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Introduction

The seventh meeting of the Global Vaccine Safety Initiative (GVSI) was held in Santiago, Chile, on 8–9 October 2018. It was hosted by the Institute of Public Health of Chile, together with the Ministry of Health of Chile.

The meeting provided a platform for exchange, interaction and information sharing between Member States and partners, as well as opportunities for partnership-building and planning.

The meeting enabled Member States and partners to discuss progress in the implementation of national and global vaccine pharmacovigilance activities. Participants had opportunities to share ideas, explore new frontiers in vaccine safety, and initiate collaborations.

Attendees included immunization program managers, pharmacovigilance staff from national regulatory authorities, representatives of UN agencies, academic institutions, umbrella organizations of pharmaceutical companies, technical partners, industry representatives and funding agencies.

This report provides an overview of presentations and key points discussed during the meeting.

Meeting objectives:

• To review progress in implementing the GVSI.
• To address new challenges and opportunities in vaccine safety.
• To facilitate further partnerships and inter-sectoral collaborations.
• To identify means to promote regulatory harmonization initiatives for vaccine pharmacovigilance.
• To examine progress with the Global Vaccine Safety Observatory.
OPENING
The world is changing, with major challenges including population mobility, climate change and multiple public health crises. Infectious diseases remain a global problem. Immunization must respond to these challenges, and national immunization programs must deliver safe and effective immunization programs to their citizens and address anti-vaccine movements, which are a growing concern. Countries need to cooperate with each other and with other stakeholders such as vaccine manufacturers to achieve these objectives.

WHO has a critical role to play in leading collaborative work between countries. With WHO support, the global community should help low-resource countries affected by public health crises to strengthen their immunization programs to safeguard local, regional and global health. In countries affected by public health crises, borders need to be opened to humanitarian assistance.

Chile is honored to host the seventh Global Vaccine Safety Initiative meeting, being held in the Latin America region for the first time. Chile has developed a robust public health system, with a strong immunization program and efficient national regulatory authorities. We aim to share our experiences and also learn from others.

"We must develop and disseminate a common single message highlighting how vaccination programs have saved millions of lives."

Honorable Dr Emilio Santelices Cuevas, Minister of Health, Chile
Immunization programs around the world have made tremendous progress in controlling many infectious diseases. Now, successful use of an increasing number of vaccines is focusing attention on possible untoward effects of vaccination.

Vaccine safety concerns can reflect genuine issues with vaccination, which need to be identified so corrective action can be taken promptly. Known vaccine reactions, very few of which are serious, need to be explained to patients and their caregivers. On the other hand, rumours, and sometimes poor science, can also affect the public perception of vaccines.

Confidence in vaccine safety can best be promoted with good science. The Global Vaccine Safety Blueprint, WHO’s strategy for vaccine safety, promotes the development of national capacity for vaccine pharmacovigilance. The GVSI is the mechanism to implement the Blueprint, in collaboration with multiple partners. Annual GVSI meetings provide opportunities to exchange experiences and understand the respective roles of each participant in furthering quality immunization activities.

The growing number of vaccine safety reports and investigations provide assurance that vaccine programs are getting stronger, with improved quality assurance mechanism. They also generate more attention on safety issues and force us to enhance our communication strategies.

It is legitimate for anyone who receives a medical intervention to question its merits and the risks related to it. By monitoring how people react to vaccines, everyone involved in pharmacovigilance is contributing to a better understanding of why and how vaccines are used.
Individual variation is critical in new vaccine development. The complexity and costs of new vaccine development require a better understanding of the elements of the immune response that correlate with protection. A promising new vaccine against tuberculosis, for example, appears to be effective in some individuals and not others.

Similar issues are important in the field of vaccine safety. Clinical trials provide valuable information about the safety profile of a product but are not sufficient to understand rare reactions, particular risk factors and long-term effects. The recent example of the dengue vaccine has illustrated this issue, as well as the role of WHO advisory committees in assessing risks and adapting immunization policies.

In emergency situations, vaccine use may be necessary with even more limited safety data. With recurring outbreaks of Ebola disease in complex settings, use of an Ebola virus vaccine with demonstrated protective efficacy to protect frontline workers and contacts of Ebola patients is a high priority.

Although only one disease, smallpox, has been eradicated, multiple vaccines are having a tremendous impact on health outcomes, particularly for young children. Measles vaccines have averted 20 million deaths in the 21st century, and Hib vaccines 1.2 million deaths. Pneumococcal conjugate vaccines prevent 100,000 deaths every year. Rotavirus vaccines cut seasonal diarrheal mortality. Epidemic meningitis A has virtually disappeared and neonatal tetanus is being controlled in most parts of the world.

In this changing world, the Sustainable Development Goals provide a benchmark for mapping progress up to 2030. Health is only one of 17 goals. Within the health agenda, immunization will be monitored through a specific coverage indicator as well as a health systems indicator. Future challenges for immunization include global demographic transitions, including a billion more people each in Africa and in Asia by 2050, as well as greater numbers of displaced people.

Emerging public health concerns are also of relevance to immunization. Better immunization coverage and new products will help to control multidrug resistance. WHO’s goal of universal health coverage will enable immunization programs to ‘reach the fifth child’.

Dr Alejandro Cravioto

Key note address: Moving towards an integrated system for sustainable development.

Global work on vaccine safety should be part of an integrated system for sustainable development to improve global health and well-being."
Furthermore, economic studies indicate that vaccination is a tool to reduce poverty. WHO is currently finalizing a high-level strategy that will provide a value proposition for immunization. This is a novel way of looking at the impact of vaccines, recognizing that equitable access to vaccines not only prevents diseases but also has other beneficial effects. It describes the full health, economic and societal value of vaccination, and articulates the full direct (individual) and indirect (population) economic impacts of vaccination – positioning vaccines as key enablers of development.

Safety is a cornerstone of this project. Tools to assess vaccine safety are very reliable. Yet mishandling of scientific information damages the image of vaccines and leads to questions about their safety. Our ability to share information and to develop a clear strategy to communicate the safety of vaccines will be essential for the global immunization system to deliver its full promise.
The Global Vaccine Safety Blueprint is the WHO vaccine safety strategy, part of the Global Vaccine Action Plan endorsed by the World Health Assembly in 2011. The aim of the Blueprint is to enhance the safety of vaccination through effective use of pharmacovigilance principles and methods. The Blueprint focuses on how national and international players can better collaborate in order to fill current gaps in vaccine pharmacovigilance, management and communication infrastructure. It attempts to define what needs to be accomplished in all countries and internationally to ensure effective vaccine pharmacovigilance. To implement the Blueprint, WHO launched the Global Vaccine Safety Initiative (GVSI) in March 2012, and has developed a Global Vaccine Safety Observatory to support countries.

Session objectives:
- To examine progress towards Blueprint objectives.
- To reflect on vaccine safety strategy post-2020.
The Global Vaccine Safety Initiative: A review of achievements

The vision of the Global Vaccine Safety Blueprint is for all countries to have established effective vaccine pharmacovigilance systems by 2020. The GVSI, the implementation framework of the WHO Global Vaccine Safety Blueprint, was based on a thorough situation analysis of the global vaccine pharmacovigilance landscape. This identified a range of key issues, including healthcare workers’ lack of knowledge of vaccine safety and pharmacovigilance systems, inadequate reporting, poor data management, the lack of regulatory and quality control systems, inadequate resourcing and a lack of political will.

The GVSI has undertaken multiple activities to address these issues. These include:

- Developing standardized reporting forms and tools.
- Producing a range of updated guides and resources, including the Global Manual on Surveillance of Adverse Events Following Immunization, Causality Assessment of an Adverse Event Following Immunization, the CIOMS Guide to Active Vaccine Safety Surveillance, and the CIOMS guide to Vaccine Safety Communication, collaborations between the Council for International Organizations of Medical Sciences (CIOMS) and WHO.
- Creating numerous training packages and e-learning courses on topics such as the basics of vaccine safety, adverse events following immunization (AEFI) surveillance and monitoring, periodic safety update reports, AEFI data management, AEFI investigation and communication.
- Developing the Vaccine Safety Net, a WHO-led network of websites facilitating health care professional and public access to reliable information on vaccine safety.
- Developing a multi-country network of hospital-based sentinel sites for identification and verification of vaccine safety signals.

Within the framework of the Global Vaccine Action Plan, an indicator has been developed to measure progress based on data reported annually to UNICEF and WHO. A country is deemed to have achieved a minimal level of pharmacovigilance capacity if it reports at least 10 AEFI per 100,000 surviving infants per year. The number of countries reaching this indicator has increased dramatically between 2010 and 2017.

Looking to the future, opportunities exist to expand GVSI partnerships. Other priorities include better methods to identify and investigate AEFI and to maintain public confidence, rolling out of training to local levels, establishing regional mechanisms to identify clusters, and use of novel tools such as text messaging and apps for AEFI reporting.

“
The number of countries with at least minimal pharmacovigilance capacity has increased significantly since the launch of the Global Vaccine Action Plan in 2010.”
The Global Vaccine Safety Observatory

The Global Vaccine Safety Observatory was proposed as a platform to help member countries to achieve Global Vaccine Blueprint targets. The Observatory concept has evolved into a central information ‘clearing-house’ site documenting member country progress, linked to information and resources to assist further progress. Launch of the Observatory is planned for the first half of 2019. It will document data sources in the following areas:

- Status of vaccine safety monitoring.
- Legal, regulatory and administrative framework for vaccine pharmacovigilance.
- Ability to evaluate vaccine safety signals.
- Regional and global technical support platforms.
- Availability of vaccine safety communication plans.
- Efforts to improve systems for interactions between partners.

The Observatory will include maps documenting each country’s progress in annual vaccine safety submissions to UNICEF/WHO. This will enable members to visualize their progress over time, relative to their neighbours.

The Observatory will also document vaccine recalls and warnings issued from regulatory authorities and manufacturers, and will include an interactive map documenting known vaccine safety episodes.

Regional nodes within the site will provide more locally relevant information, contacts, examples, stories and challenges encountered by countries and their neighbors. The Observatory will also provide global and regional links to expert resources in areas such as developing vaccine safety capacity, education and training, and vaccine safety communication.

Regional nodes have been created in Africa and South East Asia with inputs from external partners with experience in vaccine pharmacovigilance, education, capacity building, implementation and research.

"The Global Vaccine Safety Observatory will provide countries with access to data and resources enabling them to monitor and develop their pharmacovigilance systems, and to compare their progress with others."
Countries in the Americas have pharmacovigilance systems of varying degrees of maturity. As well as developing regional approaches to vaccine pharmacovigilance, the Pan-American Health Organization (PAHO) is providing technical and other assistance to develop national pharmacovigilance capacities.

Session objectives:

- To provide an overview of the vaccine pharmacovigilance systems in the Latin America region – progress, challenges and collaboration in system strengthening.
- To learn from individual country experiences in establishing a sustainable vaccine pharmacovigilance system.
Vaccine pharmacovigilance in Latin America: Progress, challenges and collaboration

In all countries in Latin America and the Caribbean, there has been an increase in the total number of AEFI notifications received at national pharmacovigilance centers. However, the number of notifications sent to the WHO global database Vigibase is much lower.

Furthermore, there are significant discrepancies between the data reported through national regulatory agencies and information collected by the immunization program and reported annually through the WHO/UNICEF Joint Reporting Form. This highlights poor coordination between national pharmacovigilance centers and national immunization programs.

In the region, PAHO is promoting active pharmacovigilance projects, for example for antimalarials and medicines to treat drug-resistant tuberculosis. PAHO countries also participated in a WHO multi-country proof-of-concept project investigating an association between the MMR vaccine and immune thrombocytopenic purpura/aseptic meningitis. This work suggested that it is possible for a collaborative network of sentinel hospitals to investigate the safety profiles of new vaccines in low- and middle-income countries (LMICs).

The Latin American Center for Perinatology in Uruguay has developed a database collating more than 40,000 electronic health records of women and their offspring in 18 countries. Work is being carried out to assess the potential of the data resource to analyse vaccine safety. PAHO is also conducting an umbrella review to pool data from systematic reviews of vaccine exposure and key maternal and neonatal outcomes.

PAHO continues to promote tools and strategies to improve coordination between national pharmacovigilance centers and immunization programs. These include assessments of national regulatory authorities, as well as procedures for coordination and definition of roles and responsibilities, promotion of joint activities, and facilitating data flow across different systems.

Regional activities have supported national programs, for example by providing technical guidance on AEFI surveillance after H1N1 influenza vaccination. No evidence of increased risk of severe reactions was seen, although under-reporting of AEFI was likely as surveillance relied on passive systems.

PAHO is now establishing a regional AEFI surveillance system, and supporting countries to develop their national AEFI surveillance systems, particularly to undertake more active surveillance and to follow up serious AEFI. In collaboration with the USA Centers for Disease Control and Prevention (CDC), PAHO’s immunization safety guidelines are being updated, drawing on the WHO’s Global Manual on Surveillance of Adverse Events Following Immunization.

“PAHO is supporting the development of national vaccine safety systems, as well as fostering collaboration to generate regional pharmacovigilance resources.”
Experience and lessons learnt from Mexico’s strengthening of its vaccine safety surveillance system

Vaccine pharmacovigilance in Mexico began in 1995, and became the responsibility of the Comisión Federal para la Protección contra Riesgos Sanitarios (COFEPRIS) in 2001. In 2002 it developed its first pharmacovigilance standard, which has been revised several times, most recently in 2018.

COFEPRIS has been recognized as a regional reference national regulatory authority by PAHO and by WHO, after establishing effective coordination procedures among key bodies and constituencies, including the national immunization program, the Department of Epidemiology, industry, providers and the general public.

In 2016, discussions at a national workshop revealed that, despite good communication among national bodies, local coordination was more challenging. As well as a national AEFI database, the Notireporta electronic platform was developed to support the local reporting of suspected reactions. It is now the sole means by which laboratories, distributors and healthcare professionals report adverse drug and vaccine reactions to the national pharmacovigilance center.

Mexico was the first country to license the Dengvaxia® dengue vaccine. COFEPRIS was responsible for evaluating its safety and efficacy, while a separate mechanism was used to assess its cost-effectiveness. After a three-year review, the vaccine was introduced in the Mexican market in September 2016. Various pharmacovigilance activities are being carried out, including a post-marketing clinical trial.

“A new electronic tool, Notireporta, is being used throughout Mexico to collect safety data.”
Vaccine safety in the USA is the joint responsibility of the Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration (FDA), both part of the Department of Health and Human Services.

The FDA is the US national regulatory authority. It conducts pre-market data review (submitted by applicant companies) and oversees post-market safety studies. CDC is in charge of the epidemiological component, organizes national immunization programs, and shares responsibility for post-marketing vaccine safety. The FDA and CDC coordinate activities and communicate regularly.

FDA considers vaccine safety throughout the life cycle of a product, from pre-clinical evaluation, through clinical trials, manufacturing and post-licensure. Efficacy, safety and benefit-to-risk ratios are the key factors in review by FDA advisory committees and FDA decision-making. At this point, post-marketing commitments are agreed upon by the FDA and the manufacturer. The FDA has the authority to mandate post-marketing studies or further clinical trials at the time of approval or when new safety information is obtained.

For example, the manufacturers of the Trumenba® meningococcal group B vaccine were asked to conduct a cohort study to examine pregnancy and birth outcomes following immunization during pregnancy, while the makers of Heplisav-B® were required to carry out an observational study comparing the risk of acute myocardial infarction in adults who received this vaccine or another hepatitis B vaccine.

In parallel, a wide range of routine pharmacovigilance activities are carried out by the FDA, CDC and sponsors. Manufacturers are required to report adverse events within 15 days if they are serious and unexpected, or quarterly for less serious events.

“There is a significant amount of investigation in the pre-market phase but this does not preclude post-licensure monitoring of safety, due to known limitations of clinical trials”
Passive surveillance through the joint FDA–CDC Vaccine Adverse Event Reporting System has several strengths, including nationwide coverage and timeliness. However, like all passive surveillance, it has limitations, including under-reporting and the low likelihood of detecting long latency events. Around 30,000 events are reported annually to this system.

The FDA and the CDC also use electronic record-based systems for active surveillance (Sentinel, a claims-based system covering 170 million people; Centers for Medicare and Medicaid Services, covering a population over 65 years; and the Vaccine Safety Datalink, covering a geographically diverse population of 10 million). The use of Sentinel data was instrumental in identifying a link between rotavirus vaccination and intussusception.
SESSION 3

COLLECTION AND PROCESSING OF VACCINE SAFETY DATA: GLOBAL, REGIONAL AND COUNTRY EXPERIENCES

The collection and processing of vaccine safety data continues to be a challenge in many countries. To guide data collection by program managers, WHO has developed a set of 25 core variables that comprise a minimum essential dataset.

This session highlighted the practical aspects of applying these core variables, as well as regional and country experiences in AEFI data management.

Session objectives:
- To describe the applied aspects of WHO’s minimum data elements for vaccine safety data.
- To share regional and national experiences of using the minimum data elements for vaccine safety.
- To discuss efforts to harmonize vaccine safety data.
An introduction to the WHO’s minimum data elements and its practical applications

The GVSI envisions a world where all countries have at least minimal capacity for vaccine safety monitoring. To develop a core pharmacovigilance dataset, national AEFI reporting forms from a range of LMICs were reviewed, and the essential elements identified and discussed at the Global Advisory Committee on Vaccine Safety (GACVS). A set of 25 variables were selected as the basis of the minimum data elements for AEFI reporting.

These core variables were used to develop a standard AEFI reporting form and other tools, software and training modules to support effective AEFI reporting. Collectively, these tools and resources form a Vaccine Adverse Events Information Management System (VAEIMS) designed to harmonize data collection, standardize AEFI data analyses, detect signals and generate causal hypotheses.

The core variables capture epidemiological information of potential value at all levels of the health care system. In addition, information systems implemented in countries support monitoring and decision-making across the entire AEFI surveillance cycle, including detection, notification, reporting, investigation, analyses, causality assessment and feedback.

The VAEIMS approach has been implemented on a range of IT platforms. These include platforms developed by countries themselves, the Java-based desktop and web versions developed by the International Vaccine Institute (IVI), and versions based on the open-source District Health Information System 2 (DHIS2).

WHO has recently developed an open-source AEFI data management training platform, “Harmonia” (http://gvsi-aefi-tools.org/aefidata/training/), including 180 simulations. The online training platform incorporates the 25 core variables, the standard AEFI reporting form, and performs initial epidemiological data analyses. It offers an opportunity to build the capacity of immunization program managers and regulators at national and subnational levels to add and use AEFI data, and to develop a national repository to guide policy and regulatory decision-making.

“Every country should have locally appropriate software solutions for managing vaccine safety information.”

Dr Madhava Ram Balakrishnan
National experience in applying the minimum data elements for vaccine safety – An experience from Chile

Prior to 2015, Chile struggled to send AEFI reports to the global database of adverse drug reactions, Vigibase, maintained by the WHO Collaborating Centre for International Drug Monitoring (also known as the Uppsala Monitoring Centre, UMC). Preparing information was time-consuming, so only a percentage of total reports were sent.

A PAHO-sponsored project was organized to improve the quantity and quality of reporting. For this project, the Public Health Institute, Chile (Instituto de Salud Pública de Chile) collaborated with the International Vaccine Institute (IVI) of Republic of Korea to develop software to send the information from the national database to the global database using the E2B format.

This project had four stages: diagnosis, harmonization, UMC compatibility testing and completeness scoring. The major challenge was faced during the harmonization stage. The national database was found to be lacking six of the 25 core variables recommended by the GACVS. These variables were added, and the database was harmonized with the E2B format.

This stage was challenging as it involved considerable changes to existing reporting systems. For example, a field recording the reason for the seriousness of a case had to be added, as previous descriptions had been limited to ‘serious’ or ‘not serious’.

The project led to an increase in the quantity of reports sent to the UMC, from 549 between 1995 and 2015 to 999 in the last two years. In addition, improvements were seen in the completeness of the information sent to UMC and the quality of the data recorded in the national database. In the future, the country aims to use the new system to send about 3000 AEFI reports to the global database annually.

Some of the key lessons learnt included the need to harmonize information at the national level so comparisons could be made with other countries through the global database. It is also important to review information in the national database to ensure that it meets global standards.

“Our new system has improved our national data gathering and streamlined submissions to global databases.”

Mrs Adiela Saldaña Vidal
Regi0nal experiences in applying the minimum data elements for vaccine safety – The African experience

AEFI data capture and documentation has been a major challenge in countries in East and Southern Africa for many years. Most countries have lacked mechanisms to record AEFI cases systematically – ‘line listing’ – at district, provincial and national level. In addition, there has been a lack of coordination between national immunization programs and regulatory authorities, leading to issues in AEFI data sharing and harmonization.

These deficiencies lead to poor reporting of AEFI nationally and to WHO. As a result, most countries have not been able to achieve the key global indicator of AEFI surveillance, reporting of at least 10 cases per 100,000 surviving infants.

Further critical issues include the lack of AEFI guidelines and tools to capture and investigate cases in many countries, ambiguity in stakeholder roles and responsibilities, and a shortage of funding to strengthen vaccine safety surveillance.

WHO has undertaken a range of initiatives to enable countries to strengthen their vaccine safety surveillance. These include supporting countries to finalize national vaccine safety guidelines, bringing national stakeholders together to clarify roles and responsibilities, conducting training and organizing events at national and sub-national levels to build capacity, and providing support to train national AEFI committee members on causality assessment.

Initiatives have been taken to enhance AEFI data collection, documentation and sharing. In addition, Malawi and Uganda have begun implementing a DHIS2-based VAEIMS platform.

More cases are now being reported, more systematic line-listing is enabling timely data analysis and corrective actions, and more countries are meeting the reporting indicator.

Surveillance-strengthening activities will continue in the future, including training of healthcare workers, promotion of line-listing in further countries, and support for countries in data analysis and follow-up responses. In addition, at least five countries will be helped to introduce VAEIMS software over the next two years.

“The number of AEFI reported in East and Southern Africa has increased tenfold since 2011.”

Dr Dicky Akanmori on behalf of Dr Sujeet Kumar Jain
IVI experience in supporting countries in implementing a Vaccine Adverse Events Information Monitoring System

VAEIMS software was developed by the IVI in collaboration with WHO. The software is designed to facilitate the transfer of AEFI data from the periphery of a healthcare system into a central database for processing and analysis to guide decision-making at different levels of a country.

In 2017, the customized VAEIMS has been deployed at a national level in four priority countries in the WHO Western Pacific Region – Cambodia, Lao PDR, Mongolia and Viet Nam. Technical support for AEFI collection has been provided in each country.

Newly developed features include versions in languages other than English, to support district-level AEFI data collection, as well as the capacity to automatically generate an AEFI bulletin in order to share AEFI data with other stakeholders. IVI has also been developing a dengue vaccine safety data monitoring system.

Lack of knowledge of standard terminology of adverse events is a critical barrier to harmonization with global databases. A training course was developed for national focal points with responsibility for pharmacovigilance to enhance their use of VAEIMS and to improve their knowledge of standard adverse events terminology (the Medical Dictionary for Regulatory Activities, MedDRA).

This first VAEIMS training course was held in Seoul, Republic of Korea, in September 2018. It was hosted by IVI in collaboration with the WHO Regional Office in the Western Pacific. The training sessions provided an opportunity to discuss and exchange information about AEFI collection, reporting and information management across countries, and to gain practical experience through hands-on workshops on pharmacovigilance tools and methods and MedDRA coding. The course was well-received, and an annual training course and additional on-site training are being considered.

“Ten participants from five countries benefited from the first regional VAEIMS training course.”
Rotavirus vaccines are very safe but carry a small risk of intussusception, where one segment of the gut telescopes into another. As rotavirus vaccines are rolled out in Africa and Asia, and new products become available, there is a need to assess the magnitude of this risk for each product in different populations. This session discussed how the risk of intussusception and other safety characteristics of rotavirus vaccines are being documented along the product life cycle.

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**Session objectives:**

- To provide an update on the use of rotavirus vaccines and their safety profile.
- To demonstrate safety surveillance activities in various parts of the world.
From the first rotavirus vaccine introductions to the present day: Rotavirus vaccine availability, use and impact

Rotavirus is a highly contagious infection and a leading cause of severe diarrhea in children. Most cases occur in low income countries, where infants less than 1 year old are particularly affected. In 2008, rotavirus was responsible for an estimated 450,000 deaths a year.

The first rotavirus vaccine, Rotashield®, was launched in the USA in 1998. However, it was withdrawn within a year because of a rare association with intussusception (one case per 10,000 vaccinated infants). Following large trials, two further vaccines were licensed in 2006; these had an efficacy of 85–98% and showed no increased risk of intussusception. Seven vaccines have now been licensed nationally or have been prequalified by WHO, and more than 90 countries have launched national rotavirus vaccine programs.

US studies have documented a significant drop in hospitalizations due to rotavirus following the introduction of vaccination. Declines have also been seen in older infants who were not vaccinated, possibly as a result of herd immunity. Similar benefits on mortality due to rotavirus have also been seen in countries such as Mexico following the introduction of vaccination.

Despite high levels of vaccine uptake and a significant decrease in cases as vaccines have been introduced across all regions, the burden of rotavirus is still high, especially in low income countries. In addition, the pace of introduction has slowed, in part due to global vaccine shortages.

“Use of rotavirus vaccines has had a significant global impact on hospitalizations due to rotavirus and acute gastroenteritis.”
Between 2009 and 2018, 34 out of 47 countries in the WHO African Region introduced rotavirus vaccination, 28 with the support of Gavi funding. Thirteen countries, including two large ones – Nigeria and the Democratic Republic of the Congo – are yet to introduce rotavirus vaccines.

Vaccine coverage stands at 47% for the region as a whole but 77% in countries that have introduced vaccination into their national immunization programs.

An analysis of 29 countries that had introduced the vaccine by 2014 estimated that 20,986 deaths had been prevented (38%) and 134,714 hospitalizations averted (46%) by rotavirus vaccination in Africa. Vaccine effectiveness in routine use is close to the efficacy seen in clinical trials.

The African Intussusception Surveillance Network was set up as a partnership between WHO and the CDC, with Gavi funding, to monitor the safety of rotavirus vaccine in routine use. Robust sentinel surveillance was established in 12 countries, using the Brighton Collaboration standardized case definition of intussusception and self-control case study methodology to explore possible associations with vaccination.

The surveillance data revealed no increased risk of intussusception after administration of monovalent human rotavirus vaccine in seven lower-income sub-Saharan African countries. As well as academic publication, data have been shared with ministries of health and other stakeholders, including national regulatory authorities, national immunization programs and pharmacovigilance committees.

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India began introducing a locally manufactured rotavirus vaccine, ROTAVAC®, in 2016. An evaluation has been carried out comparing intussusception in populations in different parts of the country, and exploring any possible correlation between exposure to ROTAVAC® and risk of intussusception.

Two studies are underway to monitor the safety of rotavirus vaccine in India, as well as to find out more about the incidence of intussusception and its possible causes.

The first study, led by Dr NK Arora from the INCLEN Trust International, has examined data from a network of sentinel sites, combining a retrospective analysis of intussusception cases from the 5-year period up to March 2016 and an 18-month prospective study of new cases from April 2016 to September 2017.

Most cases of intussusception occurred in children less than 1 year of age, and the condition was associated with a case fatality rate of 1–2%. The number of cases was significantly higher in the south of India, for reasons that are unclear.

Information on exposure to rotavirus vaccine was available for 78% of cases, and 89 infants (14.3%) had previously received rotavirus vaccine. For most infants affected (87.6%), rotavirus vaccine had been given more than 21 days previously. No cases were reported through the routine AEFI system and none died. Importantly, there was no evidence for an increase in intussusception after introduction of rotavirus vaccine.

An ongoing second study, led by Dr G Kang from the Christian Medical College Vellore, is using a case series and case control approach to assess the risk of intussusception after vaccination and possible causes of the condition. Children under 2 years of age with diagnosed intussusception are being investigated at sentinel sites across India. Preliminary analyses suggest that intussusception rates are low at the ages at which rotavirus vaccine is administered. A case control approach is also being used to compare intussusception rates in vaccinated and unvaccinated infants, although sample sizes are currently too small for trends to be discerned.

“Retrospective and prospective sentinel site surveillance is being used to explore possible links between rotavirus vaccination and intussusception in India.”
Should we continue to actively monitor the safety of rotavirus vaccines?

Post-licensure monitoring systems can be either passive – relying on routine reporting of possible adverse events – or active, with specific data collection mechanisms introduced to identify as comprehensively as possible all conditions of interest. Passive systems are more common, as they can cover large populations, detect rare events and are relatively inexpensive. However, they have drawbacks, including a risk of reporting bias and a lack of an unvaccinated control group, and are not designed to determine whether a vaccine is responsible for an adverse event.

Active surveillance systems, by contrast, aim to capture AEFI as comprehensively as possible and with sufficient supporting data to allow estimates of incidence rates and relative risk. In 2013, the Council for International Organizations of Medical Sciences (CIOMS) developed a guide to active vaccine safety surveillance. Its aim was to provide practical guidance to national authorities in resource-poor settings considering whether to introduce active safety surveillance for a new vaccine.

There are several reasons why countries might consider introducing active safety surveillance for vaccines. For example, countries may be planning to introduce a new vaccine, an important safety issue may have been identified, an immunization program may be undergoing change, or there may be concerns about the effectiveness of passive surveillance systems.

The Rotashield® experience with intussusception provides important learning for the newer rotavirus vaccines. Pre-licensure trials were large but not sufficiently so to detect very rare events. Furthermore, ‘real life’ use provides additional data on vaccine use in a wider range of age groups, populations with different background characteristics, and with different baselines rates of intussusception.

Monitoring for intussusception is challenging in many resource-poor settings, with limited high-quality data on both intussusception and rotavirus vaccination. Passive surveillance, case control and self-control case study approaches can all provide some safety evidence but all have their drawbacks.

The African Intussusception Surveillance Network is undertaking surveillance specifically to monitor intussusception following the introduction of rotavirus vaccination in 12 African countries. Its work has found no evidence of increased risk of intussusception associated with use of rotavirus vaccination (see above).
Discussion points and recommendation:

• The continuing major disease burden of acute gastroenteritis in low-income countries, despite huge reductions in diarrhea hospitalization through increased use of rotavirus vaccination.

• The importance of surveillance for monitoring vaccine effectiveness and reassuring the public of the need for vaccination.

• The wide range of possible reasons for the varying risk of intussusception in African countries.

• The importance of continued surveillance for intussusception during rotavirus vaccine use.
For new vaccines, benefit–risk assessments are made at global, regional and national levels to guide policy decisions. This session reviewed these mechanisms using the first dengue vaccine, Dengvaxia®, as a case study. Dengvaxia®, manufactured by Sanofi Pasteur, received its first marketing authorizations in late 2015 and is currently available in several Asian and Latin American countries.

In November 2017, a new analysis of long-term clinical trial data found differences in vaccine performance based on prior dengue infection. In particular, it was found that vaccine recipients who had not previously been infected by dengue virus were more likely to suffer severe disease if subsequently infected.

Session objectives:

- To review global mechanisms for vaccine risk assessment and management.
- To review the safety profile of the currently available dengue vaccine (Dengvaxia®).
- To share country experience in dealing with new vaccine safety data.
In individuals who have been previously infected by dengue virus, there is a clear and long-term benefit of being vaccinated up to six years after the first injection. However, a new testing technology allowed a reassessment of the long-term safety and efficacy data from phase IIb/III trials. This analysis found that vaccinated individuals aged 9–16 years who had not been previously infected by dengue virus were at increased risk of hospitalization for dengue and clinically severe disease.

Since 2016, public Dengvaxia® vaccination campaigns have been implemented in two countries: the Philippines (an estimated 1.62 million doses) and Brazil (671,000 doses). Dengue immunization was put on hold by the Philippine Department of Health on 1 December 2017.

Most spontaneous reports to the Sanofi pharmacovigilance database have come from these countries. The most frequent adverse events reported are pyrexia, headache, dizziness, vomiting and rash, consistent with product labeling.

Following publication of the new safety analysis in November 2017 and extensive media coverage, the Philippines saw an increased number of reported cases of dengue with fatal outcome. Since March 2018, the number of reported cases to Sanofi Pasteur has significantly decreased.

On 20 July 2018, the WHO Global Advisory Committee on Vaccine Safety (GACVS) published a report discussing the safety of dengue vaccine in the Philippines. Regarding reports of fatal cases, GACVS maintained its earlier recommendation that Dengvaxia® should not be administered to people who had not previously been infected with wild dengue virus.

In addition, it also concluded that, as it was not possible to distinguish cases linked to vaccine failure from those caused by vaccine-related immune enhancement, individual cases should not be attributed to one or the other but classified as indeterminate.

In June 2018, WHO’s Strategic Advisory Group of Experts on Immunization (SAGE) provided its updated recommendation on Dengvaxia®, supporting a pre-vaccination screening strategy to ensure the vaccine is given only to those previously infected with dengue.

Sanofi Pasteur is currently conducting a post-authorization safety study, collecting information on selected adverse events among vaccinated subjects in Brazil, the Philippines and Mexico to describe the vaccine safety profile under real-world conditions.


“An ongoing monitoring program is assessing the safety of Dengvaxia® in routine use.”
Global mechanisms for risk assessment and risk management: WHO advisory bodies (GACVS and SAGE)

In accordance with WHO’s mandate to provide guidance to Member States on health policy matters, the organization is tasked with developing evidence-based immunization policy recommendations. In 1999, an independent advisory group, the Strategic Advisory Group of Experts (SAGE), was established and charged with providing guidance to WHO. SAGE is concerned with all vaccine-preventable diseases and vaccination programs for all ages.

SAGE meets biannually to review and critically appraise the available evidence on immunization and vaccine-related topics and to formulate recommendations, which are then reflected in WHO position papers. The WHO position papers summarize essential background information on the respective diseases and vaccines and also present the WHO position from a global perspective.

WHO vaccine position papers undergo a formal review process and are designed to assist Member States with the development of optimal immunization programs.

Other technical and specialist global advisory committees support SAGE, including the Global Advisory Committee on Vaccine Safety (GACVS). GACVS was established in 1999 to respond promptly, efficiently and with scientific rigor to vaccine safety issues of potential global importance.

In turn, Regional Immunization Technical Advisory Groups help to identify specific regional challenges and define priorities. Taking into consideration local context, National Immunization Technical Advisory Groups provide guidance to national policy-makers.

The Dengvaxia® case study illustrated the role played by GACVS and SAGE. GACVS has undertaken a series of reviews throughout the clinical development of the vaccine and after its registration, which informed the recommendations made by SAGE.

“... The ongoing involvement of GACVS and SAGE in vaccine risk assessment and risk management enabled them to respond rapidly to emerging safety concerns and provide authoritative global guidance.”

Dengue is a serious public health problem in Brazil, causing thousands of hospitalizations and hundreds of deaths each year. In December 2015, Dengvaxia® was authorized by the Agência Nacional de Vigilância Sanitária (ANVISA), the Brazilian drug regulatory agency. Data submitted for vaccine registration indicated that Dengvaxia® was protective to the general population, with protection higher in individuals previously exposed to dengue virus (seropositive individuals). Data for seronegative individuals showed lower protection but no increased risk of serious adverse events. Since then, routine pharmacovigilance activities have been conducted.

Paraná state, one of Brazil’s 27 administrative areas, implemented the vaccine in its public health program. It aimed to vaccinate approximately 500,000 people in two annual campaigns, each with three vaccine doses. In total, 308,000 people were vaccinated, and a specific structure was created that included training for the healthcare professionals involved, including the notification of possible adverse events.

Adverse event monitoring has not identified any serious events linked to Dengvaxia® use. Immunization errors, which include vaccination during pregnancy, are being monitored. Inappropriately vaccinated pregnant women and their babies are being followed up in a separate study.

In November 2017, Sanofi Pasteur informed ANVISA of the increased risk of severe dengue in vaccinated individuals not previously infected by dengue virus. ANVISA adopted a risk minimization strategy, recommending that Dengvaxia® vaccine should not be given to seronegative individuals. Its major concern was to minimize risks without compromising the benefits of the vaccine or the credibility of the Brazilian vaccination program.

Clear communication strategies were adopted. In August 2018, ANVISA determined that Dengvaxia® use should be restricted to seropositive individuals from endemic areas, with serological tests used to exclude seronegative individuals. In addition, the manufacturer was requested to adopt effective measures of risk minimization and risk communication to the public and healthcare professionals.

Dr Patrícia Mandali de Figueiredo

Brazil has attempted to minimize risks and maintain public confidence in immunization without losing the benefits of dengue vaccination."

Brazil’s experience in dealing with emerging safety data
In the modern world, information sources compete for attention, global digitalization has abolished the traditional timelines of information exchange, and fake news, conspiracy theories and bad science attract more attention than reliable information. It is therefore increasingly critical to deliver the right messages, using the right channels, to fight misinformation, to reassure communities and to sustain public trust.

Individual countries have experienced distinct vaccine safety issues and adopted particular strategies to vaccine safety communication. In addition, WHO and partners have developed resources for Member States to design tailored vaccine safety information and communication strategies, paramount for maintaining public confidence in vaccination.

Session objectives:
• To learn from countries' experiences on vaccine safety communication.
• To highlight resources available for vaccine safety communication.
Lessons learnt from HPV vaccine introduction in Republic of Ireland

The Republic of Ireland has experienced opposition to human papillomavirus virus (HPV) vaccination, significantly affecting vaccine take up. In early 2016, a steering group of concerned organizations was established to identify key stakeholders who could promote the vaccine. Parental views about the HPV vaccine were explored in focus groups, current information materials audited, and social media coverage analysed.

As a result, information materials for parents were revised, with quotes from vaccinated girls, their mothers, national and international experts, and WHO. The www.hpv.ie website was also revised and short videos developed; it has been accredited by WHO as providing reliable information on vaccine safety.

Ongoing training for school vaccination teams was enhanced and a national conference held, which proved pivotal in supporting and empowering front-line teams. As a recommendation from a trusted health professional can be very influential, communication and e-learning modules were developed for primary care professionals. Fact sheets and posters were sent to all general practitioners and pharmacists.

Liaison between school authorities, teachers and parents’ associations was enhanced, with frequent presentations updating them about the vaccine, information leaflets sent to teachers and lessons developed on the safety of HPV vaccine and separating fact from fiction.

In August 2017, the Irish Cancer Society launched the HPV vaccination alliance. This is a group of 37 organizations working in areas including health, cancer control, education, women’s rights, child welfare and youth support, each of which has pledged to raise awareness of HPV vaccination and its benefits.

The 2017/18 HPV vaccination program was launched by the Minister for Health, supported by senior politicians who have been actively promoting the vaccine. A media campaign on local and national radio and social media featuring vaccinated girls, as well as a 25-year-old Irish woman, who was diagnosed with terminal cervical cancer and is a very powerful vaccine advocate.

All this activity has had a positive impact. Media coverage is now supportive of the vaccine, and stakeholders and members of the public respond rapidly to any anti-vaccine sentiment. Provisional data suggest that HPV vaccine coverage has now risen to 65%.

“Concerted efforts have been required to communicate the benefits of HPV vaccination and to tackle misinformation.”
In July and August 2018, China experienced a significant public health crisis. A Chinese vaccine manufacturer, Changchun Changsheng BioTech, was found to have fabricated production records for rabies vaccines, and to have changed process parameters and equipment during vaccine production. Furthermore, nearly 500,000 doses of substandard diphtheria, pertussis and tetanus (DTP) vaccine produced by Changsheng BioTech and 400,000 substandard DTP vaccine produced by Wuhan Institute of Biological Products were used across four Chinese provinces.

Various regulatory actions were immediately taken. The license to produce rabies vaccine was revoked, vaccines were recalled, and contact was made with regulatory authorities of countries to which rabies vaccine had been exported. Vaccine samples within manufacturers’ facilities were re-tested and expanded inspections were made of all 45 vaccine manufacturers in China.

Nevertheless, there were no reported increases in serious AEFI associated with rabies vaccine, the number of rabies cases has been falling, and no increase in pertussis has been seen. Children who received substandard vaccines were re-vaccinated and monitored. Changsheng BioTech employees have been detained, and several governmental and regulatory officials relieved of their duties.

All investigations were published in a timely fashion and information made available to the public. China’s national authorities prepared answers to frequently asked questions to respond to public concerns, provided media interviews, and urged Chinese citizens to continue to use quality-assured vaccines. National authorities issued extensive press releases and official announcements. Political leaders also vowed to ensure the security of future vaccines.

This crisis demonstrated that transparency is important for public health programs and, in a time of social-media amplification and conflation of real and perceived problems, coordination of government, public health programs and the media is essential.

Even so additional steps may be necessary to address public distrust toward China-made vaccines. This may require reform of the country’s vaccine regulatory system, as well as a better understanding public concerns to support more effective communication.

"WHO provided technical assistance and undertook extensive public communication activities when China was affected by a major vaccine manufacturing issue."

""
Japanese encephalitis is endemic in Myanmar. In 2017, with Gavi support, a nationwide Japanese encephalitis vaccine catch-up campaign was conducted, as a prelude to its introduction into routine immunization in 2018. It was the second largest public health intervention ever undertaken in Myanmar, targeting 13.6 million children (26% of the total population). It took place over two phases: school-based vaccination for 10 days in November 2017 (phase 1) and community-based vaccination for seven days in December 2017 (phase 2).

In advance, the Ministry of Health and Sports and partners pro-actively communicated to all stakeholders, especially the media and public. Various communication strategies and channels were used, and media briefings were organized. However, a major fire on the day of the media briefing diverted attention away from the campaign.

Unfortunately, a death on the second day of the campaign raised high levels of concern in the country. The investigation team worked closely with the national AEFI expert committee, and preliminary information was posted on Facebook within 24 hours. A press release was rapidly posted on the Ministry website and state-owned media shared initial vaccine safety information within 48 hours.

"Social media played a significant role in influencing the public, and parents’ power to decide based on an informed choice has improved uptake not only of Japanese encephalitis vaccine but also of other vaccines."
As a result of this prompt action, daily vaccination coverage was maintained in the days after the event. However, considerable debate continued in the media and on social media. Multiple communities engaged, including activists questioning the safety of the vaccine, but also volunteers, religious leaders and parents advocating for the vaccine.

As well as information provided through state-owned media, the campaign’s Facebook presence was an important way of engaging with families and responding to queries. The social media information and communication strategies were perceived as unbiased as the national program was not involved.

Before phase 2 started, the AEFI review committee classified all cases as being coincidental deaths, which was immediately reported in a press release on the Ministry website. Phase 2 of the campaign went ahead without incident and achieved high coverage, aided by field staff who had confidence in vaccine safety and could communicate effectively with parents.
Health information is more accessible than ever. But it can be challenging to distinguish scientifically accurate information from misleading information largely spread by various media and social networks. Health care professionals at the front line have a responsibility to inform and reassure caregivers and patients, and must be well equipped to respond to safety-related questions. It is also important to educate young children about the value and safety of vaccines, as an investment for the future.

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Session objectives:
- To discuss recent developments in the field of vaccine safety education.
Introducing vaccines and immunization in schools – a game-based educational module by WHO EURO

School settings offer a unique opportunity to reach important target groups with comprehensive health information and to promote positive behavior change in children and their families. To exploit this opportunity, the WHO Regional Office for Europe is developing a school module that aims to build knowledge and understanding of vaccines and immunization, as well as resilience against vaccine safety scares or concerns.

Targeting schoolchildren provides an opportunity to create an understanding of immunization at an early age, fostering life-long support for immunization. School-based activities can prepare children for the vaccines they will receive as teenagers and adults, and influence their attitudes as future parents.

Through a simple game-based module, the intention is to stimulate critical competencies in a way that allows children to use their knowledge and skills to initiate change in their own lives. The game will promote understanding of vaccination and immunization in a nuanced and trustworthy manner, which fits the needs of both pupils and teachers.

Everything is tied together by an overarching narrative and digital game system combining a variety of different creative tasks. The education package is accessed online but pupils will spend most of their time working on projects offline. Games are engaging and motivating, and they create a ‘sandbox environment’ where decision-making can be explored without fear of failure. Playing the game will ensure that children develop relevant skills, knowledge and competencies to be able to act on an evidence-informed basis.

The plan is now to pilot and evaluate the package in several countries in the European Region. Once it is finalised, WHO will work with partners to adapt it for global use.

"A game-based module will help to develop children’s ability to assess evidence and make informed choices about immunization."

Ms Siff Malue Nielsen
In the USA, multiple groups administer vaccines, including not only physicians, but also nurse practitioners, physician assistants, nurses, pharmacists, and medical assistants. Each group needs to be equipped to communicate effectively with vaccine recipients and parents.

Multiple educational tools have been produced, tailored to the needs of one or more of these provider types, using language and tools most appropriate to their learning needs. CDC vaccine recommendations apply to both the public and the private sector, so best practices are applicable to both sectors.

Educational methods used include on-site presentations, mostly at state immunization conferences, or remote presentations to smaller groups. The CDC has created structured webinar programs that deliver content online, and it partners with other federal agencies on new webinar programs. The CDC has also developed online self-learning tools, as well as downloadable print materials.

The National Childhood Vaccine Injury Act requires providers to use vaccine information statements and to keep records on vaccine use. Vaccine information statements are one-page documents that must be given to patients every time a vaccine is administered, and provision of information must be documented in the patient record. A specialist CDC team is responsible for producing vaccine information statements, which are prepared by a health educator, before being reviewed by the CDC, other federal agencies and the public.

High-quality educational materials are needed by a range of different types of health care professional, and by the general public.
In 2012, Chile strengthened its strategy on pharmacovigilance and monitoring of vaccine safety in 2012, following a joint project between the Institute of Public Health and the Immunization Department in the Ministry of Health.

Training formed a critical element of the new strategy – a survey found that 42% of health professionals reporting AEFI had little or no exposure to vaccine safety in their education. In 2015, a Vaccine Pharmacovigilance Bulletin was launched for health care workers, and three documents, distributed through the web, have been developed for public use following community consultations.

In 2016, the Immunization Department launched two e-learning tools to develop health worker skills in vaccine safety and AEFI detection and reporting. A further educational module was launched in 2018 on safe immunization practice and AEFI reporting.

The Immunization Department has also worked with scientific societies on vaccination courses and scientific studies, and organised training events for teams involved in pharmacovigilance in Chile’s regions.

Physicians involved with the country’s vaccine pharmacovigilance committee have also received training, for example in areas such as causality assessment.

The importance of joint work between the regulatory authority and the Ministry of Health, the use of different platforms and strategy to disseminate information (face-to-face, newsletters, e-learning) and the continuous education of health staff were identified as critical success factors.
Pregnant women and their babies are among the most vulnerable populations. Although several vaccines are now recommended during pregnancy, concerns about interventional research during pregnancy have prevented the conduct of carefully designed clinical trials. As new vaccines are being developed for use during pregnancy, it is essential that they can be assessed according to the same criteria and certainty of evidence as other medical interventions.

Session objectives:

- To review the safety profile of currently recommended vaccines for pregnant women.
- To discuss the safety monitoring of novel vaccines with specific indications for pregnancy.
Vaccination in pregnant women in Latin America and the Caribbean

In the Region of the Americas, several vaccines are administered to pregnant women in both routine and certain special situations, such as outbreaks, high risk of exposure or travel to areas where vaccine-preventable diseases are endemic. A total of 31 countries and territories have vaccination policies for influenza in pregnant women and 14 for pertussis, reflecting a steady increase in the use of these vaccines.

National immunization policies are the product of thorough consideration of WHO and PAHO recommendations by National Immunization Technical Advisory Groups. Implementation of those policies involves multiple stakeholders such as national regulatory authorities, maternal child health programs, scientific societies, ethical committees and civil society.

Pregnant women should receive a minimum of four antenatal care visits, which is achieved in 87% of countries/territories. Health workers’ recommendations are the main determinant of women’s decision to receive health care, including vaccines. Highest levels of influenza vaccination are achieved when women receive four antenatal visits. Pregnant women are requesting more information about vaccine-preventable diseases, dosage and safety. Vaccine acceptance has increased over time through harnessing of social media to provide positive messages about immunization.

During the 2009 influenza pandemic, vaccine safety in pregnant women received special attention. Guidelines on AEFI surveillance were disseminated and specific outcomes were monitored based on standardized case definitions. This increased attention revealed limitations in AEFI surveillance systems, suggesting that passive surveillance is insufficient for monitoring vaccine safety in pregnant women.

PAHO monitors vaccine safety in pregnancy through a collaborative inter-programmatic and inter-institutional initiative, which carries out literature reviews, secondary data analysis, and periodic studies. A preliminary study found no evidence for increased safety risks for recommended vaccines in pregnant women, with some beneficial effects seen for influenza vaccination.

The network of Latin American Centers for Perinatology, which links information through electronic clinical records currently used by 28 countries in the Americas, provides a further possible mechanism for monitoring vaccine safety. PAHO is currently examining the availability, completeness and degree of standardization of selected AEFI related to pregnancy or health outcomes. It aims to establish baselines for pregnant women, including comorbidities that can influence AEFI. Data will provide insight into exposure to vaccines and AEFI of interest by year, country and hospital.

“PAHO is developing a range of approaches to track vaccine safety in pregnant women in the region.”
Vaccines recommended for pregnant women: Current status and future prospects

WHO currently recommends three vaccines – for pertussis, influenza and tetanus – for use during pregnancy for a triple benefit: to reduce the severity of infection and morbidity during pregnancy, to improve fetal growth, and to reduce adverse outcomes in newborn and infant. Safety data are limited, largely because pregnancy is usually an exclusion criterion in pre-licensure trials.

Use of these three vaccines varies widely, with pertussis and influenza mostly provided in high-income countries and tetanus in low- and middle-income countries. However, implementation of maternal vaccination programs has been relatively slow, for a range of reasons. Safety surveillance in pregnancy is complicated by multiple difficulties in accurate risk assessment of pregnancy outcomes, as well as regulatory challenges. Development of countries’ AEFI reporting capacity should improve reporting vaccine safety monitoring following maternal immunization.

Since 2008, GACVS has held seven sessions on immunization in pregnancy. It reviewed extensive evidence on safety issues and drew conclusions based on expert discussion and consensus.

Given the diversity of vaccines currently available, GACVS prioritized vaccines for review based on two key criteria: their potential to reduce morbidity in pregnant women and their offspring; and their use in vaccination campaign settings where there is the potential for inadvertent vaccination of pregnant women. From this review in 2014, no concerns were identified with inactive vaccines; limited data were available for live vaccines, with very rare possible safety concerns.

In summary, available data on vaccination in pregnancy, although limited, show little evidence of vaccine-associated adverse effects on fetal, infant or maternal health. To provide more evidence, vaccine pre-licensure studies in pregnant women are required, as is enhanced surveillance and research on maternal immunization. Regulators and manufacturers also need to work jointly to provide credible information to immunization service providers and the public on maternal immunization.

“Immunization in pregnancy is too often a missed opportunity to improve the health of mothers and their offspring.”
Pregnant women may receive a medical intervention for three main reasons: unintentionally, because pregnancies were unplanned or unknown; for treatment of a maternal disorder; or for protection of the newborn. Efforts to understand the impact of interventions need to consider two important time elements: the stage of the pregnancy when the intervention is administered, as fetal development may have different vulnerabilities at different stages; and the age after birth when an impact might be detected.

When the vaccine against epidemic meningitis was introduced in 2010 in the meningitis belt, no clinical data were available on its use among pregnant women. Even so, the vaccine was administered through mass campaigns to populations that included many pregnant women. Analysis of data from an existing demographic health survey site in northern Ghana, which systematically collected information about pregnancies and vaccination, found no evidence that the new vaccine affected birth weight, gestational age, prematurity or neonatal mortality.

Although this example illustrates the feasibility of pregnancy vigilance studies in low-income settings, it is challenging to collect high-quality data. In addition, diverse definitions and methods of assessment are being used globally, and inconsistencies in data capture limit data pooling.

With respect to terminologies, many systems are available, including MedDRA, the medical dictionary commonly used in regulatory-related activities, and the International Classification of Diseases (ICD). To ensure comparability of studies, a mapping exercise is underway across MedDRA and ICD.

To facilitate harmonization, it is important to recognize that multiple factors affect the quantity and quality of data that can be collected. These include health care infrastructure, the availability of civil registration statistics, the type of study being conducted, outcomes of interest (maternal/fetal/newborn/child), and stage of pregnancy.

To understand the impact of interventions and guide policy-making, reliable data are required on outcomes. Given the multiplicity of interventions and outcomes, harmonized monitoring of maternal and neonatal outcomes could enhance the efficiency of multiple initiatives.
Vaccine manufacturers are responsible for vaccine quality, safety and efficacy during the entire product life cycle. The importance of close collaboration between regulators and industry is well recognized in vaccine pharmacovigilance activities, and guidance has been developed for jointly planning these activities. In many LMICs, however, the ability of vaccine manufacturers to obtain information about AEFI remains limited. Mechanisms and therefore needed to strengthen collaboration between regulators, immunization program managers and manufacturers.

Session objectives:

• To highlight the role of vaccine manufacturers as major stakeholders in vaccine safety surveillance.

• To discuss the importance for vaccine manufacturers to establish functional pharmacovigilance systems to ensure effective safety surveillance of marketed vaccines.
Introduction

The general public has high expectations of the safety of vaccines, as they are usually given to healthy people. National regulatory authorities have responsibility for ensuring the quality, safety and efficacy of vaccines, which extends to monitoring and responding to AEFI after licensing.

AEFI are any adverse event seen after immunization, and are not necessarily a result of vaccine administration. If not rapidly and effectively dealt with, they can seriously undermine confidence in a vaccine and immunization more generally.

Central to AEFI response is causality assessment, to determine whether an AEFI is directly linked to vaccine use. This feeds into a risk–benefit assessment to inform population-wide use of a vaccine. In the USA, surveillance has played a critical role in identifying issues with the safety of several vaccines, leading to re-evaluation of use and helping to maintain confidence in vaccination programs.

Safety surveillance is a collaborative effort involving manufacturers, health authorities and academia, with key guidance provided by global and regional bodies. While clinical trials provide rigorous assessments of safety and efficacy, post-marketing surveillance is essential given the much larger number and variety of people exposed to vaccines and very low tolerance of safety issues. Surveillance can identify very rare events associated with a vaccine’s intrinsic properties, as well as issues related to its distribution and administration.

Post-marketing surveillance can be either passive, relying on routine pharmacovigilance infrastructure, or active, where specific studies are organized to assess safety. Active studies can include large-scale phase IV trials or analysis of data from large linked databases.

Although vaccines are among the safest and most effective of public health interventions, rare adverse events do occur. Rumors about vaccines can now spread rapidly, so detecting and responding effectively to AEFI is essential to maintain the safety of programs and retain public trust.

"The aim of pharmacovigilance is to ensure that the evidence of the potential clinical benefits of a vaccine sufficiently outweighs its potential risks to justify its use in a target population."

Perspectives from the International Federation of Pharmaceutical Manufacturers (IFPMA) on vaccine post-marketing safety surveillance

Dr Veronica Urdaneta

Global Vaccine Safety Initiative 2018 meeting report
Established in 2000, the Developing Countries Vaccine Manufacturers Network (DCVMN) is an international voluntary, non-governmental, non-partisan, not-for-profit, public health-driven alliance of public and private vaccine manufacturers, research and policy organizations from all over the world.

The DCVMN is composed of 53 manufacturers in 18 countries/territories; 13 of the 53 companies supply WHO-prequalified vaccines to countries in Latin America, the Middle East, Africa and the Asia-Pacific region.

Although the specific challenges and opportunities for pharmacovigilance vary among DCVMN members, they share several overarching features:

**Challenges:**

- Lack of robust pharmacovigilance systems.
- Lack of expertise to perform pharmacovigilance activities in both domestic and international markets.
- Lack of political support.
- Variation in data sources and methods used to compile and present pharmacovigilance data.
- Integration of different pharmacovigilance systems.
- Integration of pharmacovigilance into public health programs.
- Information exchange between multiple stakeholders.

"The DCVMN aims to protect all people against known and emerging infectious diseases, by improving the availability of high quality vaccines globally."
Opportunities:

- Strengthening pharmacovigilance systems and functionality (passive and active pharmacovigilance activities).
- Improving capacity to analyse data and use in decision-making, through training and workshops.
- Strengthening communication and data exchange among manufacturers, national regulatory authorities and national immunization programs.
- Promoting research on pharmacovigilance.
- Performing post-authorization safety studies.
- Harmonizing pharmacovigilance activities in LMICs.

The DCVMN recognizes the importance of high-quality and efficient pharmacovigilance systems. This is likely to require investment in key building blocks such as infrastructure and human resources, communication pathways, and training programs.

The DCVMN has started by creating an online learning platform, including a vaccine safety course (based on WHO materials). It is also open to partnerships and input from external experts to promote strengthening of the pharmacovigilance activities of its members.
Experience from PATH: impact and benefits of collaboration between industry, regulators and technical agencies on strengthening national pharmacovigilance systems

Many new drugs and vaccines are likely to be introduced in LMICs in the near future, but countries often lack functional pharmacovigilance systems to monitor their safety. Despite numerous global initiatives, development of pharmacovigilance capacity remains slow and systems are weak and not sustainable.

There is an urgent need to improve coordination between initiatives building vaccine safety surveillance capabilities. Such collaborations optimize use of resources and expertise, create synergies, achieve greater impact and sustainability, and avoid duplication of investments.

Through collaboration with technical agencies and national regulatory authorities, vaccine manufacturers can support strengthening of vaccine pharmacovigilance in LMICs. The collaboration between the national regulatory authority of Malawi (the Pharmacy, Medicines and Poisons Board), GlaxoSmithKline and PATH aimed to strengthen national pharmacovigilance capacity and enhance spontaneous reporting of adverse events in Malawi. Through the project, more than 300 healthcare professionals were trained in basic pharmacovigilance, and the number of adverse events reported increased 200-fold.

In many LMICs, the ability of vaccine manufacturers to obtain information about AEFI remains limited. In addition, vaccine manufacturers in LMICs lack expertise in pharmacovigilance and do not have systems in place for pharmacovigilance activities. Therefore, as well as closer collaboration and better exchange of information between national regulatory authorities, vaccine manufacturers and other safety stakeholders, vaccine manufacturers in LMICs need to acquire the expertise in pharmacovigilance required to participate in national and global vaccine safety activities.

PATH provides various kinds of technical assistance to vaccine manufacturers in LMICs. Pharmacovigilance support is an important aspect of this assistance, especially for WHO-prequalified vaccines. For example, a collaboration with the Instituto Butantan in Brazil led to an upgrade of an existing pharmacovigilance system and building of advanced capacity and expertise, creating a pharmacovigilance system meeting international standards.

“By working together, partners aiming to build pharmacovigilance capacity in LMICs can achieve much greater impact.”

Ms Olga Menang
**Discussion/comments:**

- In Africa, the landscape of regulatory oversight is changing rapidly towards harmonization with the African Medicines Agency and the recently endorsed African Medicines Agency.

- The African Vaccine Regulatory Forum (AVAREF) has also changed and become aligned, by embracing all 55 countries in the Eastern Mediterranean and African Regions and all regional economic communities. The agreement is that capacity building should be holistic and sustainable.
APPENDICES
# Appendix 1: acronyms

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<tr>
<th>Acronym</th>
<th>Description</th>
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<tr>
<td>AEFI</td>
<td>Adverse event following immunization</td>
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<tr>
<td>ANVISA</td>
<td>Agência Nacional de Vigilância Sanitária</td>
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<td>AVAREF</td>
<td>African Vaccine Regulatory Forum</td>
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<td>CDC</td>
<td>Centers for Disease Control and Prevention</td>
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<tr>
<td>CIOMS</td>
<td>Council for International Organizations of Medical Sciences</td>
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<tr>
<td>COFEPRIS</td>
<td>Comisión Federal para la Protección contra Riesgos Sanitarios</td>
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<tr>
<td>DCVMN</td>
<td>Developing Countries Vaccine Manufacturers Network</td>
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<tr>
<td>DHIS2</td>
<td>District Health Information System 2</td>
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<tr>
<td>DTaP</td>
<td>Diphtheria, tetanus and pertussis</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>GACVS</td>
<td>Global Advisory Committee on Vaccine Safety</td>
</tr>
<tr>
<td>GVSI</td>
<td>Global Vaccine Safety Initiative</td>
</tr>
<tr>
<td>HPV</td>
<td>Human papillomavirus</td>
</tr>
<tr>
<td>ICD</td>
<td>International Classification of Diseases</td>
</tr>
<tr>
<td>IVI</td>
<td>International Vaccine Institute</td>
</tr>
<tr>
<td>LMIC</td>
<td>Low- and middle-income countries</td>
</tr>
<tr>
<td>MedDRA</td>
<td>Medical Dictionary for Regulatory Activities</td>
</tr>
<tr>
<td>Acronym</td>
<td>Description</td>
</tr>
<tr>
<td>---------</td>
<td>-------------</td>
</tr>
<tr>
<td>MMR</td>
<td>Mumps, measles and rubella</td>
</tr>
<tr>
<td>PAHO</td>
<td>Pan-American Health Organization</td>
</tr>
<tr>
<td>SAGE</td>
<td>Strategic Advisory Group of Experts on Immunization</td>
</tr>
<tr>
<td>UMC</td>
<td>Uppsala Monitoring Centre</td>
</tr>
<tr>
<td>UN</td>
<td>United Nations</td>
</tr>
<tr>
<td>UNICEF</td>
<td>United Nations Children's Fund</td>
</tr>
<tr>
<td>VAEIMS</td>
<td>Vaccine Adverse Events Information Management System</td>
</tr>
<tr>
<td>VSN</td>
<td>Vaccine Safety Net</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
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</tbody>
</table>
Appendix 2: list of participants

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<th>Position and Organization</th>
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</thead>
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<td></td>
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<td></td>
<td>Bangladesh</td>
</tr>
<tr>
<td>Mr Mohammad Nurul Islam</td>
<td>Deputy Director</td>
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<tr>
<td></td>
<td>Directorate General of Public Health</td>
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<tr>
<td></td>
<td>Bangladesh</td>
</tr>
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</table>

** BRAZIL **

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<thead>
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<th>Name</th>
<th>Position and Organization</th>
</tr>
</thead>
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<td></td>
<td>Gerência de Farmacovigilância - GFARM/GGMON/ANVISA/MS</td>
</tr>
<tr>
<td></td>
<td>National Sanitary Surveillance Agency (ANVISA)</td>
</tr>
<tr>
<td></td>
<td>Brazil</td>
</tr>
<tr>
<td>Dr Patrícia Mandali de Figueiredo</td>
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<tr>
<td></td>
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<td></td>
<td>National Sanitary Surveillance Agency (ANVISA)</td>
</tr>
<tr>
<td></td>
<td>Brazil</td>
</tr>
<tr>
<td>Dr Ana Goretti</td>
<td>IP</td>
</tr>
<tr>
<td></td>
<td>Brazil</td>
</tr>
<tr>
<td>Dr Sandra Deotti Carvalho</td>
<td>IP</td>
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<tr>
<td></td>
<td>Brazil</td>
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<thead>
<tr>
<th>Name</th>
<th>Title and Institution</th>
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<tbody>
<tr>
<td><strong>Dr Verónica Vergara</strong></td>
<td>FV Team, Instituto de Salud Pública de Chile (ISP) Chile</td>
</tr>
<tr>
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<td>Immunization Department, Ministry of Health, Chile</td>
</tr>
<tr>
<td><strong>Dr Carola Escobar</strong></td>
<td>Physician, Chile</td>
</tr>
<tr>
<td><strong>Dr María Paz Bertoglia</strong></td>
<td>Physician, Escuela de Salud Pública, Facultad de Medicina, Chile</td>
</tr>
<tr>
<td><strong>Dr Nahum Vergara</strong></td>
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<tr>
<td><strong>Dr Isabel Sanchez</strong></td>
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</tr>
<tr>
<td><strong>Dr Carolina Alfaro</strong></td>
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</tr>
<tr>
<td><strong>Dr Isabel Maureira</strong></td>
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</tbody>
</table>
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<thead>
<tr>
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<tbody>
<tr>
<td>Ms Dwiana Andayani</td>
<td>Deputy Director, Monitoring of Drug, Narcs &amp; Psychotropic Safety</td>
<td>National Agency of Drug and Food Control</td>
<td>Indonesia</td>
</tr>
<tr>
<td>Mr Syafriyal</td>
<td>Epidemiology expert</td>
<td>Ministry of Health</td>
<td>Indonesia</td>
</tr>
</tbody>
</table>

**IVORY COAST**

<table>
<thead>
<tr>
<th>Name</th>
<th>Position</th>
<th>Organization</th>
<th>Country</th>
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<tbody>
<tr>
<td>Dr Hamidou Kone</td>
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<td>Programme Elargi de Vaccination en Côte d’Ivoire (PEV)</td>
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</tr>
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<td>Pr Jean Claude Yavo</td>
<td>Focal Point UMC-OMS</td>
<td>Direction de la Pharmacie, du Médicament et des Laboratoires de Côte d’Ivoire (DPML)</td>
<td>Ivory Coast</td>
</tr>
</tbody>
</table>

**IRAN (ISLAMIC REPUBLIC OF)**

<table>
<thead>
<tr>
<th>Name</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Dr Seyed Mohsen Zahraie</td>
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<td>Ministry of Health and Medical Education (MOHME)</td>
<td>Islamic Republic of Iran</td>
</tr>
<tr>
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<td>Islamic Republic of Iran</td>
</tr>
</tbody>
</table>
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