporting medical information, sometimes supported by laboratory investigation. However, standardized diagnoses and diagnostic investigations are not routinely employed, and diagnoses are often based on clinical impressions. Clinical and laboratory data essential for detection of obstetric complications (e.g., preeclampsia, anemia, sepsis) are often not available, not accurately reported, or not collected in a standardized manner. Most importantly, events are usually reported as aggregate data and only represent patients who access clinical care, which may not be sufficiently sensitive, representative, or complete for tracking adverse events following immunization. People with severe disease are more likely to present for care, and in many areas a large

proportion of fetal deaths, births, and child deaths occur at home and not at facilities. Data collection and reporting systems are prone to error, often relying on hard copy or hand tabulations; data may be incomplete or lost as they are transferred through levels of the healthcare system. Reporting may be irregular and include varying numbers of facilities over time. Operationally, data systems and funding streams for HIS may not be coordinated or consistently supported. Data are not standardized within and between countries, thereby limiting the comparability of results and the ability to merge data.[126]

CHALLENGES HEALTH INFORMATION SYSTEMS

- HIS collect information only from patients accessing healthcare.
- Clinical diagnoses may be based on clinical impressions without standardized diagnostic algorithms or laboratory or imaging studies.
- HIS data may be prone to error in measurement or reporting.

Demographic and Health Surveys and Reproductive Health Surveys

Demographic and Health Surveys (DHS) and Reproductive Health Surveys (RHS) are nationally-representative, cross-sectional household surveys that capture information on population, health, and nutrition. The surveys, funded by USAID, track standardized health indicators using trained interviewers who conduct face-to-face interviews with household members. Information is collected on fertility, family planning, maternal health, child health, immunization, and child survival, and this information is used by host countries for program evaluation and policy development. Surveys use standardized modules and are conducted approximately every 5 years.[141] DHS and RHS use a stratified cluster sampling design, sampling approximately 15,000 households per country depending on population size. These household surveys reduce bias by sampling the entire population rather than persons who access care at medical facilities. Core questions are standardized and consistent across countries. DHS surveys therefore represent a reliable, representative, widely accessible, and timely system for reporting of health data across countries and regions. However, information is self-reported by persons who may lack education or medical knowledge. Also, data are not validated by medical records, clinical assessment, or standardized clinical or laboratory investigations.[142]

DHS data on pregnancy, delivery, and birth outcomes are limited. Information is collected on the number and content of antenatal visits, place of delivery, mode of delivery (vaginal or Cesarean), type of birth attendant, and birthweight. Complications of pregnancy, labor, and delivery are not recorded due to poor results in prior validation studies. Recent surveys include questions on pregnancies not resulting in a live birth, such as fetal death. Information on childhood fever, diarrhea, and cough is collected, but only for events occurring in the two weeks prior to the survey, which would not sufficiently capture AEFIs for vaccine safety monitoring. No details are collected on neonatal complications or congenital malformations.[143] DHS collects information on maternal tetanus vaccination and child vaccination from mothers' reports or from health cards when available. Because survey data are collected by household, maternal and child health data can be linked.

Nearly all data on health outcomes rely on self-report of past events that occurred during the prior 5 years, which introduces a significant source of recall bias. Self-reported medical data and pregnancy status may be inaccurate or unreliable.[144] As with HDSS, pregnancies, pregnancy loss, and other adverse events may be underreported due to cultural sensitivities. The long interval between surveys limits detailed ascertainment of AEFIs and would likely blur any temporal association of an adverse event with immunization.

In a few countries, a verbal autopsy questionnaire is collected on maternal, neonatal, and child deaths. Since many causes of neonatal deaths have similar symptoms, this method is often not a reliable tool for ascertainment of cause of death in neonates. Verbal autopsy questionnaires are not currently used to investigate underlying causes of stillbirth. Maternal mortality is assessed using one of three methods to identify the pregnancy-related deaths of siblings or other household members. The DHS sampling framework, however, is generally not sufficiently powered to estimate maternal mortality ratios.

In summary, DHS surveys lack utility for reporting on most components of pharmacovigilance due to the inadequate

capture of data on maternal and perinatal complications and outcomes of interest, a lack of validated health information, the potential for recall and misclassification bias, and infrequent survey administration.

Multiple Indicator Cluster Survey (MICS)

The Multiple Indicator Cluster Survey (MICS) program was developed by UNICEF with the intent of helping countries collect and analyze data to fill gaps in MNCH surveillance relevant to the Millennium Development Goals (MDGs). The surveys include high-income countries, but over 70% of MICS data comes from LMICs. MICS surveys were conducted every 5 years, then increased to every 3 years in 2007 to meet a growing demand for data and surveillance. MICS teams work closely with DHS to harmonize methodologies and indicators.[145]

Similar to DHS, MICS uses trained interviewers who collect data by face-to-face household interviews. The surveys collect interview data and anthropometric measurements of children under 5.[146] Sample size and the household sampling frameworks are similar to that of DHS. MICS samples are both nationally and sub-nationally representative. MICS questionnaires are structured similarly to DHS, with some notable differences. In MICS surveys, caregivers provide information if mothers are deceased or absent, thereby including data on orphans and other vulnerable children. MICS collects information specific to live births that occurred in the prior 2 years and information from the mother's immunization card.[147,148]

Similar to DHS, MICS questionnaires do not collect data on medical complications of pregnancy, spontaneous abortion, gestational age, and congenital malformations. Questions on child illness focus specifically on fever, diarrhea, and respiratory symptoms in the 2 weeks preceding the survey, which are important to determine infection-related morbidity and mortality among older children but lack utility for ascertainment of illness and cause of death among neonates. As such, both DHS and MICS do not capture essential data elements that would be needed to monitor maternal immunization safety on a population level.[149] Furthermore, information on pregnancy and medical illness is self-reported and not confirmed by medical records or laboratory diagnostics, thereby limiting the quality and accuracy of reported clinical events, including adverse pregnancy outcomes. Clinically silent events, such as hematologic, endocrinologic, or immunologic disturbances, would not be detected or reported.

Surveillance systems for birth defects

Assuring women, providers, and the general population of vaccine safety in pregnancy will require systems that can accurately monitor baseline rates of birth defects and detect, report, and evaluate birth defects in pregnancy losses, stillbirths, and newborns. National and international organizations that house, coordinate, or manage birth defects data or registries include the National Birth Defects Prevention Network, the Vaccines and Medications in Pregnancy Surveillance System (VAMPSS), European Surveillance of Congenital Anomalies (EUROCAT), the International Clearinghouse for Birth Defects Monitoring Systems (ICBDSR), WHO Collaborating Center for the Prevention of Congenital Malformations, NIH Global Network for Women's and Children's Health Research, and the Latin American Collaborative Study of Congenital Malformations (ECLAMC). Population-based registries in the United States include the Metropolitan Atlanta Congenital Defects Program and the California Birth Defects Monitoring Program.

Through its Birth Defects COUNT initiative, CDC provides funding and technical assistance for birth defects surveillance in LMICs.[150] Birth defects surveillance systems have been established or are under development in several African countries, including Kenya, Malawi, Tanzania, and Uganda and in Southeast Asia in Bangladesh, Bhutan, India, Indonesia, Maldives, Myanmar, Nepal, Sri Lanka, and Thailand. Hospital-based surveillance is conducted using standardized data collection forms and protocols; the majority of the countries in Southeast Asia submit data to the SEARO Newborn and Birth Defects Database.[151]

Most LMICs have no birth defects surveillance. When data are available, they are mostly obtained from individual, one-time studies rather than ongoing surveillance. For countries with established systems, surveillance is usually local or regional only and is typically facility based; sampling therefore is not population based or nationally representative. Surveillance facilities are often referral centers, making it difficult to obtain unbiased data or calculate rates.

LMICs face numerous challenges in detecting and reporting birth defects, including limited resources, inadequate infrastructure, and lack of expertise. Capacity for accurate diagnosis, coding, data management, and analysis are generally lacking. Above all, political will often falls short in LMICs where numerous other serious health problems compete for limited resources. Birth

defects may not be perceived as a priority, and lack of detection and reporting may continue to limit awareness and global investment.

CHALLENGES SURVEILLANCE FOR BIRTH DEFECTS

- **Most LMICs do not have ongoing programs of birth defects surveillance.**
- **Due to lack of resources and diagnostic capacity, most LMICs that conduct birth defects surveillance generally collect information only on defects that are externally visible at birth. Many major malformations, including those that affect internal organs, result in fetal loss, or manifest later in life, are unreported.**

Key elements for information systems

Key elements for building necessary capacity for the collection of baseline rates of maternal, fetal, newborn, and childhood morbidity and mortality include:

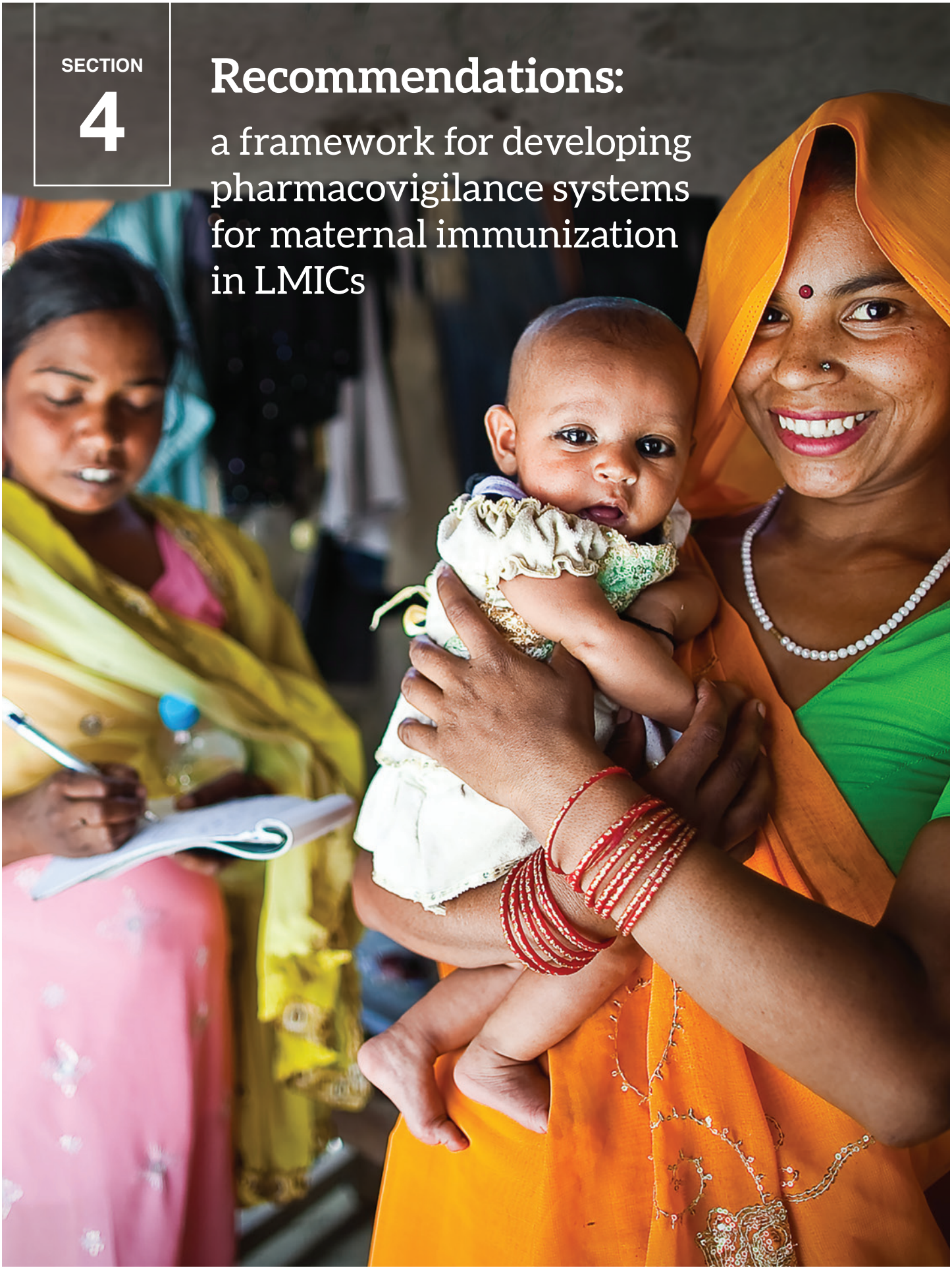
- Strengthen CRVS systems in LMICs. The main variables to be captured include births and maternal, neonatal, and infant deaths, stillbirths, and gestational age.
- Implement standardized, validated definitions for key variables into surveillance systems (for example, the definitions from GAIA for maternal, fetal, and neonatal death).
- Establish systems of reporting CRVS data to central repositories. Ensure that information technology, data collection tools, and other system requirements are developed and maintained.
- Baseline data on the rates of congenital anomalies, particularly those that may not be apparent at birth, are lacking in most LMIC settings. Given the low incidence of individual events, collecting such data will require large-scale systematic data collection. The recent global focus on congenital abnormalites associated with Zika virus infection is likely to lead to the establishment of sentinel surveillance for certain congenital anomalies and thus an expansion of available data. However, data from low-income countries, particularly those not affected by Zika transmission, are likely to remain limited.
- Clinical trials will likely never be sufficiently powered to identify an increased risk of congenital anomalies and other rare events. Thus, while major and minor congenital anomalies in clinical trials need to be consistently classified, post-licensure surveillance and case-control studies in relevant settings will be essential to detect an increased risk of congenital anomalies and other rare events.

SECTION

4

Recommendations:

a framework for developing pharmacovigilance systems for maternal immunization in LMICs



As outlined in this report, a rich, diverse, and complex array of organizations and national government entities have made important contributions and commitments to ensuring adequate monitoring of the safety of vaccines post-approval. If harnessed, coordinated, and strengthened, a focused and coherent strategy could have a major impact on the success of maternal immunization programs. The overall goal must be to develop an organized approach to developing systems that are practical, affordable, and sustainable in LMICs, building as much as possible on existing infrastructure and investments.

Data for detection and assessment of AEFIs

1 Improved data on pregnancy and newborn health

Improved detection and interpretation of AEFIs requires high quality data on the health of pregnant women, the fetus, newborn, and child. Prospective data, collected in a standardized manner through active surveillance, will be required in LMICs to systematically monitor the safety of vaccines used in pregnancy. Optimally, monitoring of women will begin early in pregnancy and vaccination information will be documented along with key outcomes that are measured and reported over time, in a linked fashion, for both the woman and her offspring. As such, standardized, prospective systems will need to be developed through implementation and enhancement of pregnancy registries and/or prospective cohorts. A practical approach would be to implement new vaccines in areas with sentinel surveillance sites such as INDEPTH or other programs that have an established capacity to follow cohorts of pregnant women. In these cases, infrastructure could be enhanced to capture key data elements in a standardized manner.

2 Prioritization of AEFI signals and clinical information

Collection of important data on pregnancy and newborn outcomes has traditionally been weak in several critical areas, including gestational age assessment, fetal loss, stillbirth, congenital malformations, and maternal morbidity. Information on concomitant illnesses, exposures to medications and other factors, family history, social and behavioral factors, and pre-existing medical conditions can affect risk of adverse pregnancy outcomes. Building prospective systems for monitoring safety will be best achieved if outcomes of interest are specified and prioritized. This provides structure in project design, training, and development of essential diagnostic services, patient education, and resource allocation. It also allows for building systems with improved data quality and standardization, allowing for comparability across sites. Field testing, validation, and implementation of the GAIA case definitions will be important for this effort. Standard collection of variables will be particularly valuable for evaluation of rare health events, where it will likely be necessary to pool data from multiple sites.

3 Denominator data, background rates, and confounding variables

Many adverse pregnancy outcomes occur in the general population with or without vaccination. Assessment of causality of AEFIs on an individual level needs to take into account many factors, including biological plausibility, the temporal association with vaccination, and the presence of other risk factors and concomitant disease. Assessment of adverse pregnancy outcomes on a population level requires comparison of rates of adverse events among vaccinated and unvaccinated populations, controlling for other variables that affect risk of an adverse event. As such, collection of denominator data from the relevant general population is needed to calculate rates of adverse health events affecting pregnant women and their children.[152] Data on vaccinated and unvaccinated populations need to be collected from comparable populations, from similar geographic areas, and at similar times.

Systems are also needed that monitor the incidence of the vaccine-preventable infections of interest. The calculated risk of AEFIs then can be compared with the population-level benefit of the vaccine to assess risk-benefit ratios. Smaller, special studies will be important to assess specific questions, such as whether maternal immunization adversely affects immunogenicity of childhood vaccines. In this way, a cohesive understanding of risks and benefits can be ascertained for a specific vaccine, ideally collected from multiple sites to strengthen statistical power, the detection of rare events, and comparisons of vaccine performance in different populations. This approach will require international and national coordination and planning to set an overall agenda, identify priorities, and review data from multiple scientific and geographic areas.

Leveraging maternal immunization safety monitoring in the context of other MNCH efforts

Leveraging existing systems and investments for MNCH surveillance will help strengthen the infrastructure for MNCH programs, improve efficiencies, reduce costs, and improve sustainability. Health and demographic surveillance sites, such as those affiliated with INDEPTH, are examples of existing platforms that, with increased investment, could track pregnant women and their offspring.[153,154] Linking programs with shared interests in building pregnancy registries or other prospective studies that monitor pregnancy and birth outcomes could yield benefits and improved efficiencies. Potential examples of collaborations in strengthening maternal and infant surveillance include Zika response programs, CRVS initiatives, WHO perinatal mortality surveillance, malaria in pregnancy programs, CDC and WHO birth defects surveillance programs, and the Bill & Melinda Gates Foundation's Child Health and Mortality Prevention Surveillance (CHAMPS) Network, which are all aimed at improving the ascertainment of maternal and/or infant morbidity and mortality.[155]

A number of public health surveillance systems share common indicators and need further investments for success. Recommended collaborative and synergistic activities include:

- Building unified surveillance systems for common exposures and adverse birth outcomes, thereby facilitating data collection within the context of routine clinical and public health work and minimizing the burden on staff collecting similar data for multiple surveillance systems.
- Development of systems that can link information on vaccines given to pregnant women with the medical records of their children.
- Collection of population-level data for assessment of baseline rates of risk factors, pregnancy complications, and adverse birth outcomes common to multiple fields of public health.
- Training and capacity building for the development and management of electronic data systems, allowing efficient review of data quality and data sharing.
- Attention to shared staffing needs (e.g., midwives, nurses, obstetricians, pediatricians) as part of a clinical team to strengthen the quality and accuracy of data collection and safety endpoints.
- Strengthened infrastructure in antenatal care settings (e.g., clinical, laboratory, ultrasonography) to improve data quality. Integration of maternal immunization with antenatal care services would further facilitate data sharing, contribute to the sustainability of efforts, and reduce the burden on providers and patients.
- Ascertainment of cognitive impairment and other long-term pediatric disabilities is expensive and logistically difficult. These assessments could be achieved through special studies integrated with other programs that focus on child cognitive and motor development.

Building engagement at the local level

Engagement of healthcare providers and community members at the local level will be a critical component of program success. Acceptance of immunizations in pregnancy varies widely by country; vaccine hesitancy can lead to challenges ranging from non-acceptance to active mobilization against immunization programs.[156] Involving communities in the design and implementation of immunization programs has been shown to build trust and acceptance of vaccines in LMICs and enhance detection and reporting of AEFIs. Several countries have demonstrated an increase in vaccine coverage with community involvement and outreach services.[157,158] When planning for the introduction of new maternal immunizations, building programs for community outreach, education, and engagement will be important for program success. Maternal immunization pharmacovigilance programs will need to engage stakeholders at the local level including healthcare providers, community health workers, the maternal child health community, influential community leaders, and community members. Programs can utilize the WHO SAGE guidelines on addressing and measuring vaccine hesitancy to ensure community engagement for new maternal immunizations.[154]

Strengthening pharmacovigilance systems for maternal immunization

Despite multiple international capacity-building initiatives, existing systems for vaccine pharmacovigilance in LMICs remain limited in their presence, scope, and effectiveness. Few LMICs have functional post-licensure safety monitoring systems for vaccines and drugs, and most do not report an accurate number of suspected adverse events. **Efforts to build maternal**

immunization pharmacovigilance systems for detecting, reporting, and responding to AEFIs should be part of an integrated global effort to strengthen pharmacovigilance systems at the national and international level.

Existing pharmacovigilance systems need to be adapted to ensure the recognition of events specific to maternal immunization programs. Recommended actions include:

- Adapt guidelines for detecting, reviewing, and responding to events specific to the safety of pregnant women and their offspring, including delayed or long-term outcomes.
- Enhance linkages between EPI, pharmacovigilance centers, manufacturers, and national MNCH programs, including antenatal, intrapartum, and postpartum maternal and newborn, care, to improve capacity and systems for detecting, reporting, and responding to potential AEFIs. Coordination and integration with national immunization programs is a key to the sustainability and feasibility of implementation on a country wide-scale.
- Develop guidelines and training programs for national pharmacovigilance program personnel in reviewing and responding to AEFIs, with particular attention to the evaluation of events that are unique to pregnant women and their children.
- Adapt pharmacovigilance systems that can detect and estimate rates of the serious events potentially associated with maternal immunization or vaccine failures.
- Build models for data sharing and communication on maternal immunization safety, including communication with manufacturers, regulatory agencies, policy makers, governmental agencies, researchers, clinicians, and the public.
- Strengthen systems to ensure the timely evaluation of relevant vaccine safety and effectiveness concerns related to new vaccines for use in pregnant women.

The report of the Safety Surveillance Working Group, developed with the support of the Bill & Melinda Gates Foundation, proposed several strategies for improving the scalability of initiatives to strengthen post-licensure safety surveillance in LMICs of relevance to maternal immunization. The report's recommendations included promoting data sharing and management to foster the timely identification of drug and vaccine safety concerns and improving efficiency and investments in training and infrastructure in a manner that lays the foundation for addressing broader drug and vaccine safety concerns.[70]

Landscape analysis of pharmacovigilance activities and stakeholders

As summarized in this report, multiple efforts are underway at the country and international level to monitor vaccine safety across the spectrum of product development, clinical trials, public health, pharmacovigilance, and clinical training and capacity building. These ongoing efforts could be leveraged through improved communication, coordination, and integration. To coordinate efforts, investments, and synergies, an extensive landscape analysis needs to be done of key stakeholders to map existing activities at the country and international levels. This landscape analysis should encompass industry, regulatory agencies, public health agencies, vaccine programs, aid organizations, country government leaders, policy makers, epidemiologists, clinical researchers, and healthcare organizations working in vaccines, MNCH, pharmacovigilance, and related fields. Initial landscape assessment efforts could prioritize countries where maternal immunization product introductions are likely to occur. In planning for the landscape assessment, it is important to take into account strategies and priorities of national and regional entities. In Africa, the African Union and WHO Strategy for the regulation of medical products provides key guidance that should be built upon. In addition, the WHO Collaborating Centers for Pharmacovigilance in Accra, Ghana and Rabat, Morocco as well as the RCOREs in Ghana and Kenya and others are key partners who should be involved in the landscape analysis as well as the deployment of any pharmacovigilance approach for maternal immunization.[159,160]

The focus of program efforts needs to begin at the country level. Mapping exercises will identify the availability of essential program elements needed for maternal immunization safety monitoring, gaps that need to be addressed, feasibility, and the current investments, political will, and opportunities for coordination across key program areas. Analyses could include reviews of in-country stakeholders, the current capacity for safety surveillance and reporting, existing vaccination efforts and national policies, data systems for maternal and infant care, and existing surveillance and research activities that can be leveraged for maternal immunization safety monitoring. Reviews could also help identify sentinel sites and build a structure for program implementation,

operation, and capacity building. In this way, systems can be built in a logical and stepwise fashion through in-country and regional partnerships that have the expertise and resources to ensure success. Maternal immunization programs are most likely to succeed if they are started on a relatively small scale in countries with existing capacity, investment, and political will and then are rolled out step-wise to larger and more challenging areas.

Coordination of maternal immunization pharmacovigilance activities

Introduction of new vaccines targeted for use in pregnant women in LMICs raises challenges for safety monitoring throughout the lifecycle of vaccine development, from clinical trials through post-licensure surveillance. Multiple activities are needed that will vary by design and implementation in different countries, populations, and clinical settings. A large number of stakeholders are engaged at the international, national, and regional levels to ensure the availability of standards and guidelines, essential data systems, training and capacity building, and prompt review and response to potential adverse events. Efforts to strengthen maternal immunization pharmacovigilance in LMICs should be fully integrated with ongoing global efforts for strengthening pharmacovigilance for all medications and vaccines.

A strategy is needed to facilitate coordination of maternal immunization pharmacovigilance activities in LMICs among all stakeholders. Maternal immunization pharmacovigilance efforts need to be conducted within a collaborative international and regional framework for the ongoing evaluation of vaccine benefit-risk profiles, with particular emphasis on vaccines that are newly introduced in LMICs for use in pregnant women. Important actions are to:

1. Improve linkages between national pharmacovigilance centers and EPI programs specifically for maternal immunization pharmacovigilance. Joint roles for EPI programs and national pharmacovigilance centers should include investigating clusters, serious events, unusual events, corrective actions, and communication.
2. Provide mechanisms for sharing best practices and lessons learned among stakeholders involved in vaccine pharmacovigilance in LMICs.
3. Engagement the pharmaceutical industry in support of efforts to improve the monitoring, review, and response to potential AEFIs in every country where maternal vaccines are introduced, with a focus on standardization of methods, data systems, training materials, and data sharing between and among countries.
4. Provide incentives and support to prioritized countries to develop enhanced vaccine pharmacovigilance capacity and support response and communication strategies to ensure sustainable programs.
5. Address gaps identified in this report through initiatives such as the Developing Country Vaccine Regulators Network (DCVRN), the WHO-African Vaccine Regulatory Forums, National Immunization Technical Advisory Groups (NITAGS), national regulatory authorities, the National Vaccine Regulatory Network, EPI programs, and the National Vaccine Regulatory Network.
6. Define and establish safety evaluation strategies prior to the introduction of new vaccines, implemented in an organized and coordinated fashion, with a robust sampling framework and sufficiently powered to detect predefined levels of excess risk of adverse outcomes of interest, including those that may be considered rare events.

Strengthening maternal immunization data quality in the pre-licensure phase

Strategies for strengthening the quality and completeness of data collected in the pre-licensure phase of maternal immunizations in LMICs should include:

- The use of research midwives, neonatal nurses, obstetricians, and pediatricians as part of clinical trial teams to improve the quantity, quality and accuracy of data collected on safety endpoints. This approach is resource heavy and may further strain staff shortages, but it is likely essential in low-income settings that lack sufficient infrastructure for collection of clinical data.
- The establishment of additional obstetric capacity (e.g., clinical, laboratory, ultrasonography and radiology) to improve data accuracy.
- Training of skilled birth attendants and community healthcare workers to increase detection of serious adverse events that do not present to medical

facilities. Research is needed to evaluate the coverage and quality of data collected through this approach.

Training and capacity building in maternal immunization program implementation post-licensure

Systems need to be put in place to develop, implement, and strengthen maternal immunization safety monitoring programs, but these system needs are not necessarily unique to maternal immunization. Ideally, they should be built within the context of existing MNCH, vaccine, pharmacovigilance, and other public health programs. Examples include:

1. **Clinical and laboratory capacity:** Healthcare systems often lack the capacity to detect and diagnose disease in the clinical and community setting. Laboratory and imaging technologies (e.g., ultrasonography) will be needed to monitor health of pregnant women and their children without adding to families' financial burden.

2. **Training of healthcare personnel:** Healthcare workers are on the frontlines of administering vaccines and detecting and reporting AEFIs. Healthcare workers and students, particularly midwives and obstetricians who may traditionally have limited linkages to vaccine programs, will need training in the appropriate administration of vaccines and in detecting, reporting, and responding to adverse events. Examples include training in clinical management of AEFIs (e.g., the management of anaphylaxis), pharmacovigilance reporting systems, and communication with patients, families, and communities.

3. **Monitoring vaccine quality, cold chain, administration:** As with other vaccines, systems are needed to ensure appropriate storage, transport, record keeping, and administration of vaccines targeted for use in pregnancy. Investment in infrastructure of antenatal care clinics may be needed.

4. **Patient education and community awareness:** Materials and methods for patient and community education and engagement will need to be developed, adapted, and field tested.

5. **Management and budgets:** Training and capacity building may be needed to meet the administrative needs of running programs both for the delivery of maternal immunization and safety monitoring.

6. **Data management:** Data management will be an essential requirement of systems aimed at detecting and reporting AEFIs. Ideally these systems will focus on capturing important variables, the use of standardized case definitions that can be compared across sites, and the capacity to compile and transfer electronic data between clinics, population-level data repositories, national regulatory authorities, and international pharmacovigilance systems.

7. **M-health:** Expanded use of telemedicine and other technologies can improve monitoring of the health of pregnant women and infants and the detection and reporting of safety data. Strategies for the use of m-health in maternal immunization pharmacovigilance could be explored as part of other MNCH initiatives. M-Health has been successfully used in immunization efforts in LMICs to send reminders, to improve recall, and for monitoring and surveillance.[161]

8. **Training programs** at the WHO Collaborating Centre for Advocacy and Training in Pharmacovigilance at the University of Ghana, the WHO Collaborating Centre for pharmacovigilance in Rabat, and the RCOREs in Accra and Nairobi are existing resources that offer capacity strengthening and training that is based on a WHO core curriculum. To the extent that additional national and international organizations are also involved in pharmacovigilance training and capacity strengthening in LMICs, those efforts should be encouraged and coordinated.

SECTION

5

Implementation plan

The development and implementation of systems that detect, review, and respond to potential adverse events following maternal immunization will not occur organically. Leadership, coordination, and investment are needed to produce organized systems with guidelines, training materials, data elements, and program management. This final section of the report outlines a framework for implementing maternal immunization pharmacovigilance programs and identifies the opportunity for key stakeholders to build functional systems that are practical, affordable, and sustainable in LMICs.

Mapping existing capacity and current stakeholders

The first step toward implementation of maternal immunization pharmacovigilance systems is achieving an in-depth understanding of current programmatic capacity, activities, and investments at the country, regional, and international levels. A comprehensive mapping exercise will allow development of a cohesive strategy that builds on existing systems, identifies gaps, and leverages existing investments. Further, it allows for development of a strategic framework for bringing together activities and organizations that ordinarily may not interact on a routine basis, creating dialogue and planning across different sectors, scientific disciplines, and programmatic areas.

The mapping exercise would have two distinct approaches. One is to identify international organizations and their program activities that are relevant for the development, implementation, evaluation, and regulation of maternal immunization and related fields (e.g., MNCH), while also outlining specific country activities being supported by these international and regional organizations. Second, a comprehensive mapping exercise of priority countries will be needed to determine, at the country level, existing organizations, activities, and infrastructure gaps that would need to be addressed for implementation of new maternal immunization pharmacovigilance programs. The mapping exercise would include a review of existing surveillance programs and data sources to track the incidence of infection and maternal-infant health outcomes; healthcare training needs; laboratory and other diagnostic infrastructure; EPI and other vaccine investments; professional obstetrical, midwifery, and pediatric organizations; community engagement and civil society; WHO and governmental leadership; international and national industry investments; clinical research infrastructure; multilateral and nonprofit engagement; and pharmacovigilance and regulatory programs and entities. A review of engagement of related fields will also identify opportunities to leverage existing in-country investments, such as programs for malaria in pregnancy, HIV, health management and information systems initiatives, malaria vaccine programs, or birth defect monitoring programs.

Leadership and coordination

This report outlines the complex array of activities needed to monitor and respond to maternal immunization safety and evaluate maternal immunization risks and benefits in LMICs. In addition, the report identifies a complex array of organizations engaged in these efforts that could be harnessed for program success. The meeting of contributors convened for the project was, in and of itself, catalytic. The meeting identified that:

1. A broad range of stakeholders have a strong interest and engagement in maternal immunization safety monitoring in LMICs, including country pharmacovigilance programs, the MNCH community, governmental and multilateral organizations, NGOs, industry, and academia.

2. Many organizations and program activities do not routinely communicate or coordinate efforts at both the international and country levels. For example, maternal immunization program efforts may not communicate with vaccine programs, MNCH surveillance activities, pharmacovigilance systems, or research initiatives.

3. Program implementation requires functional, on-the-ground systems at the country level. International organizations may not coordinate sufficiently with country programs or provide sufficient technical and financial support for their success.

The stakeholders' meeting identified the need for leadership to bring the multiple entities together to create a common direction and program plan. This leadership needs to be both top-down, from the international level, and bottom-up, from the country level. WHO was recognized as an important organization on both the international and country levels, to serve as the normative agency to define standards, guidelines, surveillance methods, case definitions, and reporting systems, and to facilitate program implementation at the country level. Meeting discussants emphasized the need for continued leadership to implement an actionable

agenda and harness and coordinate technical expertise, engagement, and investments going forward.

Leadership and coordination at the country level will be critical. Country programs may be best catalyzed by strengthening capacity in the context of one or more specific, new vaccine initiatives. That being said, development of the infrastructure needed to measure baseline incidence of infection, complications of pregnancy, and adverse birth outcomes will require considerable lead time, long before a new vaccine is ready for introduction. As such, two potential models for coordination at the country level could occur. Country-based coordination could be led by a specific industry's or organization's program (such as introduction of a new vaccine). Alternatively, a country-based effort could be led by a secretariat that serves a convening and coordinating function, in support of ministry of health and national regulatory authority programs. This coordinating function could strengthen the multiple health systems needed for maternal immunization pharmacovigilance, convene entities working in diverse program areas, and assist with coordination of international efforts that can be prioritized and tied directly to country needs. Advocacy may need to be part of this effort to garner government support and investment.

Leveraging existing systems to build LMIC capacity

This landscape review identified multiple existing programs and systems that can be leveraged for building maternal immunization pharmacovigilance programs. Based on the further mapping activities and coordination of stakeholders that are still needed, a number of program initiatives can be engaged to develop maternal immunization pharmacovigilance programs.

Data for detection of AEFIs

Efforts are underway, across a number of program areas, to address the relative paucity of population-level data on causes of maternal and newborn morbidity and mortality. Opportunities exist to identify common needs and leverage the improved collection of data needed for maternal immunization pharmacovigilance programs. In particular, the contributors' meeting emphasized the need for measurement of specific outcomes, including preterm birth, stillbirth, birth defects, and other severe birth outcomes. Coordination of these shared goals holds the promise of leveraging investments and political will and advancing the understanding of adverse health events needed for multiple programs.

Pharmacovigilance systems

A number of international, regional, and national organizations are strengthening systems for the safety monitoring of drugs and vaccines in LMICs. Currently, pharmacovigilance systems in LMICs tend to be weak. Advancing maternal immunization pharmacovigilance programs can strengthen the existing systems at the country level and add the expertise needed for detecting, evaluating, and responding to AEFIs in general and among pregnant women and their offspring specifically.

Detection of AEFIs following maternal immunization will require new programs to increase awareness of safety monitoring among midwives and obstetricians, healthcare providers who traditionally have not been deeply engaged in vaccine programs. An early dialogue with providers will define the in-country needs for baseline surveys, training materials, and in-service training programs needed in the clinical setting to operationalize maternal immunization pharmacovigilance programs. Similarly, understanding and anticipating questions and concerns among populations of pregnant women could guide the development of education materials and community engagement.

Step-wise program implementation

Through the mapping exercise described above, countries will be identified that have existing platforms for the introduction of new maternal immunization programs post-licensure. Examples of key areas of capacity include existing pharmacovigilance programs as well as platforms for measuring, on a population level, the incidence of infection and adverse events. Program success will likely be improved by starting maternal immunization programs and safety monitoring, on a relatively small scale, in countries with existing infrastructure, and then building out in a step-wise fashion to larger populations and more challenging program conditions. Early programs can be used as venues for implementation research, to document not only program successes but also identify strategies to improve uptake, reporting of events, and capacity building. These sentinel sites for program implementation will benefit from overall strengthening of the national and local pharmacovigilance systems and from improvements in the quality of care for pregnant women and their infants.

Global investment

Successful implementation of maternal immunization pharmacovigilance programs will require political will and the mobilization of financial and human resources at both the international and country levels. Pharmacovigilance systems and MNCH data systems are often rudimentary in the countries that have the greatest need and potentially would benefit most from maternal immunization programs. Countries will likely need technical assistance in building safety monitoring and identifying resources for program support. For example, countries could include funding requests specifically for safety monitoring as part of their Gavi applications.

Industry and international organizations are already recognizing and investing in safety monitoring. Advocacy is needed to ensure that the introduction of new vaccines is accompanied by the political and financial support to track safety, thereby protecting the integrity of the program and maintaining the trust of the country and general population. Investment in pharmacovigilance systems for assessment of maternal immunization safety could be transformative for understanding the safety of medical care for pregnant women across multiple disciplines.

Glossary of Key Terms

Adverse event – Any unfavorable or unintended sign, abnormal laboratory finding, symptom, or disease.

Adverse event(s) following immunization (AEFI) – Any untoward medical occurrences that follow immunization, which do not necessarily have a causal association with the usage of the vaccine.[162]

Benefit-risk – A description or assessment of both positive and negative effects of a medicine (not necessarily expressed in quantitative terms) as far as they are known and as perceived by an individual. This is the critical information that health professionals and patients need to make wise therapeutic decisions.[163]

Causality assessment – The systematic review of data about an AEFI case to determine the likelihood of a causal association between the event and the vaccine received.

Individual case safety report (ICSR) – Reports sent by health professionals or patients when an adverse event has occurred in a patient taking one or more medicines. These have also been referred to as adverse drug reaction (ADR) reports or adverse event (AE) reports.

Maternal immunization (MI) – The process of vaccinating women during pregnancy to boost immunity against diseases that affect pregnant women and their infants. Maternal antibodies are transferred transplacentally to the infant starting in the second trimester of pregnancy. Maternal immunization protects the mother, fetus, and infant from potentially serious morbidity and mortality.

Pharmacovigilance - The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem.

Pharmacovigilance system – Systems, structures, and stakeholders necessary to ensure the safety and effectiveness of drugs and vaccines and to protect public health.

Pre-marketing – The developmental stage before a drug or vaccine is approved and available for prescription or sale to the public.

Post-marketing – The stage when a drug or vaccine is approved and generally available on the market.

Prequalification - The procedure for assessing the acceptability of medicines, diagnostics, and vaccines for purchase by the United Nations.

Registry – A list of patients presenting with the same characteristic(s) such as a disease (disease registry), condition (pregnancy registry), or a specific exposure (drug registry/vaccine registry). Registries collect information in a standardized and prospective fashion.

Regulatory authority – The legal authority in any country with the responsibility for regulating all matters relating to drugs or vaccines.

Sentinel site – A selected reporting unit, with a high probability of seeing cases of the disease or condition in question, good laboratory facilities, and experienced and well-qualified staff.

Signal (safety signal) – The Council for International Organizations of Medical Sciences (CIOMS) defines a signal as “information (from one or multiple sources) which suggests a new potentially causal association, or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action.”

Surveillance – Systematic ongoing collection, collation, and analysis of data and the timely dissemination to those who need to know the information in order for actions to be taken. The type of surveillance implemented is determined by the type of data collection:

- Passive surveillance relying on passive reporting;
- Stimulated surveillance relying on stimulated reporting;
- Active surveillance based on a systematic search for cases, seeking to completely ascertain the number of adverse events via a continuous pre-organized process.

Vaccine pharmacovigilance (PV) – The science and activities relating to the detection, assessment, understanding, and communication of AEFIs and other vaccine-related issues, and the prevention of untoward effects of the vaccine.[164]

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