World Health Organization
Essential Medicines and Health Products (EMP)

Global Vaccine Safety Initiative Meeting
13-14 October 2014, Tianjin, China

Secretariat Report

This report contains the collective views of an international group of experts, and does not necessarily represent the decisions or the stated policy of the World Health Organization.

Meeting's presentations can be found under: http://workspace.who.int/sites/gvsimeetings/3rdmeeting/default.aspx

The Third Global Vaccine Safety meeting took place in Tianjin, China on 13-14 October 2014. This general meeting guides the Global Vaccine Safety Initiative (GVSI), which is the implementation mechanism for the Global Vaccine Safety Blueprint.
During two days, immunization programme managers and national regulatory authorities pharmacovigilance staff from more than thirty countries gathered with representatives from UN agencies, academic institutions, pharmaceutical companies umbrella organizations, partner and funding agencies. Participants reported on initiatives relevant to the Blueprint objectives, shared experiences to strengthen vaccine pharmacovigilance, and identified needs and opportunities for further development.

Meeting Objectives:

The overall objective of the meeting was for countries and partners to interact and exchange information on progress with implementation of national and global vaccine pharmacovigilance activities and define plans for further development.

The specific objectives of the meeting were to:

- Review the achievements of the second year of implementation of the GVSI,
- Discuss needs and opportunities at country level for strengthening their vaccine pharmacovigilance system,
- Explore mechanisms to further strengthen collaboration in support of GVSI.

This report summarizes the key points of discussion and outcomes of the meeting.

DAY 1 – MEETING CHAIR: DR LI QUANLE

Opening ceremony and welcome remarks

The opening ceremony was done by the Counsel General Mr Zhang Yao-hua, from the Department of Drug and Cosmetic Supervision from the China FDA who delivered his speech in presence of

Ms LI Fang, Director of the Division of Drug Monitoring and Re-evaluation, Department of Drug and Cosmetics Supervision.

On behalf of China Food and Drug Administration, Mr Zhang Yao-hua welcomed the meeting's participants to Tianjin.

Mr Zhang stated that China is a developing country with the largest population in the world, and that its public health system has a significant impact on a billion of people's welfare. He acknowledged that vaccines are the most effective way for the control and prevention of diseases, playing an important role on the combat on communicable diseases. In the 1960s, China succeeded in eliminating smallpox; in 2000, achieved the goal of zero-polio and in 2012, eliminated tetanus for new born babies. The total manufacturing capacity of Chinese vaccines industry now accounts for 1 billion dose every year, with an annual lot release of 700 million. China produces 61 categories of vaccines for the prevention of 34 diseases.

Mr Zhang reiterated how Chinese government attached great importance on the safety of vaccines. With the rapid development of vaccine industry in recent years, the safety monitoring of vaccines has been significantly enhanced. Furthermore, in July 2014, Chinese vaccine regulatory system has successfully passed the NRA assessment, and such achievement has increased international attention.

China has continuously improved its legal framework with regard to the Regulations on the Distribution of Vaccines. In 2010, the State Food and Drug Administration (SFDA) and the Ministry of Health jointly issued a National Monitoring Plan on the Abnormal Reaction after Vaccination, which specifically set up clear requirements on AEFI monitoring and reporting, investigation and diagnosis, data analysis to support informed decision. China has established a three-level monitoring system from Central government, Provinces and Municipalities, covering 31 provinces and 330 municipalities. The AEFI information system covers 2856 counties in all 31 provinces, which can be used by both the National Health and Family Planning Commission (NHFPC) and SFDA system directly.

The number of reports has significantly increased. Comparing the number of reports collected in 2005 when they first established their monitoring system (1900 reports), in 2013 they have received more than 130 000 reports, covering 95% counties.

Their capacity on data analysis and assessment has been drastically enhanced. With the technical support of the World Health Organization, workshops on AEFI causality assessment, on vaccine signal detection, on PSUR drafting and evaluation have been conducted that greatly improved their capacity to analyze and assess their data. End of 2013, when the hepatitis B vaccine incident happened in Hunan province, their vaccine regulatory and safety monitoring system have proven its efficiency through a proper management of the incident.

It was concluded that China monitoring system is still facing challenges such as imbalances among regions, therefore they still need technical support from international organizations and other institutions. The 3rd GVSI Meeting held in Tianjin will provide them with a great opportunity to learn from foreign experiences, so as to comprehensively improve their vaccine safety monitoring system and to let made-in-China vaccines make more contribution to the diseases control and healthcare in many other countries.

Following the opening speech, Dr Clive Ondari, SAV Coordinator in WHO HQ, officially launched the release of "The Global Manual for the Surveillance of Adverse Events Following Immunization", the WHO guidelines for setting up AEFI surveillance systems with standardized methodologies and tools. The manual was developed within the framework of the Global Vaccine Safety Initiative.

The Global Vaccine Safety Initiative: review of achievements
Dr A. Dodoo

Dr Alex Dodoo, in his quality of GVSI Planning Group Chair, presented the report of the Global Vaccine Safety Initiative achievements for the past 2 years of implementation.
He reminded the participants about the GVSI background by presenting the mission, vision and the three Global Vaccine Safety Blueprint strategic goals, the GVSI operational framework and implementation mechanism. A strong appeal was addressed to vaccine safety stakeholders to contribute to the Initiative by submitting their activities and projects into the portfolio of activities, the GVSI core management tool:
(http://www.who.int/vaccine_safety/initiative/GVSI_portfolio_directory_1_July_2014.pdf)

Products developed by partners and within the GVSI framework for the past two years (2012-2014) were presented to the audience:

- Vaccine PV toolkit developed by the Ghana pharmacovigilance centre which provides access to current WHO-approved tools and resources for vaccine PV,
- Brighton Collaboration Case definitions for AEFI,
- The UMC WHO Global Individual Case Safety Reports database with over 9 million reports relating to ADRs and AEFIs,
- A desktop based AEFI management tool as well as a web-based tool (the VAEMS – web-based Vaccine Adverse Events Management System) developed by IVI-Korea to assist countries in sending their AEFI reports to local/global databases. Discussions have been initiated with India, Bangladesh, Vietnam, Sudan, Iran and Uganda to pilot the tool,
- A series of vaccine safety courses were developed such as the Basic vaccine safety course for all health staff, the E-learning course on vaccine safety basics (in English, French and Russian), the WHO Advanced course on causality assessment of AEFI for senior staff, the Period Safety Update Report preparation and evaluation and the Signal detection training. A WHO course on vaccine communication is also available upon request from countries,
- A multitude of tools were also developed to assist countries in their daily pharmacovigilance activities such as: the Global Manual for the Surveillance of AEFI, the AEFI core variables and the standard AEFI reporting form, AEFI investigation

form, the AEFI causality assessment users' manual developed following the revised WHO methodology on AEFI causality classification, the causality assessment aide-memoire, the info-sheets on observed rates of vaccine reactions etc.,

- To address the need for enhanced pharmacovigilance capacity, support to conduct active surveillance for new vaccines has been provided (e.g. Rotavirus and intussusception; MenA conjugate in pregnancy), and Guidance documents are in the pipeline such as guidance for malaria vaccine introduction. In addition, a network of hospital sentinel sites for AEFI signal verification and hypothesis testing, the Global Vaccine Safety Multi-Country Collaboration project is being established, involving 16 countries from all regions,
- With regard to communicating and reaching out to GVSI stakeholders, a quarterly GVSI bulletin is being published as well as a Vaccine Safety Net Newsletter,
- On a global level, within the GVSI framework, vaccine safety crisis for at least 4 different vaccines in 3 different countries were adequately managed by providing countries with access to the WHO Global Advisory Committee on Vaccine Safety (GACVS) expertise, tools, field visits and advice on crisis communication,
- GVSI interventions consist of projects, programmes, partnerships and advocacy all acting in concert to contribute to the achievement of the Blueprint strategic goals. The monitoring and evaluation of progress towards and achievement of results is essential to enhance GVSI stakeholders learning, to ensure informed decision-making and to support substantive accountability. A GVSI monitoring and evaluation framework is being developped in this regard.

Finally, the presentation ended with a call to all stakeholders for an effective collaboration to ensure that "*everyone everywhere receive the safest vaccines possible*".

Session 1: lessons learnt from country experiences

During this session, a panel of countries shared their experienced and lessons learnt around three topics:

- Strengthening AEFI surveillance system,
- Establishing collaboration between NRA and EPI for an effective vaccine safety system,
- Monitoring the safety of newly introduced vaccines.

1- Strengthening AEFI surveillance system: Nepal (Dr S. Jnawali) and Tanzania (Dr K. Mbwana)

The representative from the Nepal Ministry of Health and Population, Department of Health, introduced his session by presenting the Nepal country profile, the number of Serious AEFI reported since 2011, the AEFI structure and process, some data about the AEFI cases per antigen in 2014 and the classification of AEFI per cause for the period 2011-2013. We were then presented with a detailed case study of an AEFI cluster from August 2012.
The representative from the Tanzanian Food and Drugs Authority presented the country profile, the main vaccines stakeholders, their roles and responsibilities, the vaccines used in Tanzania and the list of newly introduced vaccines – HPV in May 2014, MR in October 2014 and IPV in January 2015. She then presented the AEFI surveillance reporting structure with

timelines, their recent activities with regard to vaccine pharmacovigilance such as training on causality assessment of AEFI, the nomination of the AEFI review committee members, the finalization of their AEFI surveillance guidelines, the next steps and challenges faced with regard to funding, lack of expertise and incompleteness of AEFI reports.

Main discussion points:

- Need to adopt a collaborative approach to strengthen an AEFI surveillance system by involving all stakeholders to participate in the revision/development of the Country AEFI surveillance guidelines where role and responsibilities are being defined, flow of information and all operational and managerial aspects should be detailed,
- To promote reporting, it is important to avoid any punishment of health workers following an AEFI, including programmatic errors, but rather learn from any experience to take appropriate action to further improve the system (e.g. through training, supervision…),
- Provision should exist in country legislation for health care workers to report AEFI.

2- Establishing collaboration between NRA and EPI for an effective vaccine safety surveillance system: Chile (Dr A. Saldaña) and China (Dr D. Dong)

The representative from the Institute of Public Health from Chile introduced her session by presenting some general information about the population size of the country and the health system. In Chile, the pharmacovigilance system was setup in 1995 but it is only in 2011 that reporting was made mandatory. It is not usual to see cross programmes collaboration but in the case of vaccines, they realized that it was critical to work with the Immunization Programme for the safety of vaccines. She then presented the Chile agenda with regard to vaccine pharmacovigilance with three main points: the need for enhancing the detection and reporting of Adverse Event Following Immunization (AEFIs), the monitoring and evaluation of the national AEFI surveillance system performance and the need to evaluate vaccine safety signal.
With regard to the level of AEFI reporting, to improve their system, they started working on activities such as designing the AEFI reporting form, writing AEFI guidelines, providing trainings to health care professionals (HCP) on safety of vaccines. All activities were done together with the Immunization Programme (IP). The result was immediate: the reporting rate jumped dramatically from 2009 to 2013.
With regard to the monitoring and evaluation of the performance of the national AEFI surveillance system, they first mapped the vaccine PV national stakeholders and created their AEFI review committee with the involvement of the IP and the NRA in its composition. Finally, to be able to evaluate vaccine safety signals, they work on qualitative and quantitative detection.
She concluded her presentation by stating that their progress in vaccine pharmacovigilance was due to the close collaboration they established with the Immunization Programme, taking into consideration technical and regulatory aspects and training healthcare professionals. How critical and effective is it to work in close collaboration with all vaccine safety stakeholders to encompass all aspects of vaccine safety to eventually address population needs, was the main message conveyed.

The representative from China introduced her session by providing an overview of the country vaccine PV system organized along two main pillars: the China CDC and the China FDA with a covering top down organizational structure from National, provincial, city and county levels. He then presented the legal framework with, at the basis, the National Guideline for AEFI Surveillance, with provisions for ADR reporting and monitoring, the regulations on administration of vaccine circulation and preventive vaccination, all this under the Drug Administration Law. He then presented the National Guideline for the Surveillance of AEFI in detail. The guideline was issued in 2010, it contains paragraphs on definitions, reporting, investigation, assessment, communication, responsibilities, etc. The various stakeholders responsibilities are clearer and the focus is given to the sharing of information between NRA and EPI. Procedures with regard to reporting, investigation and diagnosis, identification, information feedback, information sharing and communication, technical support and organization and cooperation are more explicit. The reporting system is uniform for vaccines and is shared between CDC and ADR at all levels.
The outcomes of the effort is the dramatic increase in AEFI reporting that climbed from 1932 to 137414 reports from 2005 to 2013 from approximately 98% of the counties.
To further strengthen their vaccine pharmacovigilance system, Chinese regulators and immunization programme authorities:

- hold regular monthly meetings with participants from various institutions involved in vaccine safety to discuss the surveillance of AEFIs, vaccine safety issues and others topics,
- prepare in close collaboration for NRA assessments,
- perform vaccine safety evaluation (i.e. JE vaccine) in collaboration with NRA, EPI, WHO and the manufacturers,
- are trained jointly on causality assessment of AEFI, signal detection and PSUR,
- perform joint sites visits with manufacturers.

In summary, the Chinese AEFI surveillance system involves different agencies at four different levels, therefore collaboration and harmonization is key for success. The National Guideline for AEFI surveillance is the basis of their work. Good progresses have been achieved but more still need to be done particularly in provinces with weak AEFI reporting, as well as in terms of risk management.

Main discussion points:

- Importance for NRA and EPI to jointly develop national AEFI surveillance guidelines to ensure ownership,
- Regular meetings for information exchange, as well as joined activities (training, data review…) are success factors for efficient collaboration.

3- Monitoring the safety of newly introduced vaccines : the HPV vaccine in Brazil (Dr S. Deotti) and Argentina (Dr N. Katz)

The Brazilian representative from the Ministry of Health introduced her session by presenting the country administrative division and population and the MOH organogram. She then presented a list of criteria, tools and strategies used in preparing the HPV vaccine introduction. She then described the overall AEFI surveillance system followed by data on AEFI after the first dose administered. Of a total number of close to 4 600 000 administered, 1007 cases were non serious AEFI, 29 AEFI were reported as serious, 94 were classified as

immunization error-related reaction and 33 unclassifiable. Furthermore, causality assessment classification showed that 553 cases were classified as vaccine product related reactions as showed in the literature, 464 were classified as immunization anxiety related reaction, 15 were classified as indeterminate and 3 were classified as coincidental.
After the second dose, 106 non serious AEFI were reported and 21 serious (18 immunization anxiety related reaction and 3 ongoing investigation). However, the serious AEFI triggered a vaccine safety crisis in Brazil to what Health authorities were not prepared to respond. To overcome the crisis, health authorities had to put in place a series of actions to re-assure the population about the safety of the vaccine though MOH site visits from the public, interviews with MOH representatives and scientific societies on TV, radio, newspapers, social media, telephone calls, medical assistance to vaccines, manufacturers sending letters to doctors and other health professionals.
The presenter concluded that to achieve high vaccination coverage and maintain confidence, the dissemination of reliable information to parents and the public is critical, that misperception on issues related to vaccine safety needed to be timely addressed, that AEFI needed to be continuously monitored and that teenagers needed to adhere to the subsequent doses (especially the 3rd dose given the long period between the 1st and 3rd dose).

The representative from Argentina shared their experience by presenting the country profile and the different actors and component of the AEFI surveillance system, the national immunization schedule and how it has evolved since 2003, the rationale for the HPV introduction by describing the burden of cervical cancer in the country. The vaccine safety monitoring was focused around 3 main strategies which are: to ensure the quality of vaccines, the safe injection practice and the passive surveillance system. The reporting was organized as follows: at local level they were detecting cases, investigating and monitoring and classifying cases, and at central level, they were in charge of the investigation & additional follow-up, and decision making and recommendations with the support of their AEFI review committee. The committee was established by the ministerial resolution n°259/13 and its goals were described as providing technical advice to the MOH relating to vaccines safety and technical and scientific support in the analysis and serious cases closure rumours or clusters. The committee is composed with representatives from the EPI (ProNaCEI), the regulatory authorities (ANMAT), PAHO, Paediatrics' and Infectious diseases societies; and experts from other specialties. The EPI and NRA reporting forms were put together to create a unique AEFI reporting form and data were transmitted to a unique NRA-EPI database. This improved AEFI passive surveillance system resulted in an increased notification and improvement in the quality of data. The public and private sectors vaccines were notified and more reports of recently introduced vaccines were sent to the database allowing a detailed AEFI analysis. This enhanced reporting provided the Argentinian health authorities with the capacity for action and decisions.

<u>Main discussion points:</u>

- Challenges of establishing background rates of potential AEFI and how they are diagnosed and managed in communities, challenges with regard to the public and HCW perception of disease and vaccine; and the community attitude to vaccines,
- Highlight the fact that communication is critical in case of vaccine safety crisis and health authorities should identify a spoken person prior programme implementation, who could deal with communication aspects in a timely manner,
- Vaccine safety crisis communication should not only target communities but also clinicians.

Session 2: regional initiatives

During this session, representatives from all WHO regional office presented their programme of work around the GVSI Blueprint objectives.

Building vaccine pharmacovigilance system in resources limited settings in Africa - Dr D. Akanmori

The WHO AFRO region comprises 47 sub-Saharan countries. A significant number of countries are progressively introducing new vaccines in their national immunization programmes comprising pneumococcal conjugate vaccine, rotavirus vaccine, meningitis conjugate vaccine and HPV vaccine. Measles vaccine is being replaced by Measles-Rubella vaccine, and inactivated polio vaccine is being deployed as part of the Polio End game strategy. New vaccines against protozoan parasites are in the pipeline and the RTS,S malaria vaccine is in phase 3 clinical trial in 7 countries of the region, which if licensed and prequalified could be added to the list of vaccines introduced.
Research and development efforts are intense in the region, where there is the highest burden of infectious life threatening diseases such as malaria, HIV, TB, and now Ebola.
Vaccine safety and pharmacovigilance has therefore assumed more significance in the WHO AFR. However, despite the conduct of several workshops and trainings, and the technical and financial support provided, there is still no palpable improvement in AEFI surveillance, reporting and pharmacovigilance in general in the region.
A review of live births and AEFI cases distribution by WHO region show that although AFRO region contribute to 24 % of live births, it does contribute to only 1% of the total AEFI reported globally. The institutional capacities are weak in most of the 47 countries, due to several challenges running from limited resources, competing priorities, framework inadequacy, lack of inter-sectoral collaboration, communication and information sharing.
Using the GVS Blueprint as a framework, WHO has recently supported eight Anglophone countries (Ethiopia, Ghana, Kenya, Malawi, Nigeria, Tanzania, Uganda, Zambia) and 7 francophone countries (Burundi, Côte d'Ivoire, Cameroun, Democratic Republic of the Congo, Guinea, Togo) to develop work plans for vaccine safety and pharmacovigilance for 2014 and 2015. These plans were developed in consultation with all stakeholders, WHO and partners in each country. The activities are defined, with timelines, defined roles and responsibilities and clear monitoring and evaluation plans.
The countries have started implementation of their plans. This includes establishment or training of national expert committees, establishment of mechanisms for collaboration between stakeholders, collection, analysis and reporting of AEFIs. Evaluation of the status of implementation and support where required is ongoing through teleconferences and email exchanges.

<u>Main discussion points:</u>

- The current crisis due to the Ebola outbreak might impact the whole process by diverting resources and attention,

- A lot more needs to be done. With limited national resources the continuous engagement of all key partners is essential as well as collaboration across programmes (vaccines and medicines),
- Slow progress are being made in intersectoral collaboration and efforts in this regard need to be sustained.

Vaccine safety events: managing the communication response EURO guideline – Dr O. Polishchuk

Vaccines are some of the most efficient public-health tools for promoting individual health and reducing the burden of infectious disease. Yet, vaccine safety receives more public scrutiny than vaccine efficacy. Because there is no visible effect when a vaccine works properly, it is easy to forget or disregard its benefits, instead focusing on the extremely rare adverse events associated with it.
Affirming immunization benefit is not as easy as it was a decade ago in an environment of heightened mass media interest, and where communication technologies ease the dissemination of information, whether correct and incorrect. Increasingly programme managers are being asked to respond to communication issues. A recent WHO EURO guideline: http://www.who.int/vaccine_safety/initiative/communication/en/. This Guide provides informative strategies and tools to support effective communication planning and management in response to vaccine safety events. It is accompanied by a Quick Guide and is designed to be used by immunization programme managers and partners.
Employing strong communication principles and strategies is not a substitute for evidence-based risk analysis. This document should be used as a companion to WHO guidance for Managing risks associated with vaccine safety.
Because each country is different, it is suggested that countries adapt this information for local context and develop their own national Vaccine-Related Events (VRE) communication plan or manual.
This manual focuses solely on communication strategies for VREs. It does not address other crisis situations (such as a public health emergency or international concern).

Main discussion points:

- It was suggested to involve the media in the preparation for new vaccine introduction; it allows the media to get educated and to become a true partner communication with the public,
- Strong need to strengthen countries capacities to not only manage the communication response to vaccine safety events, but to maintain public confidence in vaccines. This is a global issue requiring attention in both developed and developing countries. Various research projects are ongoing and should be further pursued to study the various aspects and complexity of the issues faced and to best adapt to the evolving environment.

Establishing Multi-Country Collaboration for vaccine safety signal evaluation in PAHO – Mrs P. Bravo

Timely and effective evaluation of vaccine safety signals is essential and may prompt the conduct of epidemiological risk assessment studies involving countries where the vaccine is used. The need for large sample sizes to investigate hypotheses related to possible rare vaccine-related reactions call for a multi-country collaborative approach. In this context, the Global Vaccine Safety Initiative is establishing a global network of hospital-based sentinel sites for vaccine safety signal verification and hypothesis testing, the Global Vaccine Safety Multi-Country Collaboration project, sponsored by the US FDA.
15 hospitals from 7 countries from the PAHO region (Argentina, Chile, Colombia, Costa Rica, Honduras, Peru and Uruguay) were selected to participate based on their capacity in terms of catchment area, capacity in terms of database system availability, diagnosis coding system used (ICD-9 or ICD-10), access to relevant immunization records and capacity of linkage between hospitalization and immunization events.
Those institutions successfully completed a simulation exercise, allowing them to assess the resource needs for conducting vaccine safety signals studies, while allowing WHO/PAHO to assess their capacity to contribute complete and quality data. All sites are now preparing for a proof of concept collaborative study aiming to assess the feasibility, quality and potential for sustainability of an international hospital-based active surveillance system for the evaluation of vaccine safety. In this study, two well-established relationships between a vaccine and an adverse event following it will be measured in order to assess the capacity of participant sites and the collaborative network as a whole to verify these known associations. It will be used measles-containing vaccines and hospitalized thrombocytopenia (as recognized positive association) and measles-containing vaccines and aseptic meningitis (as recognized negative association).
The study is being conducted with the support of an international group of experts and the Erasmus University Medical Centre (The Netherlands) is in charge of data management and data analysis. The data collection is scheduled for the first trimester 2015. This project provides opportunity for participating countries to enhance their research and data analysis skills, that is being seen as highly beneficial in the context of new vaccines introduction, where active surveillance study are being envisaged.

Main discussion points:

- The limitation of relying on the ICD coding for discharge diagnosis was discussed: it is often used improperly to justify additional funding for the hospital. It is therefore critical to confirm cases by a review of patient medical records,
- While countries are implementing electronic health data record and electronic immunization record system, particular attention should be given to allow data linkage between those various electronic health data record for optimal use.

Regional strengthening causality assessment of adverse events following immunization: lessons from inter-country workshop in SEARO
Mr S. Guichard

Serious or unexpected adverse events following immunization (AEFI) can raise concerns about the safety of vaccines for local health workers, communities and families leading to an undermining of public confidence in a country immunization programme. As vaccine adverse

events differ by age group, population health status, concurrent illnesses, programme delivery as well as by specific vaccine and/or combination and manufacturer, every country needs to have good AEFI surveillance systems and review causality assessment of AEFIs as part of their vaccine pharmacovigilance programme. To address this need in the South East Asia Region (SEAR), the WHO Regional Office in 2003 established a Global Training Network Centre in Colombo, Sri Lanka, to provide training on AEFI monitoring to SEAR Member States and to other WHO regions. Initially, the course focused on AEFI due to programmatic errors and systems for early detection of serious AEFI cases and their management. By 2005, with strengthened National Regulatory Authority (NRA) capacity to regulate vaccines, the course was expanded to reach out to sub-national programme managers and immunization service providers. Since 2008, WHO SEARO has provided training support to NRA, National Immunization Programme and members of the national AEFI committee to strengthen capacity to detect, report, investigate and to carry out causality assessment for serious AEFI. For some member countries, SEAR also provides support for development of infrastructure and small scale pilot projects to test and validate procedures, skills needed for quality AEFI reporting and causality assessment. These combined efforts have led to a marked increase in AEFIs being reported in SEAR countries including serious AEFIs. However, the causes of the reported AEFIs have not always been well understood leading in some instances to local health care worker, public and/or political concerns about vaccine safety that have caused disruptions in routine immunization program in many countries. To help address this AEFI potential for loss of public confidence in vaccines, SEAR countries have expanded the expertise on their national AEFI causality assessment committees.

Recognizing that most of countries in the regions acquire their vaccines from the same manufacturers and acknowledging that AEFI causality assessment is an important need for LMIC and that a lack of formal opportunities exist for countries to share experiences and concerns about AEFI surveillance and causality assessment, SEAR organized an intercountry workshop in February 2014. The main objective was to enhance regional capacity to evaluate investigated AEFI and carry out causality assessment of serious AEFI previously assessed by country committees. Use of harmonized terminology, standardized of AEFI investigation processes and causality assessment by countries would promote data aggregation from several countries for signal detection as many of the countries use vaccines from regional manufacturers.

Participants determined a range of AEFI and causality assessment needs in SEAR such as adapting WHO AEFI causality assessment algorithm, CIOMS and Brighton definitions, WHO verbal autopsy to fit context, to requesting a practical guide -AEFI definition, time interval, rates AEFI different vaccines and evidence for vaccine related causes of death under 24 hours.

<u>Main discussion points:</u>

- Inter-country regional workshops on AEFI and causality to share country experiences and concerns, grow skills and help deal with difficult AEFI,
- Importance to consider LMIC resources and training when developing AEFI guidelines, algorithms and definitions to make sure it is applicable in LMIC settings.

Needs and opportunities in evaluating national AEFI surveillance system: learning from WPRO experience – Dr A. Amarasinghe

In an effort of continuous AEFI surveillance system improvement, there is a need in providing countries with tools to facilitate the objective assessment of their vaccine pharmacovigilance system and its performance, to identify areas to be strengthened through and develop a work plan accordingly.
The WHO Western Pacific Regional Office pilot tested a combined WHO NRA assessment tool and country specific tool in this regard.
The combined tool defines the key components of the system, and provides main indicators to measure their status. These indicators were measured through data collection at the relevant level of the health system (national, regional, provincial and health facility level), through questionnaires, record review, in-depth interview, and observation of practice.
All stakeholder (immunization programme, national regulatory authorities, national pharmacovigilance centre) were involved in the assessment, giving them an opportunity to gain knowledge on the requirement and experience in such review.
The combined tool allowed a thorough review of a country system performance , enabling the country to develop very detailed work plan to address weaknesses identified, that may vary from upon regions, provinces and health facilities.

Main discussion points

- Although full involvement of national stakeholders is critical in assessing an AEFI system, external experts should lead the review team for an independent review. WHO maintains a roster of experts that could support such assessment,
- Some AEFI due to programmatic errors are being linked to bad management of the cold chain. Including an assessment of the cold chain system in AEFI surveillance review was judged appropriate,
- Importance to adopt an holistic approach when assessing pharmacovigilance system, to include both medicine and vaccines; an international consultation is ongoing to revise the WHO NRA assessment tool accordingly.

DAY 2 – MEETING CHAIR: DR STEN OLSSON

Preparing for deployment of experimental Ebola virus vaccine
Dr P. Zuber

Dr Patrick Zuber from WHO Safety and vigilance team discussed the epidemiology of the 2014 Ebola outbreak in Liberia, Sierra Leone and Guinea. He outlined the steps undertaken for its containment: The experimental vaccines under consideration for development, testing, licensure and use were discussed. The vaccines under consideration are based on protection in non-human primates, the cAd3-ZEBOV from GSK and rVSV-ZEBOV from NewLink. Both vaccines have been successfully tested in macaque monkeys. However, there are indications that after 6 months the protection decreases. The phase 1 trials (in humans) in USA, UK, Mali, Gambia and Switzerland for cAd3-ZEBOV and the phase 1 trials in USA, Germany, Kenya and Switzerland for rVSV-ZEBOV and the plans for phase 2 for both vaccines were discussed.

Main discussion points

- Conducting placebo controlled vaccine trials with limited doses of vaccines of unknown efficacy is difficult. Such trials could be proposed to be conducted on health care workers in high risk areas and the success measured by the new vaccines offering them protection,
- The GVSI discussed the need for specific committees to address ethical aspects on vaccine deployment and use, public and private access to the safety and efficacy data from the trial sites, the need for closer collaboration between all partners, sharing of the studies findings, the need for each site to have their data monitoring boards. Also discussed were the process of licensing and producing go in parallel.

Substandard, spurious, falsely labelled, falsified, counterfeit (SSFFC) medical products: WHO global surveillance and monitoring project
Mr M. Deats

Michael Deats discussed the WHO Global reporting system on SSFFC Medical Products including the rationale to protect public health and the prime objective to reduce the harm caused to Public Health by SSFFC medical products. Reporting is indicated for medical products that are suspected or confirmed to be falsified or counterfeit, or to have caused unexpected adverse reactions, including a lack of efficacy or genuine medical products that are suspected or confirmed to be intentionally manufactured in non-compliance with National standards and Medical products which are confirmed as diverted. To date, 230 Regulatory personnel from 80 Member States have been trained in 8 workshops. To date, 18 large procurement agencies have been trained and over 400 Suspect Products Reported.
The WHO has devised a multipronged approach for the prevention, detection and response to SSFFCs. There are standard reporting forms and a database for reporting to.
Falsified vaccines have been reported from Nigeria, Cameroon, China, Portugal and Philippines. More than half reports of SSFFC products are from the EURO and AFRO regions (erectile dysfunction drugs and antimalarials). Most reports have been life threatening or have resulted in death. 55% have been classified as falsified and 25% suspected as

falsified. The vulnerabilities to reporting SSFFCs include unregulated supply chains, difficult access to quality and safe products and lack of effective laws and criminal justice system.

Main discussion points

- Need to integrate the work done by several organizations encouraging a Regional approach identifying what drives the demand to identify gaps and vulnerabilities,
- WHO focuses on identifying the problem rather than policing; some countries like China have played an important and supportive role,
- Monitoring SSFFCs faces challenges through offshore companies, free trade zones and spurious bank accounts,
- Products that don't maintain standards are delisted as per the WHO prequalification programme.
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Session 3: stakeholders' perspective and projects

The Brighton Collaboration viral vector vaccine safety working group
Dr B. Chen

The Brighton Collaboration Viral Vector Vaccines Safety Working Group (V3SWG) was formed to maximize transparency, comparability of key info, and public acceptance of new vaccines in 2008 at encouragement of WHO HIV Vaccine Advisory Committee and the WHO Initiative for Vaccines Research. It aims to standardize the collection, analysis and dissemination of safety data regarding viral vector vaccines in both pre– and post-licensure settings.

The group has identified subjects of critical importance needing further investigation such as additions to the report of the WHO informal consultation on characterization and quality aspect of vaccines based on live viral vectors, Geneva, Dec 4 - 5, 2003; proposing variables that could Influence Recombination Between a Vectored Vaccine and Circulating Wild Type Virus Minimizing Viral Vector Recombination; Sample Archiving for Potential Adventitious Agent Contamination of Vaccines and assessment of Transmissibility of Viral Vector Vaccines. The group communicates and works through email, monthly one-hour conference calls, and secure Brighton Collaboration web platform. The secretariat is at the US CDC.

The major activities of the Brighton Collaboration Viral Vector Vaccines Safety Working Group currently include developing a standardized template describing the key characteristics of a novel viral vaccine vector. This facilitates discourse among key stakeholders by increasing the transparency and comparability of information. Gaps in data are inevitable but can help prioritize future research. The group also adapted an internal tool developed by the International AIDS Vaccine Initiative (IAVI). It is hoped that all developers/researchers of viral vector vaccines, especially those entering human trials in near future, will complete and submit to V3SWG and BC for peer review, publication and will hopefully be maintained "wiki-" style on BC website by vector-specific researchers. Vaccine safety stakeholders (e.g. NRA, EPI, GAVI), may wish to encourage the use of tools developed by the Brighton Collaboration Viral Vector Vaccines Safety Working Group.

Promoting collaboration and information exchange between NRA, EPI, vaccine manufacturers and multilateral agencies: the CIOMS working group on vaccine safety plan and progress – Ms K. Holm

CIOMS is an international, independent, non-governmental organization jointly created in 1949 by WHO and UNESCO. The membership of CIOMS includes 50 international, national and associate member organizations, representing many of the biomedical disciplines, national academies of sciences and medical research councils. The main objective of CIOMS is to facilitate and promote international activities in the field of biomedical sciences with the benefit of the input of all relevant stakeholders.
Through a Working Group mechanism, CIOMS produces and publishes consensus documents and reports primarily on bioethics and drug safety as recommendations and guidelines that will be useful to many stakeholders and which other groups may voluntarily incorporate or endorse.
In line with the objective 8 of the GVSI Blueprint project, CIOMS proposes collaborating mechanisms between the public and private sectors to put in place systems for appropriate interaction between national governments, multilateral agencies, and manufacturers at national, regional and international levels, and to develop and endorse guidance documents on harmonized tools and methods for the conduct of vaccine pharmacovigilance between stakeholders. A balance of experts in vaccines is ensured by representatives between regulatory, public health, academia, WHO including collaborating centres and industry, from both high-income, emerging markets, and low- and middle-income countries. There is also a mix of geographic regions of the world and gender.
Currently CIOMS is working on developing tools and methods when "rollout" for a newly-introduced vaccine occurs in country with limited regulatory capacities immediately after licensure occurs. The focus will be to implement a successful "launch triangle" that includes baseline safety information, surveillance programs and crisis response.

Revised vaccine pharmacovigilance guidance in the EU, including new evidence-based communication advice – Dr P. Bahri

Since 2012 the new EU pharmacovigilance guidance has replaced "Volume 9A" for implementing revised legislation strengthening pharmacovigilance. The Module I focuses on pharmacovigilance system and its quality systems. There are 14 further Modules for processes and the Annex I on definitions.
Good pharmacovigilance practices in the EU (EU GVP) - Product and population-specific considerations include Part I Vaccines for prophylaxis against infectious diseases which consist of 3 sub-parts: Part A on Introduction to GVP, Part B on Structures and Processes, and Part C on Operation of the EU network; P.II. Biological medicinal products (for which drafting is ongoing); P.III. Medicines used by pregnant women and P.IV. Medicines used by older patients.
P.I. focuses on Vaccines for prophylaxis against infectious diseases. It addresses issues related to antigen, the adjuvant, impurities, contaminants and the vaccine as a whole, and to interactions of the vaccine components and also Pharmacovigilance Plan and Signal management.
The safety communication aspects addressed include an integrated approach, addressing specific target groups, keeping the principles of Transparency and understandability. The idea is to have clarity on the objectives, contents and concepts so as to advise health care professionals, have a clear communications plan, a collaborative approach, and a

standardized approach to the media. This would ensure evidence-based guidance for risk communication. The "Proof of concept" was demonstrated using the example of influenza pandemic vaccines.
The next steps envisaged by the EMA include communication guidance for biologicals, medicines used in pregnancy, geriatrics, paediatrics etc. and developing a GVP Module XII on continuous pharmacovigilance and Research advocacy.

Main points of discussion

- The EMA guidelines focuses mainly on drugs and will be available only in English. There is no intention of translation. However, for questions asked the response is provided in the same language,
- Challenges are faced addressing incidents reported in the media and therefore media sensitization prior to new vaccine introduction is important. The GVP can be easily downloaded and can be incorporated and acknowledged where needed.

GAVI, the Vaccine Alliance: an approach to support vaccine safety
Mr J. Pearman

The partnership consists of WHO, UNICEF, World Bank, Pharmaceutical industry, civil society, research institutes, implementing countries and a large number of heterogeneous donors. GAVI vaccination programmes include vaccines for MR, HPV, meningitis A, pneumococcus, rotavirus, measles, pentavalent, Hib, yellow fever and hepatitis B. GAVI has recently been involved in the procurement of the inactivated polio, japanese encephalitis and typhoid conjugate vaccines. Of the 73 countries supported by GAVI, about 326 new vaccine will have been introduced in national programmes in 2015; this is expected to go up to 479 introductions by 2020.
The experiences and milestones for pentavalent vaccine introduction was discussed. The number of countries that introduced the vaccine exceeded the target in 2012 and 2014 with achievements of 101% and 106% respectively; however the coverage fell short by 16% because of the need for better achievement in India and Indonesia. GAVI started supporting pentavalent vaccine in 2000 in Kenya and Gambia – but vaccine supply was limited. 7 countries introduced the vaccine by 2001, but supply limitations & other challenges resulted in slow rate of introductions. Initially there was a single supplier of the vaccine, however after the WHO and SAGE recommendations and other manufacturers such as Crucell, Shantha Biotech and Panacea entered the market with their own pentavalent vaccines. This resulted in better vaccine availability and higher coverage. After 2011, with the entry of 4 more suppliers, the vaccine prices dropped considerably. Currently 200-250m doses are supplied for vaccine costs of nearly US$ 0.5b. GAVI cash outflow projections has progressively increased from US$ 160 million from 2001 to 2005, to US$ 640 million from 2006 to 2010, to US$ 1,200 million from 2011 to 2015 and to US$ 1,800 million from 2016 to 2020.
GAVI has observed that the absolute numbers of AEFI has been increasing with new vaccine introduction combined with increase in number of doses of vaccines administered. AEFI reporting rates vary in different WHO regions with the lowest rates reported from AFRO and SEARO. Temporary suspension of immunization due to safety concerns have occasionally disrupted introduction efforts. This is being addressed with better collaboration between the various stakeholders and recent ep.

Main discussion points

- Market dynamics determine the prices. Usually when competition sets in prices drop.
- GAVI supports countries through their health system strengthening work plans in which vaccine safety can be included; however it has been observed that about 25% of allotted funds are not utilized. It was clarified that WHO has the mandate for monitoring the safety of the new vaccines and other products that have been developed and have been prequalified. It was noted that several GAVI countries are graduating. Financial support has been helpful in improving their performance. The future strategy continues to be discussed within GAVI. Gradual decline in support is possible but is to be finalized. There will not be a significant policy change currently and some flexibility is being proposed. The US CDC has actively supported new vaccine introduction particularly related to guiding policy decisions and supporting decisions made by the national committees.

Vaccine manufacturers perspective

1 – Janssen - Dr M. Wang

Dr Min Wang, the Global Medical Safety Officer, Infectious Diseases & Vaccines TA, Global Medical Safety presented on behalf of Janssen. It was emphasized that real time communication in reporting of AEFI is a key element in the surveillance programme. This has to be coordinated by all parties involved including the local users (vaccine programmes or HCPs, Vaccinees, Parents), local health authorities, vaccine manufacturers and funding agencies.
The information about AEFI need to be as comprehensive as possible, this includes details from vaccine manufacturer (batch number), clinical signs and symptoms including final diagnosis, event onset relative to date of vaccination, event outcome and patient medical history (including concomitant disease(s)).
The value of manufacturer information in reporting AEFI include further assessment the safety of marketed products based on the post market surveillance (PMS) data including regulatory agencies regulation and industries compliance. The biggest drawback when manufacturer information missing includes multiple reporting for the same case resulting in case duplication in the health authority databases and/or global databases thereby introducing bias and/or error when conducting epidemiologic study and safety signal detection.

2 - Sanofi Pasteur - Dr A. Abou-Ali

Dr Adel Abou-Ali, the Deputy Director of Global Pharmacoepidemiology & Risk Management Global Pharmacovigilance, presented the views of Sanofi Pasteur. The vaccine safety blueprint is the basis for providing support to the countries by the manufactures. This is done through epidemiological studies to assess potential causal relationships and pooling information from multiple countries by standardizing data collection procedures and methodologies. The manufacturers are bound by local
laws, such as the federal and state/provincial regulations. There are also differing laws globally
privacy acts that manufacturers have to adhere to.

3 - Razi Vaccine and Serum Institute - Dr M. Noofeli

Dr Mojtaba Noofeli, Director of Human Vaccines Production & Research presented on behalf of the Razi Vaccine & Serum Research Institute (RVSRI). The RVSRI recommended that countries should develop new pharmacovigilance systems to ensure that regulations are effective. Governments can completely revise their pharmacovigilance legislation to make it convergent with that of stringent regulatory authorities and also consistent with the regional harmonization guidelines within the specific region and other international guidance. Regional harmonization initiatives should include strengthening collaboration and information sharing about product safety and security of the supply chain by ensuring active participation of all countries in the region. Governments should create a single pharmacovigilance centre that can integrate adverse events reporting for all health products and consolidate post-marketing surveillance departments. Governments should consider reviewing resource allocations for regulatory activities and identify an evidence-based approach for allocating adequate resources for post-marketing surveillance activities. Governments should adopt international reporting standards and explore opportunities to use new information technology for improving adverse events reporting.
Governments should be supported to improve their regulatory systems and enforcement capabilities for responding to fake products. Governments should encourage routine documentation of the reasons for treatment switches in the patient's case file. Governments should explore opportunities for establishing sentinel sites for active surveillance. Donors of medicines or vaccines and health technologies should require their programmes to conduct spontaneous reporting, active surveillance, and risk management, particularly for newer medicine, vaccines and medical products.
Governments should expand training on pharmacovigilance to enable health workers to appreciate the contributions of adverse events reporting in safeguarding patients and improving treatment outcomes. The current adverse events reporting system is burdensome for the busy clinicians and the system does not motivate the reporter. Governments should consult with stakeholders in open forums to discuss the best approaches for improving adverse events reporting at the level of the health worker, facility, private pharmacy, consumer and pharmaceutical industry. In the absence of adequate legislation and enforcement in developing countries, the pharmaceutical industry should perform due diligence and have product stewardship to meet safety monitoring requirements locally as they do in better regulated markets. Civil society should motivate their members' interest in pharmacovigilance as part of its role as watchdog for good governance in the pharmaceutical sector.

Session 4: fostering collaboration between national pharmacovigilance centres and public health programmes

WHO safety and vigilance unit: structure, vision, mission and strategy Dr C. Ondari

Dr Clive Ondari introduced the WHO reform and perspectives for Medicines Regulation, and described the primary function of WHO to act as the directing and coordinating authority on international health work emphasizing the role to assist member states in strengthening health services upon request. The WHO reform covers three main areas namely Programmatic reform (that focuses on leadership priorities, specifically in the area of increasing access to essential, quality and affordable medical products including vaccines); Governance reform (to strengthen oversight and engagement with partners and stakeholders and better align

actions to promote health and wellbeing) and Management reform (to build an organization that is more effective, efficient, responsive, objective, transparent and accountable).
The new organizational structure under Essential medicines and health products department (EMP) brought together three teams, Medicines, Vaccines and Substandard/Spurious/Falsely-labelled/Falsified/Counterfeit (SSFFC) under one umbrella of Safety and Vigilance (SAV). This has been done to synchronize, coordinate and develop policies, norms, standards, and methods for vigilance, post market surveillance and safe use. This process supports countries to adapt and implement policies, norms and standards, build global capacity especially through NRA strengthening activities, promote contribution to and effective use of the global safety data base, facilitate exchange of information and global learning. It also promotes new approaches, collaborates on vigilance activities with public health programmes, responds to safety concerns and crises of international importance and encourages systematic and structured reporting.
Inter-linkages are being identified and encouraged between the three teams.
The need to use opportunities for harmonization between the different international platforms such as ICDRA, the Annual Meeting of National Pharmacovigilance Centres, the Advisory Committee on Safety of Medicinal Products (ACSoMP) and the International Working Group on Drug Statistics Methodology for the Medicines; the GACVS, the Global Vaccine Safety Initiative, the GVSI General Meeting and the GVSI Planning Group 3 meetings; and the SSFFC Member State Mechanism, the WHA and the Global network of focal points for SSFFC were emphasized.
A short-medium-term and a long-term SAV strategy were also described. The former includes advocating the PV strategy using WHA/ICDDRA as platforms to engage with the governments at the highest level, developing partnerships by engaging WHO CCs and other partners to build and strengthen safety surveillance, developing minimum infrastructure, active surveillance systems, building capacity and developing effective monitoring tools and systems. The latter focuses on strengthening basic surveillance, implementing active surveillance, developing additional areas of focus (patients, MEs, SSFFC), strengthening regulatory oversight, develop additional data management tools and improving directed market surveillance.

WHO programme for international drug monitoring: a framework for collaboration - Dr S. Pal

Established in 1968 in response to the thalidomide disaster, the WHO Programme for International Drug Monitoring (PIDM) provides a forum for WHO Member States to collaborate in the monitoring of drug safety, and notably, the identification and analysis of new adverse reaction signals from data submitted to the WHO global individual case safety report (ICSR) database by member countries. The programme consists of a three-part network:

- National pharmacovigilance centres from WHO member countries are responsible for case reports sent to the WHO ICSR database (managed by the Uppsala Monitoring Center (UMC) in Sweden),
- UMC oversees the WHO programme operations, including:
    - Collecting, assessing and communicating information from member countries about the benefits, harm, effectiveness and risks of drugs,
    - Collaborating with member countries in the development and practice of pharmacovigilance,

    - Alerting NRAs of member countries about potential drug safety problems via the WHO signal process.
- WHO headquarters in Geneva, Switzerland is responsible for policy issues and strategic framework; develops appropriate standards and guidelines, with a focus on LMIC; promotes exchange of safety & regulatory information; establishes and coordinates the work of relevant WHO Collaborating Centres; provides a global platform for PV Centres and Public Health Programmes to meet and discuss PV issues.

As of October 2014, 148 countries had joined the programme. WHO collaborating centers are key partners: WHO Collaborating Centre (CC) for Drug Statistics Methodology, Oslo, Norway ; WHO CC for Advocacy & Training in Pharmacovigilance, Ghana ; WHO CC Rabat, Morocco; WHO CC for PV in Education and Patient Reporting, the Netherlands.
The WHO Advisory Committee on Safety of Medicinal Products (ACSoMP) was established in 2003 to provide advice to WHO, including its Collaborating Centre for International Drug Monitoring (the UMC), and through it to the Member States of WHO, on safety issues relating to medicinal products. It guides WHO on general and specific issues related to Pharmacovigilance (PV). The Committee is composed of 12 members drawn from the WHO Expert Advisory Panels for Drug Evaluation and for Drug Policies and Management and, where appropriate, in consultation with other relevant WHO clusters and expert advisory panels. ACSoMP meets once a year to discuss ongoing and new PV topics, with particular focus on issues related to public health programmes.
Other partners include WHO Regions and Country offices, Public Health Programmes(HIV, TB, Malaria, NTDs, Vaccines..); National Experts & Consultants; Global Health Initiatives (Global Fund, USAID, BMGF…); CIOMS, IFPMA, ICH, DIA, ISOP…
Annually, the WHO PIDM organizes the National Pharmacovigilance Centre meeting providing an important and exclusive platform to all national Pharmacovigilance (PV) centres to discuss topics of current interest.

A collaborative approach for monitoring vaccine safety: the Global Vaccine Safety Initiative - Dr P. Zuber

Ensuring the safest use of vaccines should be the standard for all immunization programmes. Numerous examples illustrate how vaccine safety issues can derail immunization programmes:
In addition to those time limited vaccine safety incidents, we have to address the true vaccine reactions that can only be minimized. Program errors, sometimes fatal are usually reported through AEFI surveillance systems or through the media. Cases of anaphylactic reactions, although very rare are spectacular and occasionally fatal if not properly managed. Vaccine associated paralytic poliomyelitis remains the price to pay for completing the eradication of polio and we have recently learned that disseminated BCG disease was a frequent complication in HIV infected infants, leading to complex programmatic decisions for the prevention of paediatric tuberculosis in countries with high prevalence of HIV.
Finally, we also have to deal with rumours and unfounded allegations that can be extremely detrimental.
In 1974 in the United Kingdom, the mass media became involved in the safety of vaccines when a case series of neurological events, which had occurred after DTP vaccination was made core material for a television documentary. This and the public debate that followed undermined profoundly the public confidence in pertussis vaccines, leading to a decreased

immunization coverage and a subsequent increase in the number of pertussis cases, in particular among very young infants where the disease is the most severe.
The example of poliomyelitis vaccine in Nigeria is another notable example. In 2003, some religious leaders in the North of the country advised against vaccination with oral poliovirus vaccine (OPV) because of alleged issues of quality with the vaccines used for the mass campaigns. This resulted in a suspension of immunization activities for a year, which led to a massive rebound in the number of poliomyelitis cases. Travellers from Nigeria re-introduced the disease to a dozen countries in Africa and even in Asia where poliomyelitis had previously been eliminated.
In addition to the general need for more and better pharmacovigilance, low- and middle-income countries increasingly use vaccine products that are different from those used in countries with well-functioning pharmacovigilance systems. Market segmentation is one reason, but an even more important phenomenon is the emergence of vaccines designed specifically for those parts of the world, like the meningitis A conjugate vaccine introduced in West Africa in 2011. In the next few years, we expect to see more use of vaccines against a number of important health problems such as malaria, dengue, Japanese encephalitis among others.
The Global Vaccine Safety Blueprint was designed as a framework to strengthen national vaccine safety system through collaborative support. The aim of the Blueprint is to enhance the safety of vaccines through effective use of pharmacovigilance principles and methods. Its three strategic goals are: to assist LMIC to have at least minimal capacity for vaccine safety activities; to enhance capacity for vaccine safety assessment in countries that introduce newly developed vaccines, that introduce vaccines in settings with novel characteristics, or that manufacture and use prequalified vaccines; and to establish a global support structure for vaccine safety.
The GVSI constitutes the implementation mechanism for the Blueprint, and the annual GVSI meeting serves as a forum for vaccine safety stakeholders. The initiative started in 2012, and progressively reach out to an extended number of participants.
To provide independent advice on vaccine-related safety issues, WHO established in 1999 the Global Advisory Committee on Vaccine safety (GACVS), with the aim of enabling WHO to respond promptly, efficiently, and with scientific rigour to vaccine safety issues of potential global importance. The Committee meets twice a year, and its reports are published in the WHO Weekly Epidemiological Record.
As a part of the Global Polio Eradication Initiative (GPEI), IPV is planned to be rapidly introduced into the routine immunization programmes of all member states by the end of 2015. This will be an enormous challenge as this has not been done before. Countries have been categorized based on their risk profiles. IPV will be administered with the 3rd dose of DTP as an additional dose along with OPV. The safety aspect of the addition of a "new" vaccine is to be carefully considered before introduction.
Increase attention to the safety of vaccines is a direct result of the successful implementation of global immunization programmes. More effective disease control strategies and new vaccine introductions require important improvements in vaccine safety practices. The GVSI is a WHO mechanism for structured efforts into enhancing vaccine safety globally. Efforts aimed at building vaccine safety capacity could ultimately be leveraged for the development of systemic and sustainable PV that should benefit all health products.

Main discussion points:

- Significant ADR reports related to traditional medicines are being received by UMC,
- Although WHO guidelines and standard are available to monitor the safety of traditional medicines, the regulation and pharmacovigilance of traditional medicines is lacking behind. It was recommended to tighten WHO support to countries around the regulation of traditional medicines,
- The access to the WHO global database Vigibase is currently limited to national pharmacovigilance, which create difficulties in some countries for vaccine safety focal point to contribute and access the data when the interaction with the national PV center at country level is not yet established. WHO is currently considering an open access to the Vigibase. Beyond the access, countries are requesting WHO to reconsider the WHO policy on access and contribution to Vigibase to open it to public health programmes that wish to contribute data.

Learning from country experiences

During this session, country delegates highlighted the importance of sharing safety information and expertise across various vigilance systems, and reported on their experiences in doing so in the USA, sharing new initiative from Morocco aiming to implement a global vigilance system, a one-stop shop for all vigilance information in the country, how Croatia has involved patients and the media as equal stakeholders in pharmacovigilance, the models and benefits around this concept, and how Uganda has integrated PV within HIV programme in the country.

1- USA - Dr S. Anderson

The Food and Drug Administration (FDA) is an agency within the U.S. Department of Health and Human Services. It consists of the Office of the Commissioner and four directorates overseeing the core functions of the agency: Medical Products and Tobacco, Foods and Veterinary Medicine, Global Regulatory Operations and Policy, and Operations. The Office of Medical Products and Tobacco provides high-level coordination and leadership across the centers for drug, biologics, medical devices, and tobacco products. The Center for biologics evaluation and research (CBER) is the center within FDA that regulates biological and related products including blood, vaccines, allergenics, tissues, and cellular and gene therapies for human use.

CBER's review of new biological products, and for new indications for already approved products, requires evaluating scientific and clinical data submitted by manufacturers to determine whether the product meets CBER's standards for approval. After a thorough assessment of the data, CBER makes a decision based on the risk-benefit for the intended population and the product's intended use. Although medical products are required to be safe, safety does not mean zero risk, since all medical products are associated with some level of risk, hence the need to conduct post-marketing surveillance. FDA can require the manufacturer to conduct post-marketing studies or clinical trials at time of approval or post approval should new safety information become available. In addition, passive and active surveillance programme are being run in collaboration between the FDA and the CDC.
The Vaccine Adverse Event Reporting System (VAERS) is a national vaccine safety surveillance programme co-sponsored by the Food and Drug Administration (FDA) and the Centers for Disease Control and Prevention (CDC). The purpose of VAERS is to detect

possible signals of adverse events associated with vaccines. VAERS collects and analyzes information from reports of adverse events (possible side effects) that occur after the administration of US licensed vaccines. Reports are submitted by patients, parents, health care providers, pharmacists and vaccine manufacturers.
Population based surveillance using databases containing health related information is also conducted by FDA with the post-licensure rapid immunization safety monitoring (PRISM) component of the mini-sentinel programme, and by the US CDC with the Vaccine Safety datalink.
So each product is being carefully monitored throughout its lifecycle with shared surveillance activities between FDA and CDC, and regular communication.

2- Morocco - Dr R. Soulaymani

The national pharmacovigilance center of Morocco is promoting the concept of global vigilance encompassing all "products or agents from human activities" (health products, consumable products and environmental exposure and agents). The centre has been mandated by the national health authorities to develop a one "stop-shop" reporting system targeting both health professionals and the general public, to report any safety issues resulting from the exposure to "products or agents from human activities". This integrated vigilance system aims to overcome the challenges faced in running multiple vertical vigilance systems while hampering the opportunity for cross-learning. It also builds on the commonalities of vigilance core activities that are not specific to a product nor to its use, and includes data collection and validation, data analysis and signal detection, risk assessment, alert generation, and intervention to reduce harm.
The national pharmacovigilance centre has been established in 1989, and has continuously developed its capacities to cover vigilance in all health programmes (communicable and non-communicable diseases), medications errors and patient safety, teratovigilance, phytovigilance, cosmetovigilance and materiovigilance. Over time the centre has developed its technical expertise while gaining the confidence and the credibility with health professionals, the media and the public.
To implement the integrated vigilance, the centre is working on the development of common terminologies, taxonomies and procedures, common reporting form, an integrated information system and tools for data management, and is developing appropriate training for the stakeholders.

3- Croatia - Dr V. Macolic Sarinic

Conducting a campaign and receiving extensive media coverage directly influence the rate of adverse drug reactions (ADR) reporting. This was one of the incentives for the Croatian Agency for Medicinal Products and Medical Devices (HALMED) to conduct a public education campaign, directed primarily to the patients and medicine users, promoting the importance of ADR reporting and the Patient Information Leaflet (PIL) reading.
The set of communication channels and mechanisms used was wide and closely adapted to the target group. During the first month of the campaign, billboards were set up by main roads and highways with easy to-remember messages promoting the importance of ADR reporting and PIL reading.
In addition, the advertisements were repeated at regular intervals in daily newspapers, as well as on selected radio stations, while on-line banners were placed on news portals and on several patient organizations' websites. The second part of the campaign included setting up

freestanding advertising pillars in pharmacies which contained information leaflets on how to report ADRs. Simultaneously, in many Croatian healthcare institutions, in waiting rooms of general practice, paediatric, dental and gynaecological offices in healthcare centres, posters inviting patients and medicine users to report ADRs were also set. In addition to encouraging an active patient approach to treatment and to monitoring the safe use of medicines, which brings a great number of benefits, the campaign also brought an increase in health professional reports and contributed to a more comprehensive media approach to issues related to medicinal products safety. The increased rate of patient ADR reporting has been sustained, demonstrating that the campaign succeeded in achieving a more permanent impact on ADR reporting in Croatia.
In the case of vaccines, after the issue around the pandemic flu vaccine, anti-vaccination campaign became more active in Croatia, and were largely relayed in the media. Patients started to report AEFI directly to the journalists rather than the public health agency, leading to more media coverage and loss in vaccine confidence.
Engaging the media and encouraging patients to report to the health authorities must be sustained to further contribute to Croatian patients obtaining a more active role in the healthcare system and in the treatment process, as well as in the monitoring of safe use of medicines.

4- Uganda - Ms H. Nassali

The pharmacovigilance centre has been established in 2005 in Uganda, and comprises 14 regional PV centres plus one national centre, all housed in referral hospitals. Those centres rely mainly on spontaneous reporting (SR) and experienced the usual challenges of under reporting (quality and quantity). The awareness on pharmacovigilance is low, the transfer of forms from the regional centres to the NPC is slow and the NPC could not determine the rates of reactions and effectively identify risk factors.
Targeted spontaneous reporting (TSR) focuses on capturing adverse drug reactions in a well-defined group of patients on treatment. Uganda initiated in collaboration with the national AIDS control programme, a TSR project focused on Tenofovir and renal toxicity. TSR was piloted in two regional pharmacovigilance centres, where patients on Tenofovir were recruited into ‘cohort’ and monitored by assessing renal function at each visit. Lessons were learnt from the pilot and factored into the roll-out activities to other centres.
As a result of this project, there has been a general increase in the ADR reporting rate affecting not only the tenofovir. The increase awareness of health professionals encouraged spontaneous reporting
The national PV centre not only carefully monitor the safety of the drug, but even advise the AIDS programme to use affordable method to monitor renal impairment of treated patients.
Increased awareness of pharmacovigilance among health professionals and patients, ultimately did contribute to an improvement in patients care.

Main discussion points

- To ensure sustainability of time-limited project, it was recommended to use as far as possible existing structures and tools (e.g. established Regional PhV centers, existing ADR reporting form, existing reporting guideline, ADR database…),
- Importance of demonstrating through such project the added value of collaboration between PHP and NPC, where the expertise varies and are often complementary.

5- India - Dr A. Ramkishan

Ministry of Health & Family Welfare, Government of India has initiated a nation-wide Pharmacovigilance
programme (PvPI) for protecting the health of the patients by assuring drug safety. The Indian Pharmacopeia Commission (IPC) is functioning as a National Coordinating Centre (NCC) and operates under the supervision of various Panels and Committees.
The AEFI Surveillance Programme was established in India in 1986 as a component of the Universal Immunization Programme and the first National AEFI Guidelines were issued in 2005. Field level AEFI reporting and investigation are supported by District and State AEFI committees and the National AEFI Committee established in 2008 provides technical policy and programme direction. Over the last years, the programme has been strengthen with the establishment of the Immunization Technical Support Unit (ITSU) of the Public Health Foundation of India (PHFI) under the Ministry of Health and Family Welfare. A national AEFI Secretariat has been established at ITSU. The National AEFI Committee has been reconstituted to include specialists from a broader range of expertise. Quarterly Causality Assessment meetings are being conducted to enable timely assessment of AEFI cases, explore safety signals and share findings with other vaccine pharmacovigilance stakeholders.
To increase AEFI detection and reporting health workers have been trained in 9 states on AEFI reporting and management.
A data sharing arrangement between the IPC and the ITSU-MoHFW AEFI Secretariat has been established for ensuring convergence in vaccine safety reports and their adequate investigation. This collaboration also resulted in an AEFI edition of the PvPI newsletter, the quarterly bulletin of the pharmacovigilance programme to augment AEFI reporting. Within the national regulatory authorities, there is a dedicated AEFI division in Central Drugs Standard Control Organization (CDSCO) responsible for collecting all the adverse events/SAE reported by the immunization division and IPC, as well as information submitted by manufacturers through PSUR, which are then reviewed by an expert committee constituted for this purpose for taking further regulatory action.
Communication guidelines for handling AEFIs have been developed, aimed at health workers to enable timely and appropriate response to a vaccine adverse event and undertake crisis management if required. To improve investigation of AEFI deaths, autopsy protocols and verbal autopsy protocols are being specifically developed to be a part of the revised National AEFI Guidelines.
A guidance document for Good PvPI practices is under finalization. It provides guidance to manufacturers to perform specific safety study throughout the product life cycle and it defines the roles and responsibilities of all the stakeholders namely CDSCO, IPC, Immunization Division, MAH, private and public practitioners and outlines the Risk Minimization Action Plan.
Monthly coordination meetings are being organized with key stakeholders in vaccine safety monitoring and training programme are being attended and/or organized collaboratively.

Conclusions

The meeting was the opportunity to display progress made in decentralizing vaccine pharmacovigilance capacity-building with presentations from countries demonstrating the build-up of AEFI monitoring, improved collaboration between immunization programme and regulatory authorities and examples of enhanced pharmacovigilance activities. Each regional

office also presented their own programme of work which reflects a greater autonomy around the Blueprint objectives. The participation of several pharmacovigilance centres with limited vaccine expertise provided an additional dimension to the discussions.