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This annual report is produced by the Strategic Priority Group of the Global Vaccine Safety Initiative (GVSI) to inform stakeholders in vaccine pharmacovigilance about its key activities.

Read more about GVSI here: http://www.who.int/vaccine_safety/initiative/en/
The global vaccine pharmacovigilance landscape is evolving rapidly: new vaccines are being developed for exclusive deployment in low- and middle-income countries with little or no vaccine pharmacovigilance infrastructure; existing methods and approaches for detecting and analysing vaccine safety concerns are being reviewed; newer tools and methods are becoming available; and the tools, approaches and methods of communication are all changing quickly, requiring frequent changes in approach and strategy. In addition to these, outbreaks of highly infectious and dangerous diseases like Ebola virus disease has put the spotlight on the need for the global public health community to provide rapid access to vaccines which are effective and safe, even though these need to be produced and tested in highly compressed time-scales. These are daunting challenges which must be overcome despite the generally limited financial resources available for vaccine pharmacovigilance.

The GVSI is about collaboration. Its vision of a world where all countries have at least minimal capacity for vaccine safety monitoring can be achieved if we all work together. The sum total of the individual efforts of academia, industry, patient groups, donors and technical agencies is often exponential, not additive.

In the past 12 months, the GVSI has achieved a lot. It has undertaken trainings, provided guidance, developed tools and deployed methods and approaches in all six WHO regions. This annual report provides highlights of these. We present here a report which highlights the work undertaken by several different players and bears testimony to the fact that together we can achieve more. The GVSI is for everyone and we welcome your comments, suggestions and criticisms as a contribution towards the goal of effective vaccine safety systems in all countries.
Introduction

Vaccines are an essential component of health service delivery. Hundreds millions of vaccine doses are administered each year in the world to protect from multiple diseases. To ensure that vaccines are able to improve individual and societal health, they must also be safe and of assured quality. 65% of World Health Organization (WHO) Member States – including the majority of the low- and middle-income countries (LMICs) – do not have a functional post-marketing surveillance system to monitor vaccines adverse events and ensure they are as safe as possible. Resources and expertise to establish these systems are limited worldwide, and the global community must determine how to ensure monitoring systems are available at local, regional and global levels.
In response to the weak vaccine safety monitoring infrastructure in several LMICs, WHO and partners developed the Global Vaccine Safety Blueprint in 2011. The Blueprint is a strategic framework for strengthening vaccine safety activities at the global level and propose solutions to overcome identified challenges. Its three main goals are to:

1. Assist LMICs to have at least minimal capacity for vaccine safety activities;

2. Enhance capacity for vaccine safety assessment in countries that introduce newly developed vaccines, that introduce vaccines in settings with novel characteristics, or that both manufacture and use prequalified vaccines; and

3. Establish a global vaccine safety support structure.

To implement these three overarching goals, eight strategic objectives are proposed:

- four directly related to vaccine pharmacovigilance and four related to supporting elements needed for a functioning vaccine safety system.

These strategic objectives are:

- To strengthen vaccine safety monitoring in all countries
- To strengthen the ability of countries to investigate vaccine safety signals
- To develop vaccine safety communication plans at the country level to promote awareness of vaccine risks and benefits, understand perceptions of risk and prepare for managing any adverse events and concerns about vaccine safety promptly
- To develop internationally harmonized tools and methods to support country vaccine safety activities
- To promote a legal, regulatory and administrative framework for the safety of vaccines at the national, regional and international levels
- To strengthen regional and global technical-support platforms to meet countries’ expressed needs
- To provide expert advice on vaccine safety issues at the national, regional and international level
- To put in place systems for appropriate interaction between national governments, multilateral agencies and manufacturers at the national, regional and international level.
Implementing the Blueprint is a task that requires coordinated participation of vaccine safety stakeholders worldwide. To that effect, the WHO launched the Global Vaccine Safety Initiative (GVSI) in March 2012. The GVSI is neither a legal entity, nor a partnership. It is a WHO mechanism for enhancing vaccine safety by providing a platform for WHO to convene its Member States and partners for the implementation of the Global Vaccine Safety Blueprint. As a collaborative forum for vaccine safety stakeholders, it highlights existing tools and resources, develops new ones, creates synergies and prevents duplication of efforts and waste of resources towards the achievement of its objectives. The WHO GVSI Secretariat supports the work of the GVSI.

GVSI participants include governmental institutions (immunization programmes, regulatory authorities, pharmacovigilance centres and other relevant entities) and agencies involved in regulatory activities; intergovernmental organizations (including World Health Organization), international non-governmental organizations; academic institutions; international industry associations and umbrella organizations that have a demonstrated interest and experience; and WHO collaborating centres. Participating organizations join the GVSI network by agreeing to the GVSI terms of reference.

This report, which covers the period 2013 to 2014, reviews the made through the GVSI with particular attention to each of the eight strategic objectives. It illustrates progress around each objective, highlighting the work of WHO partners in GVSI.
At the operational level, the WHO GVSI Secretariat helps facilitate project-based collaborations. Its core management tool is the GVSI portfolio, which is a dynamic listing of activities proposed by GVSI participants. The portfolio characterizes and classifies priority activities for implementing the Blueprint, as reviewed by the Strategic Priority Group.

Each activity is listed with a summary of its purpose, relevance, description of work, deliverables, indicators for progress monitoring, budget and level of priority. Prioritization is based on specific criteria such as impact, geographic relevance, feasibility, usefulness, sustainability and prioritizes activities for which funding is immediately needed, activities for which funding is recommended, and activities that should be part of a full GVSI work plan.

Activities submitted to the portfolio are not necessarily WHO activities, but rather those that have been identified by the Strategic Priority Group as valuable contributions towards the shared mission of the Blueprint. Submission of activities to the GVSI portfolio is primarily for information purposes to assist WHO in coordinating global activities. WHO is neither responsible nor accountable for activities implemented by GVSI participants outside specific project agreements. WHO aims at bringing together donors and participants and coordinates interaction between them.
The main methodological achievements of the GVSI for 2013-2014 include:

- Harmonized tools and methods for detection and investigation of adverse events following immunization (AEFI), including definitions of 22 core variables and creation of a standard AEFI notification form used and adapted by countries;
- A user manual and an aide-mémoire for assessing the causality of an AEFI;
- A desktop version of the Vaccine Adverse Events Management System (VAEIMS) to efficiently and effectively transfer AEFI data from local health care centres to a central database;
- A new global manual for the surveillance of AEFI;
- A new vaccine pharmacovigilance toolkit;
- A WHO e-learning course on vaccine safety basics in English and French;
- A vaccine safety basics training toolkit for trainers;
- Several publications derived from studies to inform stakeholders about the latest vaccine safety issues:
  - A study on meningococcal vaccine administered during pregnancy in one WHO African Region country;
  - A WHO African Region consultation to develop harmonized methodology for the surveillance of the intussusception;
  - The adverse events of special interest (AESI) following immunization during pregnancy and guidance for their assessment;
- The development and evaluation of narcolepsy case definition and investigation of reporting patterns of narcolepsy over time;
- The safety of immunization during pregnancy, a review of the evidence by the Global Advisory Committee on Vaccine Safety (GACVS);
- The human papillomavirus (HPV) and yellow fever case study; and
- The new definitions and application of terms for vaccine pharmacovigilance developed by the Council for International Organizations of Medical Sciences (CIOMS).

By providing countries with standardized tools and procedures, the GVSI promotes information exchange across countries. This material is further disseminated through training of national health care professionals on the effective use of pharmacovigilance principles and methods. The GVSI impact is tremendous and can be measured by the interest of WHO Member States in strengthening their vaccine pharmacovigilance systems. These early successes need now to be consolidated, in order to ensure that everyone everywhere will benefit from vaccination administered with a proper safety monitoring system.
Nearly half of the world’s population live in countries without a functional vaccine safety monitoring system as at 2009. While LMICs administer nearly twice as many doses vaccine as high-income countries, a situation analysis discovered limited capacity for surveillance for adverse events following immunization in these countries (WHO, March 2012).

One of the most basic elements of vaccine safety monitoring is a system by which AEFI can be quickly reported; this simply requires the ability to detect, report, receive, log and analyse data from a wide variety of sources, as well as undertake any needed remedial action. The aim of the first strategic objective – to strengthen vaccine monitoring in all countries – therefore reflects the need for AEFI reporting systems in all countries with the following defined targets:

- Target 1: Effective spontaneous reporting of AEFI in all countries;
- Target 2: Enhanced capacity for vaccine pharmacovigilance in countries that manufacture vaccines and countries where newly available vaccines are being introduced.
Effective Spontaneous AEFI Reporting in China

China is a rapidly developing nation, and its public health system has a significant impact on the welfare of more than 1 billion people. The country’s health system is on a scale not seen anywhere else in the world. Its vaccines industry has the capacity to produce more than 1 billion doses each year for the prevention of more than 30 diseases. The country is also a showcase of spectacular development of an AEFI monitoring system.

China has established a three-level monitoring system that now covers its central government, 31 provinces and 330 municipalities. Its AEFI information system covers more than 2,800 (2856) counties; the National Health and Family Planning Commission and the China Food and Drug Administration directly use the system. The number of reports of AEFI has significantly increased since China established the system. In 2005, the system received 1,900 reports; in 2013, it received more than 130,000 reports, covering 95 percent of the country’s counties. The reports from China will no doubt contribute greatly to global vaccine safety and several lessons can be learnt by all countries – big or small – on how to establish effective vaccine pharmacovigilance systems at multiple levels.
Number of AEFI cases reported & percentage of counties with reporting, 2005-2013, China
Bangladesh Increases Reporting Rates by Training Programs

Bangladesh has made significant progress both in the production and monitoring of vaccines. The country recently established two production facilities, helping Bangladesh transform into a vaccine-producing country. The Ministry of Health and Family Welfare has greatly enhanced its ability to detect and report AEFI. After a slight decrease in the number of districts reporting AEFI cases in 2012, the ministry conducted refresher trainings in 17 districts and three cities. It also launched a training-of-trainers regimen at the national level. Since 2012, the number of reported AEFI countrywide has more than doubled from 423 in 2012 to 894 in 2013.
Bangladesh Total Number of Reported AEFI

2011: 100
2012: 400
2013: 900
2014: 900

Total Number of Reported AEFI: 19
The Power of Mobile Phones to Collect AEFI Data in India

India’s large population and significant resource limitations can pose serious challenges to establishing well-organized data collection systems. However, the recent explosion of mobile phone use – there are now about 920 million mobile users in India, or about 75 percent of the population – presents an opportunity to collect data and communicate directly with the population including vulnerable populations like pregnant women and infants.

The Antenatal and Infant Monitoring (AIM) system is an initiative started by the Christian Medical College of Vellore, India. AIM uses interactive voice response technology to provide contact with and support for pregnant women in the antenatal period and then monitor vaccination, infant well-being and the occurrence of AEFI, with information being provided directly by the mother.

AIM is being piloted in two areas in Vellore, Tamil Nadu. About 500 mothers in urban Kaspa and 300 mothers in rural Kathalampet were the first users, and the system has been designed to communicate in the local language, Tamil. A six-month analysis showed that about 40 women reported at least one AEFI, and the voice system reminded them to seek emergency services. The associated field workers visited the mothers who reported AEFI for follow-up medical attention.

Fig 1: Balance of money available to mothers at two pilot sites in Vellore to make phone calls.
United Republic of Tanzania was one of eight countries that participated in an April 2014 multi-stakeholder workshop in Ghana during which participants assessed their needs and developed national vaccine safety work plans. Stakeholders included National regulatory authorities (NRAs), Expanded Programme on Immunization (EPI) and pharmacovigilance centres, with the support of WHO country office focal point for Essential Drugs and Medicines and the focal point for Immunization. The WHO Collaborating Centre for Pharmacovigilance provided tools and resources for vaccine safety.

Later in 2014, United Republic of Tanzania commenced implementation of its plan. The EPI program and the Tanzania Food and Drugs Authority worked closely together to establish a national AEFI committee and started the joint development of national AEFI guidelines, with WHO support. The work plan developed at the April 2014 workshop was the foundation of a national work plan to ensure consistent AEFI investigation and causality assessment practices, enhance national capacity for AEFI data analysis and data management, communicate effectively for vaccine safety issues and clearly demarcate the roles and responsibilities of different stakeholders in vaccine safety.

The efforts that started at a multi-stakeholder planning workshop translated into tangible public health initiatives just months later – and United Republic of Tanzania stands as a shining example of how to assist a country in strengthening vaccine safety surveillance.
Active Surveillance for New Vaccine Introduction in Sudan

Based on past experiences with rotavirus vaccines, WHO’s Global Advisory Committee on Vaccine Safety encourages countries planning to introduce the vaccine only to develop a system of post marketing surveillance for intussusception related to these vaccines – which is what Sudan successfully did in July 2011.

Because of various factors, safety reports that occur around the time of rotavirus vaccination can be particularly difficult to interpret. Several countries have responded with active sentinel surveillance systems. Brazil and Mexico have adopted the self-controlled case-series analysis method, which is a robust, scientifically valid and resource-efficient approach that could be used in the monitoring of oral rotavirus vaccine safety with regard to intussusception.

The same approach has been adopted by Sudan. With the technical support of the United States Centers for Disease Control and Prevention and WHO, hospital sentinel sites received training to identify intussusception cases and ascertain the vaccination status of the cases.

Preliminary results confirmed a good safety profile of rotavirus vaccine in Sudan.
IT Bridge in Chile

The National Regulatory Authority and the Expanded Immunization Program in Chile share responsibility for surveillance of AEFI in the country. Both entities use separate software to document and manage AEFI information. Until now, the systems were not compatible for data exchange and analysis. That is why, and having the support of the International Vaccine Institute, an information technology bridge is being developed to foster data exchange between these institutions, strengthening their data analysis capacity and facilitating reporting to the WHO global individual case safety reports database Vigibase.
Strategic Objective 2

Strengthening the Ability of Countries to Evaluate Vaccine Safety Signals

**Background**

Monitoring is an essential part of ensuring vaccine safety. However, countries must also consider the next logical step: the ability to assess a safety-related signal in order to determine if this represents a public health threat warranting action or if it is just a spurious association.

Prompt assessment is especially important for newly introduced vaccines. Investigating safety signals involves not only the ability to verify the signal’s source, validity and type but also building local capacity to conduct verification quickly and developing an effective plan for disseminating information about validated vaccine safety issues to the local stakeholders and the international community.

The targets developed under the second strategic objective – to strengthen the ability of countries to evaluate vaccine safety signals – include:

- **Target 1**: Countries, alone and/or in collaboration with others, have the ability to verify vaccine safety signals and initiate appropriate public-health actions;
- **Target 2**: Countries have the ability to investigate a potential public-health risk; and
- **Target 3**: Countries have the ability to interact internationally for signal evaluation and internationally concerted public-health action.
Ten countries – Bangladesh, Bhutan, India, Indonesia, Maldives, Nepal, Sri Lanka, Thailand, Timor-Leste and Viet Nam – participated in an inter-country workshop on causality assessment of AEFI. The workshop allowed participants to share knowledge and lessons learned, ultimately building capacity throughout the region.

The three-day workshop, held in Bangkok in February 2014, provided hands-on participatory training on the revised WHO causality assessment methodology using 26 actual AEFI case reports which occurred in recent years in the participating countries.

The workshop helped build national and regional capacity to investigate AEFI, assess causality using the revised WHO methodology, streamline AEFI data collection procedures by introducing standardized formats and data transmission methods, and set prerequisites for sustainable collaboration of sharing of vaccine safety data at regional and global levels.
Investigating the Safety of Meningococcal Vaccines Protecting Pregnant Women and their Newborns

In the meningitis belt, an area that spans from Senegal to Ethiopia, the risk of epidemic meningitis is extremely high – yet a new meningococcal A meningitis conjugate vaccine provides excellent protection and is well-tolerated. Despite the lack of clinical trial data among pregnant women, WHO and its advisory bodies advise that pregnant women should also benefit from protection with this vaccine. The Global Advisory Committee on Vaccine Safety has recommended that medical officials should follow up with vaccinated pregnant women to better document the safety profile of this important vaccine during pregnancy.

This first study on this topic, conducted by Ghana’s Navrongo Health Research Centre (NHRC), took advantage of the periodic monitoring of a whole population to identify women who were pregnant at the time of a mass vaccination campaign. In the surveillance areas, Kassena-Nankana East and Kassena-Nankana West districts, more than 156 000 individuals receive visits by study teams about three or four times per year to update their demographic and health status.

The NHRC is a member of the International Network for the Demographic Evaluation of Populations and Their Health in Developing Countries (INDEPTH), a global network of members who conduct longitudinal health and demographic evaluation of populations in low- and middle-income countries.
A mass meningococcal A vaccination campaign was held in Ghana in October 2012, targeting individuals between 1 and 29 years of age, including pregnant women. While pregnant women were not excluded from receiving the vaccine, some elected not to receive the vaccine. This provided an opportunity to evaluate the safety of the meningococcal A vaccine by studying the pregnant women who received the vaccine and those who did not. A second age- and season-matched historical control group was assembled to document pregnancy outcomes in a time period before the immunization campaign.

A total of 1,730 pregnant women were vaccinated during the campaign, while 919 pregnant women elected not to be vaccinated. A total of 3,551 pregnant women were in the historical unvaccinated control group. Comparing the outcomes, there was no significant difference in any of the pre-specified outcomes between women who received the meningococcal A conjugate vaccine and those who did not, either in the concurrent or historical comparison groups.

Mean birth weights and gestational age were the same in each group, and rates of miscarriage and stillbirth were lower for the vaccinated group. Prematurity was slightly higher. This landmark study shows that by using innovative approaches, we can successfully illustrate the safety of a vaccine during pregnancy in a resource limited setting.
A Worldwide Effort to Study AEFI

To investigate possible rare vaccine-related events, meaningful sample sizes often require a multi-country collaborative approach. GVSI is establishing a global network of hospital-based sentinel sites for vaccine safety signal verification and hypothesis testing. Sixteen countries from across the world are participating in a proof-of-concept collaborative study; in this study, two well-established relationships between a vaccine and an adverse event will be measured to assess the capacity of participant sites and the collaborative network as a whole to verify these known associations.

The 16 countries participating in the Multi-Country Collaborative network of hospital-based sentinel sites for vaccine safety signal verification and hypothesis testing are Albania, Argentina, Australia, Chile, China, Colombia, Costa Rica, Honduras, Peru, India, Islamic Republic of Iran, Singapore, South Africa, Spain, Uganda and Uruguay.

Scientific and technical guidance is being provided by Vaccine.Grid, a network of international vaccine safety experts.

This study is expected to provide an empirical basis for establishing a formal collaborative framework. It will help document potential methodological challenges of using harmonized methods, agreeing on case definitions and comparing the value of different analytical approaches. It should also help document practical challenges, such as consistent ethics review at global and institutional levels, ensuring proper data management. The results of this study will provide answers on the feasibility of such approach across settings with variable resources. It will also document costs and practical challenges associated with multi-country collaborations in preparation for eventual new hypothesis testing.
Countries participating in the proof-of-concept study
Strategic Objective 3

Vaccine Safety Communication

Background

Communicating vaccine-related information to the public cannot simply be a government instructing individuals on what they should do. Rather, it must involve an open line of communication among communities, health care workers and decision-makers about the benefits and potential risks of specific vaccines and vaccine-related policies. Countries must have communication strategies that involve providing appropriate and reliable information in a prompt, ongoing manner and ensuring that information is tailored to each audience; this must include an effective crisis-communication plan for handling AEFI and other vaccine-related issues requiring rapid response.

The targets developed under the third strategic objective – to develop vaccine safety communication plans at country level to promote awareness of vaccine risks and benefits, understand perceptions of risk, and prepare for managing any adverse events and concerns about vaccine safety promptly – include:

- **Target 1:** To develop or strengthen the ability of countries to support ongoing communication among local communities, health-care workers and decision-makers about important vaccine safety issues (local or international) that include risk preparedness; and

- **Target 2:** Vaccine safety concerns of local and global significance will be investigated promptly and communications strategies put in place; in some cases, even if a concern is discovered to be unfounded, communication strategies will be needed to manage persisting public concerns.
Developing Stronger Communication Guidelines for Vaccine Safety Response

EPI managers, NRAs, health promotion personnel and health care personnel are increasingly called upon to plan and respond to communication issues around vaccine safety. In response to this demand, WHO developed a communication resource guide to equip professionals to effectively plan and implement communication actions. The guide is meant to help healthcare professionals promote an understanding of vaccines’ importance in preventing illness and preventable death and awareness of vaccines’ risks and perceptions of risk, as well as help them promptly manage communication in case of vaccine safety concerns such as AEFI to maintain public trust in vaccines and compliance with immunisation programmes.

This guide is available at http://bit.ly/1L4ONm6
Sri Lanka has had an efficient AEFI surveillance system in place since 1996. The country has a recognized WHO Global Training Network centre, and introduction of every new vaccine is used as an opportunity to train staff on AEFI monitoring.

In 2008, four deaths and 20 serious illnesses temporally associated with administration of a newly introduced pentavalent vaccine attracted public attention. Questions were raised concerning the quality of the vaccine and the coverage of these issues threatened confidence in the national immunization programme. The national authorities executed a wide-ranging communication strategy to address public concerns and to rebuild confidence.

The communication strategy included messages and approaches tailored to various audiences. Health care worker training focused on risk-benefit of vaccines and raising staff confidence was conducted, and a vaccine safety information module was developed in local languages. Key politicians received briefings on the risks and benefits of vaccines, as well as the achievements of the National Immunization Programme.
High-level representatives from both the print and electronic media, as well as regional journalists, working in all three official languages attended seminars about the benefits of immunization. In addition, a six-month intensive mass campaign in both electronic and printed media using traditional masks representing diseases was implemented to sway public opinion.

Because of this campaign, vaccine coverage increased (compared to before the crisis) and public trust on the National Immunization Programme was re-established.
A workshop was held in Tunisia in July 2013 that drew 45 participants from across the Eastern Mediterranean Region. With inputs from UNICEF, WHO and the London School of Hygiene & Tropical Medicine, the workshop introduced a pilot training package to enhance communications capacity for vaccine safety and helped strengthen capacity of national health officials to develop and plan risk communication activities for specific contexts, like immunization campaigns and the introduction of new vaccines.

Sessions were interactive with group exercises, role-playing and videos used to enhance learning. Participants had the opportunity to define desired communications outcomes and prepare key messages. Significant time was spent on media communication, with participants experiencing their skills through mock interviews. The program also included updates on international technical resources available to support risk communication based on the latest Global Advisory Committee on Vaccine Safety statements on pentavalent vaccines and HPV vaccines.

At the end of the course, national officials committed to assess the implementation status of communication plans in their countries using a checklist that allows the establishment of a brief capacity baseline. This checklist will provide the basis for a progress assessment on a semi-annual basis.
Why Communicate?

- Understand the conclusions and corrective actions.
- Maintain confidence and advocate NIP.
- Promote transparency and accountability.
- Contribute to determining research needs.
- Manage crisis situations.
The Vaccine Safety Net project

Many websites provide misleading and incorrect information about the safety of vaccines. The Vaccine Safety Net project was launched to address this misinformation by establishing explicit criteria about the features that constitute valid, credible and responsible content for vaccine safety information.

The project includes identifying websites from all parts of the world, in a variety of languages that meet relevant GACVS criteria, as well as producing through the WHO website an online list of websites that provide reliable information on vaccine safety. As a result of their combined efforts, the Vaccine Safety Net and its membership help to ensure that key stakeholders, including parents and other caregivers, public health authorities, health professionals and the media have access to balanced evidence-based vaccine safety information. Participating sites are re-evaluated every two years to ensure they continue to meet GACVS criteria.

According to Google Analytics reports, VSN webpages were the fifth-most visited pages on the WHO Global Vaccine Safety website in 2013 and the third most-visited in 2014. Page visits and returning visitors have almost doubled from 2013 to 2014 – showing the high demand for scientifically valid information about vaccine safety.

This guide is available at http://bit.ly/1fP4tyE
To optimize public health responses, it is paramount to detect, analyse and understand public concerns and the drivers of public confidence. Understanding the origins, drivers, and dynamics of these concerns and their impact on vaccination coverage can inform public health responses and provide insights and guidance for future vaccine introduction programs.

Public concerns around sudden infant death syndrome (SIDS) following pentavalent vaccine have spread in India and South-East Asia with the potential to escalate to widespread vaccine hesitancy and suspension of marketing authorizations. A total of 539 public media reports were identified pertinent to pentavalent vaccine and India. The dynamic evolution of positive and negative news items published over time demonstrated how analysis of available data may allow for correlation of sentiment quality and quantity with important events in the immunization program life cycle. This highlights the potential for utilizing the available resources for real-time monitoring of public sentiment.

The searches on the three social networks resulted in 4,779 original messages on pentavalent vaccine and 3,919 original messages on SIDS. Geographic information system processing and visualization of reports illustrates that pentavalent vaccine is discussed globally, with hot spots in India and South-East Asia. This highlights the potential utility of social media as complementary resources for real-time monitoring in LMICs.

To reduce the time need for human review and manual annotation of databases text mining algorithms can be utilized to (pre-)annotate the large volume of reports. Machine-learning methods were utilized to train and test classifiers for automatic sentiment annotation. The pilot demonstrated optimal sensitivities of 96% and specificities of 84% for different classifiers. This suggests a promising route for automated pre-processing of large news volumes for global media monitoring prior to targeted human review and thus represents a major step towards real-time monitoring.

In summary, the London School of Hygiene and Tropical Medicine, the Erasmus Medical Center and the Brighton Collaboration Foundation, have developed an innovative method and approach to monitoring public confidence related to Pentavalent Vaccine and SIDS. Funded by WHO, the partners in this project demonstrated the feasibility and usefulness of public and social media monitoring in low resource settings.
Strategic Objective 4

Globalization can be harnessed to build our collective knowledge about vaccine safety. Building a broader base of vaccine safety data is essential due to the rarity of serious vaccine-attributable adverse events and the fact that pre-licensure clinical studies are often too small to fully characterize a vaccine safety profile before licensure. The ability to combine data from multiple studies can raise collective awareness of safety-related issues, but only if these studies use similar definitions of AEFI and comparable methodologies for measuring similar outcomes. The availability of comparable data could allow for global-level databases to not only store and search for information, but also to test hypotheses about potential conditions connected with vaccines (Black, 2008).

Tools and Methods

The targets developed under the fourth strategic objective – to develop internationally harmonized tools and methods to support country vaccine safety activities – address this need for collective knowledge gathering and harmonization. They include:

- **Target 1:** Standard procedures and methodologies will be available for identification of vaccine safety signals;
- **Target 2:** Standard procedures and methodologies will be available for analysing and investigating vaccine safety signals; and
- **Target 3:** Various tools will be available to facilitate vaccine pharmacovigilance.
Effective AEFI surveillance is essential to vaccine pharmacovigilance, and global guidelines can help institutions build capacity in a way that allows for comparison and discussion of data on the global level. In September 2014, WHO published a manual that provides guidance on improving the quality and efficiency of AEFI surveillance activities for managers of immunization programs, NRA staff at national and subnational levels, immunization service providers, pharmacovigilance centre staff and other stakeholders in immunization services.

The manual discusses basic principles of immunization and vaccines, newer AEFI concepts, establishing AEFI surveillance systems (including methodology and reporting tools), and investigating and performing causality assessment using the revised classification of cause-specific AEFI. It also includes information on making the best use of surveillance data and on crisis response, including a communication strategy on immunization safety for the public and the media.

Countries are encouraged to adapt the global manual to their specific needs and prepare national AEFI surveillance guidelines. For example, several countries of African Region lack specific guidelines for monitoring AEFI, which is part of the reason why the region accounts for the lowest proportion of reported AEFI among WHO regions even though it has nearly a quarter of global live births. Adapting the global AEFI guidelines as a basis for establishing systems to report and review AEFI could address this gap and ensure countries from the African region are adequately represented in global statistics and decision-making related to AEFI.

This guide is available at http://bit.ly/1FjRiPy
For the purpose of signal detection, data collection tools should be as simple as possible. However, when signals are detected or in cases of serious AEFI, additional data are essential to determine potential associations with vaccines and to assess the need for further investigation and action. Collection of harmonized AEFI data allows for better comparison and pooled analysis using findings from vaccine safety surveillance systems.

In collaboration with a network of countries and independent experts, WHO proposed a list of core variables and designed a standard AEFI reporting form. This form is meant to be simple, appropriate for AEFI reporting and investigation, and have well-defined sections, as well as collect only required information in logical order.

This manual is available at http://bit.ly/1KHVD56
AEFI can be a serious health concern for individuals and communities. This means that the ability to accurately attribute causality to AEFI is essential in ensuring safety, especially in the cases of AEFI considered severe, of public importance and programmatically disruptive.

After a thorough review of innovative methods for determining causation for drugs and biologicals, WHO designed an algorithmic scheme that incorporates additional elements of causation. To ensure international consistency and collaboration, this scheme was harmonized with a newly developed algorithm by the Clinical Immunization Safety Assessment programme in the United States of America and the new definition of AEFI proposed by CIOMS.

The new WHO causality assessment classification method is meant to function as guidance for countries’ expert teams in assessing causality. It includes a manual and an aide-mémoire. The framework is meant for use by staff at the national and sub-national levels and will allow for a systematic, standardized global causality assessment process for AEFI. It can also serve as an educational tool for trainers and researchers and as a reference guide on AEFI causality assessment.

This document is available at http://bit.ly/1JBwrv9
Information Sheets for Better Understanding of Adverse Events Rates

To help national public health officials and immunization program managers evaluate AEFI and prepare communication materials about specific vaccines, WHO developed information sheets providing details on expected rates of occurrence of specified adverse events to selected vaccines, including those that are single antigen and combined in a single product. These documents were developed to be periodically updated as new evidence becomes available.

Documents are available at http://bit.ly/1F7XUpu
Impact of Standardised Definitions: Narcolepsy

In 2013, a narcolepsy case definition and a report on changes to reporting patterns in international databases were published. This project involved creating case definitions and guidelines for adverse events of special interest following influenza vaccines, as well as evaluating the case definition in international databases. A case definition for narcolepsy as an AEFI was needed immediately as part of European Centres of Disease Control studies that sought to harmonise international signal verification and hypothesis testing. The global review, standardisation and publication process was finalised as part of the GVSI in 2013. The case definition was used in collaborative European investigations and was cited by more than 22 publications globally. This experience demonstrated the value of Brighton Collaboration standard case definitions as part of an early harmonisation of methods for concerted investigation of improved data comparability and meta-analysis.
Reviewing Evidence on the Safety of Immunization During Pregnancy

Vaccination of pregnant women may provide important benefits to the mother and/or her infant. WHO already recommends several vaccinations during pregnancy, and some promising new ones are currently in development, while antenatal immunization against tetanus, influenza and pertussis is recommended and increasingly utilized in many countries. However, several challenges exist related to addressing the safety of immunization during pregnancy. Limited data is available on vaccine safety for pregnant women and on fetal risk; liability concerns and methodological issues in assessing vaccine safety during and after pregnancy limit their study through controlled clinical trials. The GACVS established a working group in 2011 to review the evidence available for six groups of vaccine products and address ongoing issues.

This guide is available at http://bit.ly/1IMxnJa
The variability of terms and definitions of AEFI represents a missed opportunity for optimal monitoring of safety of immunization in pregnancy. In 2014, the Brighton Collaboration Foundation and WHO collaborated to address this gap.

Two Brighton Collaboration interdisciplinary taskforces were formed. A landscape analysis included a systematic literature review of adverse event definitions used in vaccine studies during pregnancy (led by Emory University), a worldwide stakeholder survey of available terms and definitions and a series of taskforce meetings (led by Baylor College of Medicine and the University of Washington).

Based on available evidence, task forces proposed key terms and concept definitions to be refined, prioritized, and endorsed by a global expert consultation convened by WHO in Geneva in July 2014.

Using pre-specified criteria, 45 maternal and 62 fetal/neonatal events were prioritized, and key terms and concept definitions were endorsed. In addition, recommendations to further improve safety monitoring of immunization in pregnancy programs were specified. This includes elaboration of disease concepts into standardized case definitions with sufficient applicability and positive predictive value to be of use for monitoring the safety of immunization in pregnancy globally, as well as the development of guidance, tools and datasets in support of a globally concerted approach.
Optimizing Signal Analysis for Vaccine-Related Individual Case Safety Reports

Individual case safety reports are collected on a global scale to enhance the ability to identify early signals of harm related to medicinal products exposure, with reports submitted to VigiBase from approximately 120 countries. This project aims to increase algorithms’ sensitivity and validity with the hope that earlier and better signals of vaccine-related problems may be identified in the future. Outcomes will include improving statistical algorithms for routine use, providing statistical associations to the clinical review team to assess their validity and sharing new signals that clinical reviewers consider interesting with WHO and national pharmacovigilance centres.
Most developing countries in Asia and Africa lack the ability to create and maintain databases for AEFI. The availability of a common database for vaccine safety stakeholders to collaborate on assessing AEFI and the performance of AEFI monitoring would be highly beneficial.

The Vaccine Adverse Event Information Management System (VAEIMS) is software that has been developed by the International Vaccine Institute in South Korea in technical collaboration with WHO. The software is designed to transfer AEFI data into a central database for processing and convert raw data into information for action using core variables, which are directly reported from the periphery of the health care system.

This new tool is developed keeping in mind the diverse data collection, collation, transmission, analysis and feedback systems existing in different countries. VAEIMS was successfully piloted in Sri Lanka and is now being made available as open source software at request of countries.

VAEIMS is meant to simplify AEFI reporting for health care workers while also ensuring that data collection, analysis and interpretation is standardized. In addition to pooling data, VAEIMS also provides local capability to rapidly detect and analyse vaccine safety concerns and is expected to encourage signal detection related to rare and significant AEFI. The tool is useful for countries that do not have existing capability to manage AEFI. The visual presentation of data into meaningful formats enhances the ability of local, regional and national authorities to detect and characterise potential vaccine safety signals.
Improving Risk Evaluation and Management Capacities

The pharmacovigilance network of focal points in the Region of the Americas has drafted two reference documents, one on risk management and one on periodic safety update reports. A practical approach to the documents implementation will be taken, and the national regulatory authorities will be discussing and exchanging information for decision making on the field through the Regional Platform of Access and Innovation for Health Technologies in 2015 and 2016. This will allow strengthening NRA capacities for risk assessment, management and communication.
As with all medicinal products, a regulatory system must exist for vaccine pharmacovigilance that is backed up by appropriate laws, regulations and procedures. NRAs must serve as effective administrators and coordinators for safety systems within their countries, and collaboration between NRAs and immunization programs is essential to continuously ensure vaccines are safe after licensing. Many countries do not have functional NRAs with regulatory provisions that outline who is accountable for what. Countries need to have national vaccine pharmacovigilance centres, and existing centres must be strengthened to allow vaccine safety issues to be discovered and addressed in a timely manner (WHO, March 2012).

The targets developed under the fifth strategic objective – to promote a legal, regulatory, and administrative framework for the safety of vaccines at the national, regional, and international levels – include:

- **Target 1**: All countries have provisions for establishing vaccine pharmacovigilance, including lines of accountability; and
- **Target 2**: Vaccine pharmacovigilance is established as an international responsibility.
Better Collaboration Between Regulatory Authority and Immunization Programme in Brazil

Brazil has made considerable progress since 2001, the National Regulatory Agency (ANVISA) has created the Pharmacovigilance Department and the Drugs Monitoring Centre. It is also a member of the WHO’s Uppsala Monitoring Centre. But only in 2008, joining efforts and working together with the National Immunization Program (NIP) of the Ministry of Health began to improve the vaccines’ pharmacovigilance.

The ministry has since created the AEFI National Committee, with the participation of members from the NRA, NIP, the National Institute of Health Control and Quality and vaccinology experts (paediatricians, neurologists, immunologists, epidemiologists and pharmacist). Its mission is to help institutions analyse and make causality assessments of all serious and rare AEFI, as well as questioning and generating suggestions of studies and researches.

Brazil participated in several regional and global surveillance efforts during this period. Trainings on causality assessment of AEFI have been organized with the support of the Pan American Health Organization.

There were improvements, such as better investigations with a standardized AEFI reporting form. The notification flow, now ruled by law, includes state immunization coordinators, the NRA representatives and manufacturers. In 2014, the country’s AEFI Manual underwent significant revisions, including a new pharmacovigilance chapter and the inclusion of Portuguese translations of the Brighton Collaboration definition cases. With the aim to facilitate communication and data transmission, the NIP introduced a new online AEFI information system.

Following international standardization of data records will facilitate management, analysis and the exchange of information and the global identification of vaccine safety signals.
Networking, Assessment of Regulatory Functions and Coordination Among NRAs and Immunization Programs in Countries of the Americas

The Region of the Americas network of pharmacovigilance focal points is fully active, with 24 countries participating in monthly virtual meetings and periodic exchange of information and experiences. As an example, in 2014 the network discussed the following vaccine-related problems: quality problems with a tetanus-diphtheria vaccine that led to its withdrawal from the market in Chile; fainting events apparently associated with the HPV vaccine in Colombia that proved to be not related with the vaccine; the deaths in Syria during measles vaccination (not related to the vaccine); the withdrawal of 12 batches of meningococcal C conjugate vaccine in Brazil because of quality problems; and the follow up of the investigation in Colombia of events supposedly attributable to vaccination or immunization after administration of a Cuban leptospirosis vaccine.

Three NRAs were pre-evaluated (through a self-assessed questionnaire or a visit to the country) in 2014. Evaluators used a reduced set of indicators from the NRA assessment tool to evaluate their regulatory functions including pharmacovigilance and the coordination with the EPI to manage AEFI. That allowed identifying gaps and proposing the appropriate improvements in the coordination of procedures among both entities.
Regional NRA Alliance Working Group on Pharmacovigilance in the Western Pacific

The Regional Alliance for National Regulatory Authorities for Vaccine in the Western Pacific was officially launched in March 2013.

The Alliance steering committee agreed on establishing a working group on pharmacovigilance, import, export and market surveillance to support AEFI surveillance activities in the region.

The annual meeting of NRA in September 2014 discussed on regional priorities and one of them was to formulate sub-regional AEFI causality assessment committee and assist Pacific Island Countries and Areas through desk review.
Strategic Objective 6

A situational assessment conducted for the blueprint and reports from WHO regional offices uncovered an urgent need for strengthening national systems to monitor medicine and vaccine safety (WHO, March 2012). A number of resources are available at the international and national level to provide guidance – including technical agencies, academic institutions, experts from national immunization programs and regulatory agencies – but these must be accompanied by appropriate training program to develop effective country capacities. WHO provides a process for strengthening national regulatory systems through an institutional development plan, which can be used as part of efforts to build local capacity related to vaccine safety (WHO, March 2012; WHO, 2003).

Technical Support and Trainings

Background

The targets developed under the sixth strategic objective – to strengthen regional and global technical support platforms that meet countries’ expressed needs – include:

- **Target 1**: A strengthened global or regional mechanism that facilitates access to learning/training for the development of national vaccine pharmacovigilance capacity;
- **Target 2**: A global or regional mechanism that provides technical support to respond to specific vaccine safety issues; and
- **Target 3**: Identification and strengthening of a global and regional infrastructure that coordinates multi-country studies related to vaccine safety issues.
Following the successful implementation of minimal vaccine safety monitoring capacity in other parts of the world, countries from the WHO Regional Office for Africa have been identified as the next priority for GVSI.

In 2014, two workshops were conducted to initiate planning. These workshops involved participation from eight Anglophone* and seven Francophone countries*, including national EPI, NRA, and pharmacovigilance centre staff, as well as WHO country office focal staff for vaccines and essential medicines. Participating countries mapped their vaccine pharmacovigilance resources and developed work plans for strengthening AEFI surveillance, which has enabled prioritization and identified focal persons, strategies and deadlines. WHO is currently providing technical support to each country in implementing their work plan, and a new group of countries will initiate planning during 2015.

*Ethiopia, Ghana, Kenya, Malawi, Nigeria, United Republic of Tanzania, Uganda, Zimbabwe
*Burundi, Côte d’Ivoire, Cameroon, Democratic Republic of Congo, Guinea, Madagascar, Togo
Field AEFI Investigation Simulation Training

In November 2014, WHO conducted an AEFI field investigation simulation training that was newly developed and organized in Sudan. This training was held for 36 surveillance officers from 18 provinces, the national EPI, the NRA and the national AEFI causality assessment committee. An AEFI related storyline was developed by WHO, reviewed and translated by the Ministry of Health.

The training began with classroom sessions on AEFI investigation and AEFI causality assessment followed by orientation to the field investigation methodology. The participants were then assigned to groups with facilitators. Site visits were made and interviews in groups were conducted with vaccinator, parents, hospital and immunization centre staff.

After the site visits, each group prepared an investigation report that was presented to the audience. One final report and dossier based on the documentation, observations and feedback obtained during the exercise was prepared jointly by the groups and presented to the National AEFI causality assessment committee members the third day. This training was a good opportunity to evaluate and validate the AEFI investigation form that was translated into Arabic by the EPI team of Sudan. The feedback from the trainee indicated that facing a mock AEFI crisis provided an excellent learning opportunity. Support from the facilitators and interactions with colleagues helped them build confidence to tackle any potential AEFI case. The field simulation promoted teamwork; the groups quickly learnt that AEFI investigation is a meticulous process where teamwork is critical particularly in obtaining information and expertise from different geographic locations with varied skills, experiences and background.

The training was used as an opportunity for the national AEFI causality assessment committee to revisit the AEFI causality assessment methodology in presence of WHO facilitators. It also provided surveillance officers with a first-hand experience of an assessment exercise performed by the national AEFI causality assessment committee members.
Creating a Vaccine Pharmacovigilance Toolkit

Promoting the use of vaccine safety monitoring tools is an integral part of technical assistant and training. To aid in promotion, the WHO Collaborating Centre for Advocacy and Training in Pharmacovigilance in Accra, Ghana, and the GVSI Planning Group led the development of a vaccine pharmacovigilance toolkit, providing guidance in terms of contents, accuracy and diversity.

The toolkit’s structured in a similar way to the drug pharmacovigilance toolkit, also developed by the Accra centre. The vaccine pharmacovigilance toolkit brings the tools and resources necessary for effective vaccine pharmacovigilance together in one website. Because the toolkit is web-based, it can be frequently updated and gives links to relevant websites. In addition, an offline USB version is available for use by practitioners in LMICs where Internet access is limited.

Training on Pharmacovigilance and Regulatory Decisions for Vaccines

Many countries require that pharmaceutical manufacturers, in addition to health professionals and public health programmes, be involved in the collection, processing and evaluation of patient safety information. To respond to this need, the Uppsala Monitoring Centre (the WHO Collaborating Centre for International Drug Monitoring) began offering a module in their annual pharmacovigilance training course in 2013 on how to improve vaccine safety data collection from immunization programmes and industry activities, feeding into the analysis and decision making of a national drug regulatory authority.

The two-day training, conducted in collaboration with the U.S. Food and Drug Administration, is targeted at health care professionals involved with pharmacovigilance in the public sector and industry and discusses the application of pharmacovigilance in regulatory decisions for vaccine safety. It is meant to support the development of effective national programmes for collection and analysis of vaccine safety data in support of regulatory decisions and communication with professionals and the public.
Using E-Learning for Vaccine Safety Basics

Health care professionals and managers in public health authorities aim to identify and respond appropriately to vaccine safety issues. To help strengthen this capacity, GVSI supports countries with basic and advanced training courses on vaccine safety and causality assessment. These trainings aim to promote the understanding of the origin and nature of adverse events, the importance of pharmacovigilance, and risk and crisis communication.

WHO introduced an e-learning course on vaccine safety basics in 2012 to help establish a shared understanding among all stakeholders involved in vaccine pharmacovigilance and improve countries’ vaccine safety practices in a cost-effective manner. The course, designed using input from international vaccine experts, serves a broad range of institutions and individuals involved in vaccine safety such as vaccinating health professionals, national regulatory staff and immunization staff.

English, French and Russian versions were launched in 2014. The course was also translated in Indonesia Bahasa language. Indonesia is a major producer of prequalified vaccines that are used in many LMICs, and strengthening AEFI monitoring in Indonesia was a priority to document the safety of vaccines locally produced.
The China Food and Drug Administration (CFDA) and China’s National Health and Family Planning Commission (NHFPC) are facing greater demands related to patient welfare and safety, which requires standardized monitoring, data validation, analysis and signal detection to ensure safe vaccine delivery. To strengthen national regulation, WHO is coordinating with CFDA and NHFPC on an institutional development plan to help improve national-level surveillance and analysis – a decision being made based on the needs expressed by the country.

Enhancing Signal Detection in China

To improve staff technical capacity in detecting vaccine safety signals, WHO conducted two workshops on signal detection in China: one in 2012 and one in 2014. These workshops were designed to help participants understand common definitions and data mining methods, appropriately respond to signals, and develop hypotheses for abnormal signals as well as validate possible causes, among other goals. More than 30 staff from the CFDA and NHFPC participated in the 2012 workshop, as well as staff from 17 provinces. In 2014, 35 staff from CFDA and NHFPC participated to the same.
Training of NRAs Using the African Vaccine Regulatory Forum Platform

The African Vaccine Regulatory Forum (AVAREF) is a regional network founded by WHO in 2006, to address a need in regulatory approval and oversight of clinical trials of vaccines to ensure safety of participants and generation of reliable data for regulatory approval of products. The network meets annually, bringing together NRAs and Ethics Committees of 19 African countries. One of the key objectives of AVAREF is to promote convergence towards harmonization of regulatory practices and processes. One of the key functions of regulatory authorities is post-marketing surveillance.

NRAs are also key stakeholders in monitoring of the safety of vaccines throughout their lifecycles.

The GVSI was presented to participants at the seventh-annual meeting of AVAREF in Libreville, Gabon. The Blueprint and its objectives were also discussed, and presenters demonstrated WHO tools and other resources. The participants were encouraged to take the WHO course on vaccine safety online.
Nationally, WHO promotes the use of national immunization technical advisory groups and AEFI review committees (WHO, March 2012; Bryson et al, 2012); additionally, each WHO region has a technical advisory group that provides countries with policy guidance. Support is available at the global level as well – including through the Expert Committee for Biological Standardization, the Strategic Advisory Group of Experts on Immunization, the Immunization Practices Advisory Committee and the Global Advisory Committee on Vaccine Safety (WHO, March 2012). WHO established GACVS in 1999 to respond promptly, efficiently and with scientific rigour, to vaccine safety issues of potential global importance. Through GACVS, WHO maintains the global safety profile of WHO recommended vaccines, provides advice on conducting studies that assess vaccine safety signals of global importance and reviews the results of those studies. The group is responsible for conducting risk assessment and looks at vaccine safety issues that are either causing public concern or have the potential to do so, including general safety issues relevant to all vaccines, as well as vaccine-specific concerns and safety issues for vaccines that are new or in development. Current and past GACVS members represent a broad range of disciplines related to immunization safety from all WHO regions. The advisory committee’s assessments of vaccine safety are published regularly both in print and on the WHO website.

The targets developed under the seventh strategic objective – to provide expert advice on vaccine safety issues at the national, regional, and international levels – include:

- **Target 1:** Immunization advisory bodies at the national, regional, and global levels to provide expert advice on managing unwanted vaccine reactions; and
- **Target 2:** GACVS maintains the global safety profile of all vaccines and advises on the conduct of studies for assessing vaccine safety signals of global importance.
GACVS Advice on New Vaccine Introduction

GACVS plays an important role when new vaccines are introduced. This was recently demonstrated at the global level with the introduction of HPV vaccine, and in India with the introduction of the pentavalent vaccine.

**HPV vaccine**

The HPV vaccines became available in 2006. GACVS reviewed their safety in 2007 and 2009 and was satisfied with its safety profile. However, while surveillance data and epidemiologic studies on the HPV vaccine have remained very reassuring, allegations have surfaced in the media and elsewhere about possible safety issues.

In June 2013, GACVS reviewed updated information about the HPV vaccine’s safety using data from the United States, Australia, Japan and from the manufacturers of the two currently available products. Data from all sources continue to be reassuring about the safety of both vaccines. After cases initially resembling complex regional pain syndrome (CRPS) were reported from a WHO Member State, a review by an expert advisory committee could not ascertain a causal relationship between vaccination and CPRS. In its advisory capacity, GACVS has urged careful documentation of each case and a thorough search for a definitive diagnosis by medical specialists in order to best guide treatment.

In December 2014, GACVS reviewed evidence related to autoimmune disease and the HPV vaccine, with a focus on multiple sclerosis. Multiple studies in Sweden, Finland, France and the United States of America have demonstrated no increase in risk of autoimmune diseases, including MS, among girls who have received HPV vaccine. GACVS remains reassured by the safety profile of the vaccine, but noted the importance of continued surveillance and epidemiological investigation with an emphasis on the collection of high-quality data.
India introduced pentavalent vaccine from the Serum Institute of India in the states of Tamil Nadu and Kerala in December 2011. This was followed by expansion of vaccine usage in the states of Goa, Pondicherry, Karnataka, Haryana, Jammu and Kashmir, Gujarat and Delhi during late 2012 and early 2013. By June 2013, 83 serious AEFI cases – including deaths – had been reported in relationship with pentavalent vaccine.

GACVS reviewed India’s investigations, as well as those from Bhutan, Sri Lanka and Viet Nam, during a June 2013 meeting and suggested that it is important for countries to understand their infant mortality rates and underlying causes when evaluating a safety signal. Additionally, GACVS suggested that if a serious AEFI is identified as a concern, additional epidemiological studies should be conducted to test such hypothesis.

India subsequently decided to undertake a well-designed study to systematically examine potential associations between the administration of pentavalent vaccination and unexplained sudden deaths and other serious AEFI among children between two and six months old in India. This study is currently underway in two states, Kerala and Tamil Nadu, and two districts, Kollam and Coimbatore, led by International Clinical Epidemiology Network (INCLEN).
Strategic Objective 8

Vaccine safety issues are the responsibility of those who provide and administer the vaccines, as well as those who develop or manufacture the products. The importance of close collaboration between national authorities (regulators and immunization programs) and industry is well recognized in vaccine pharmacovigilance activities but may not always occur.

Manufacturers need information about adverse events from national authorities, and national regulators need up-to-date safety information from manufacturers as well. GVSI aims to promote a more efficient and rapid collection and exchange of information on vaccine safety issues among national regulatory authorities, vaccine manufacturers and multilateral agencies.

The targets developed under the eighth strategic objective – to put in place systems for appropriate interaction between national governments, multilateral agencies and manufacturers at national, regional and international levels – include:

- **Target 1:** To promote a more efficient and rapid collection and exchange of information between NRAs, multilateral agencies and vaccine manufacturers; and
- **Target 2:** Harmonized tools and methods for vaccine safety monitoring activities are agreed upon by NRAs, multilateral agencies and manufacturers.

Public-Private Interaction

**Background**

Vaccine safety issues are the responsibility of those who provide and administer the vaccines, as well as those who develop or manufacture the products. The importance of close collaboration between national authorities (regulators and immunization programs) and industry is well recognized in vaccine pharmacovigilance activities but may not always occur.

Manufacturers need information about adverse events from national authorities, and national regulators need up-to-date safety information from manufacturers as well. GVSI aims to promote a more efficient and rapid collection and exchange of information on vaccine safety issues among national regulatory authorities, vaccine manufacturers and multilateral agencies.
A Forum for Vaccine Safety Dialogue

CIOMS provides a forum in which dialogue can take place among representatives from regulatory and public health agencies, academia and industry. The CIOMS/WHO Vaccine Safety Working Group, established in 2013, aims to:

• promote a more efficient and rapid collection and exchange of information among NRAs, multilateral agencies and vaccine manufacturers;
• develop and endorse harmonized tools and methods for vaccine safety monitoring activities among NRAs, multilateral agencies and vaccine manufacturers; and
• propose mechanisms for vaccine safety monitoring in difficult settings, such as settings with minimal infrastructure.

The expected outcome of this working group is to produce a series of consensus publications by 2016.

The CIOMS working group on vaccine safety is currently focused on developing a template dossier to support countries with limited regulatory capacity when introducing a new product, as well as developing a guidance document on setting up active surveillance systems. The dossier could potentially become part of the WHO prequalification process or be used to guide information transfer from manufacturers to donors and regulatory agencies, which could dramatically improve communication exchange and inform decision-making related to setting up appropriate vaccine safety surveillance systems. As of November 2014, a template had been developed and piloted with three products. The guidance document for setting up active surveillance systems is scheduled for completion in 2016; it will complement the WHO Global manual on surveillance of adverse events following immunization.

This guide is available at http://bit.ly/1FjRiPy
Progress on the Three Blueprint Strategic Goals

When WHO and partners developed the Global Vaccine Safety Blueprint in 2011, they outlined three overarching goals:

1. assist LMICs to have at least minimal capacity for vaccine safety activities;
2. enhance capacity for vaccine safety assessment in countries that introduce newly developed vaccines, that introduce vaccines in settings with novel characteristics, or that both manufacture and use prequalified vaccines; and
3. establish a global vaccine safety support structure.

Each of the 88 projects listed in the GVSI portfolio of activities is underpinned by these goals. A significant number of those projects are still ongoing (47), some are in the planning stage (13) but listed as key priorities to achieve Blueprint goals and 28 are completed with outputs directly impacting vaccine pharmacovigilance systems worldwide.

Among completed projects, the majority (21) consisted in developing tools and methods (objective 4) for vaccine pharmacovigilance and implementing those through technical support and trainings to countries (objective 6).

Ongoing activities developed within the GVSI framework (40%) address needs identified in the AEFI detection and investigation field, as well as a long-term, ongoing effort in developing tools and best practices in vaccine safety communication. For the immediate future, the initial focus on tools development will give place to additional technical support and training on the GVSI agenda. Other long-term ongoing activities also include strengthening the vaccine pharmacovigilance regulatory framework, as well as putting in place meaningful mechanisms between programs, regulators and the industry to improve information exchange.

Other activities to attain Blueprint objectives address gaps identified in the field of vaccine safety communication (tools and training programs), advanced tools (in detecting and investigating AEFI for specific vaccines, adverse events of special interest, active surveillance tools) needed for enhanced capacity and the need to continuously train members states in building strong vaccine pharmacovigilance systems.
Conclusion and Next Steps

The Global Vaccine Safety Initiative aims at implementing the Blueprint vision of effective vaccine pharmacovigilance systems established in all countries. In other words, everyone everywhere should receive vaccinations with a proper safety monitoring system in place. There is, in particular, a clear need of building capacity for better monitoring and response to vaccine safety concerns in LMICs. While many technical solutions for enhancing vaccine pharmacovigilance are available, the awareness and use of those established solutions as well as solutions enhancing international, regional and global interactions remain limited in many parts of the world.

Projects developed within the framework of the Initiative are covering all six WHO regions. In aggregate, they involve more than 50 countries and have a potential outreach toward 77% of the world population. Of the 88 projects registered in the GVSI portfolio, many are still ongoing or have yet to begin. This means that while significant gains have been made under GVSI, substantial work remains to meet all of the initiative’s goals by 2020.

Building minimal capacity at country level was a GVSI focus in 2013 and 2014. In addition, the anticipated availability of new vaccine products provided exciting opportunities for conducting enhanced vaccine safety projects in several countries. In parallel, the Initiative is expanding its network of expertise, drawing from new colleagues participating in recent projects. An important next step will be to document progress against clear benchmarks in order to measure successes and gaps. To that effect, GVSI and its partners are preparing an evaluation framework.
Appendix

GVSI GOVERNANCE AND MANAGEMENT

The initiative is not a legal entity, nor is it a formal partnership; instead it is a mechanism providing a framework for implementing the blueprint and a forum for collaboration. Representatives of participating organizations, agencies and institutions gather for an annual GVSI meeting; observers may be invited to these gatherings. During the annual meetings, participants review activities reports, make proposals, offer non-binding recommendations and endorse the initiative’s work plan (Zuber et al, 2012).

GVSI meeting participants appoint a GVSI Planning Group comprising experts in the field to coordinate GVSI’s work and oversee implementation of the portfolio of activities. The group is responsible for tasks such as analysing portfolio gaps, planning initiative-related communication, conducting outreach to stakeholders, and discussing fundraising strategies (Ibid). Additionally, WHO acts as a hub for information and documentation on the blueprint’s implementation, and GACVS acts as the scientific advisory committee for implementation.

Some of GVSI’s managerial tools to oversee day-to-day activities and progress include monthly teleconferences with the GVSI Planning Group and the WHO GVSI secretariat, as well as biannual Planning Group retreats. Additionally, a GVSI website is maintained and publically available to find information about initiative-related developments; products such as quarterly GVSI bulletins and GVSI reports are posted on this site. The initiative also uses stakeholders’ mailing lists and publications in relevant journals and literature to disseminate information (Ibid).
THE GVISI STRATEGIC PRIORITY GROUP MEMBERS

<table>
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Appendix

GVSI CONTRIBUTING PARTNERS AND DONORS

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- Brighton Collaboration Foundation
- Council for International Organizations of Medical Sciences
- GAVI: the Vaccine Alliance
- International Vaccine Institute
- United States Food and Drug Administration
- WHO Collaborating Centre for Advocacy and Training in Pharmacovigilance, the Centre for Tropical Clinical Pharmacology and Therapeutics, University of Ghana Medical School
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Acronyms

AEFI: Adverse Events Following Immunization
AESI: Adverse Events of Special Interest
AVAREF: African Vaccine Regulatory Forum
CIOMS: Council for International Organizations of Medical Sciences
EPI: Expanded Program on Immunization
GACVS: Global Advisory Committee on Vaccine Safety
GVSI: Global Vaccine Safety Initiative
LMICs: Low-and-middle-income countries
NRAs: National regulatory authorities
SAGE: Strategic Advisory Group of Experts
UN: United Nations
VAEIMS: Vaccine Adverse Events Information Management System
WHO: World Health Organization
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