

Report of the 1st Meeting of the Global Vaccine Safety Initiative 20-21 November 2012 Hurghada, Egypt

The first Global Vaccine Safety meeting took place in Hurghada, Egypt on 21-22 November 2012. This general meeting guides the Global Vaccine Safety Initiative (GVSI), which is the implementation mechanism for the Global Vaccine Safety Blueprint.

During two days, EPI managers and national regulatory authorities pharmacovigilance staff from fifteen countries gathered with representatives from UN agencies, academic institutions, pharmaceutical companies umbrella organizations and funding agencies. Participants reported on initiatives relevant to the Blueprint objective, shared experiences to strengthen vaccine pharmacovigilance, and identified needs and opportunities for further development.

Meeting Objectives:

The overall objective of the meeting was for network 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.

Specific objectives were to:

- Report on national and global initiatives and experiences to strengthen vaccine pharmacovigilance.
- Identify needs and opportunities to support countries in implementing an effective vaccine pharmacovigilance system.
- Provide a platform to develop collaboration in support of GVSI.

Expected Outcomes:

- Needs and opportunities to support countries in implementing an effective vaccine pharmacovigilance system identified.
- Approach for collaboration between different stakeholders to support GVSI established.
- Recommendations developed to feed the GVSI planning group work plan.

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

*Meeting agenda and presentations are available on: <http://workspace.who.int/sites/gvsimeetings>
Login details: Username: ADS\gvsimeetings Password: hurghada2012*

DAY 1 - MEETING CHAIR: PROF. R. FERNANDOPULLE

Opening and introduction

Dr Patrick Zuber opened the meeting and welcomed participants. He presented the meeting objectives and enumerated the expected outcomes. This was followed by a presentation from Dr Christine Maure (WHO Secretariat) on the background, objectives and implementation of the Global Vaccine Safety Initiative followed by Professor Alex Doodoo (chair GVSI Planning Group) who gave an updated report on the work of the GVSI Planning Group. The session concluded by a presentation from Tom Bollyky on the work of the Bill and Melinda Gates Foundation (BMGF) Safety Surveillance Working Group (SSWG).

Synopsis of the presentations

- Blueprint development, vision, goals and endorsement by WHA in May 2012.
- GVSI work plan aligned with the Decade of Vaccines.
- Convergence of PMS network and Blueprint to the GVS Initiative (2012 – 2020) with the following outputs: minimal capacity for all; network for enhanced vaccine pharmacovigilance and global support structure.
- The way forward for the GVSI.
- GVSI as a forum for vaccine stakeholders guided by the GVSI planning group (GVSI PG).
- Structure, membership of the GVSI PG and modus operandi.
- Terms of reference and goals, partners and progress of the SSWG; report to be finalized by December 2012.
- GVSI Portfolio of activities ongoing/planned 2012 to 2020.

Main conclusions including gaps identified

- Need for global support platform to handle vaccine safety concerns.
- Need for GVSI countries and partners to strengthen vaccine pharmacovigilance through exchange of experience at global and national levels.
- Need for GVSI countries and partners to exchange information on national and global pharmacovigilance activities.
- Developing a global map of activities to synergize stakeholders, identify gaps and avoid duplication of efforts. This map should expand to a broader group of stakeholders.
- Alignment of the GVSI portfolio to address identified gaps.
- Need for effective vaccine pharmacovigilance systems in countries as more vaccines reach countries through GAVI, Global Fund and others.
- Develop practical, scalable work plan that could be implemented within available limited resources.
- Address urgent needs of countries in coordination with other stakeholders to build upon and complement existing initiatives, not duplicate efforts.
- Explore integration of drugs and vaccines pharmacovigilance systems.
- Need to make affordable tools available to countries to assist in AEFI monitoring and reporting.

Strategic objective 1: AEFI detection and reporting

MODERATOR - PROF. ALEXANDER DODOO

Synopsis of the presentations made for objective 1

China

- China has 36 domestic manufacturers producing over 40 vaccine products, with some 1 billion doses for marketing each year. Chinese database has 3 million AEFI case reports. Regulations/guideline, information system, training, expert group, data analysis and feedback, and financing are available. However, causality assessment, signal detection and post marketing assessment of vaccine safety capabilities are still developing to fully take advantage of available information resources

Sudan

- Intussusception surveillance was successfully established and sustained under guidance and continuous support from WHO & CDC. No reported cases of intussusception within one week after administration of any of the low dose Rotavirus vaccines. The findings are showing a good safety profile but final conclusion will be reached after completion of the study sample size and analysis of the findings. Challenges identified include high turnover of staff, difficulty in obtaining vaccination status from immunization cards (which may not even exist or be poorly filled), and difficulty in contacting immunization center for missing data.

Sri Lanka

- A study was conducted to review and evaluate case detection, reporting and recording functions of AEFI surveillance in the country, and to evaluate the impact of AEFI surveillance training. Overall reporting of AEFIs at primary administrative level is good. However both over-reporting and under-reporting of AEFIs are observed. Despite the training, lapses in record keeping exist and close supportive monitoring is necessary. Future training needs to focus on reasons given for non-investigations. Immunization safety practices have been adopted at clinics (screening, advices, observation for immediate AEFI following immunization). Help is needed however to address knowledge gaps (immunization workers are not aware of contra-indications to immunization) and to deal with time constraints (since health workers complain of lack of time).

Brazil

- The vaccination programme was created in 1973 and offers 26 vaccines in 27 states. The challenge is to quantify and analyze adverse events associated to vaccines, roles and responsibilities should be well defined. Information systems are needed. Telephone notification is helpful. Challenges identified include high social demands for vaccines, to maintain high coverage, to use nominal vaccination information record systems, and to ensure vaccine safety and AEFI surveillance.

Discussion

- AEFI reporting (both increased and decreased observed) need to be assessed and addressed.
- Reporting rates are potential indicators that can be used to monitor system performance.
- Supportive monitoring is another capacity building strategy in addition to training.
- Immunization safety practices adopted at the sites are very helpful; need to determine if successful models can be disseminated.

Gaps identified

- Guidance document on the type of surveillance system (active, passive, stimulated etc...) that is “appropriate” for different sets of circumstances.
- What are the performance indicators / markers for AEFI surveillance?
- Degree of reporting of adverse events should be quantifiable (zero reporting suggested).
- Quality of investigations needs to be improved, reasons for non-investigations need to be determined and addressed as well.
- Documentation and record keeping at all levels need to be addressed.
- Strategies to promote teamwork/information exchange between EPI, NRA and marketing authorization holder need to be explored.
- Need to share the positive experiences (e.g. training for anaphylaxis, for health workers on case management etc...).

Strategic objective 2: Evaluating vaccine safety signals

MODERATOR – MR STEN OLSSON

Synopsis of the presentations made for objective 2

Lymphadenitis after BCG in Iran

- Intradermal BCG has been administered at birth since 1984, with a current national immunization coverage of 99% , among 1.3 million population aged under 12-months. Annual reports of severe lymphadenitis with Pasteur strain have varied between 2000 and 4000 between 2007 and 2012, with an average rate of 3.2 cases per 1000 doses administered, most cases starting during the first 6 months after vaccination. The country is conducting research activities, varying some of the parameters of vaccination (vaccine strain, mode of administration), to clarify the relationship between vaccine administration and the occurrence of AEFI. The country proposes to share experience and accumulate incidence data from multiple programs in order to clarify the expected rate of the reaction.

Global GBS study

- This project was launched during the 2009 pandemic influenza vaccination campaign. The rationale for this project was to explore the feasibility of a multi-country study for addressing rare adverse events following immunization in the context of a global immunization activity.

This project took advantage of the self-controlled case series design in order to allow focusing on case detection and full documentation. Cases were contributed from 16 countries with a total of 705 cases of which 256 had received the vaccine. Findings from the analysis revealed an increase in the first 3 weeks following vaccination compared to pre-vaccination incidence. There was also a stronger risk estimate with un-adjuvanted versus adjuvanted vaccines.

Signal detection in spontaneous and electronic health care records

- Passive surveillance only assesses exposed persons with the adverse events, rely on individual causality assessment and cannot estimate actual incidence. It does allow signal detection but not verification or hypothesis testing. The evaluation of safety signals is about assessing the association between vaccination and occurrence of a specific health problem. The use of electronic health care records provides the most cost-efficient opportunity to apply the standard designs of cohort or case control studies to test associations of interest (other designs include self-controlled case series and case cross-over designs). Such approaches have helped addressing recent issues such as the risk of narcolepsy in Europe related to H1N1 2009 pandemic influenza vaccine. The review of electronic data in 9 countries revealed the variability on narcolepsy occurrence. It also allowed testing the association in 6 countries that had not signaled an association.

Gaps identified

- Data analysis capacity needs improvement e.g. estimating local AEFI rates, conducting epidemiological studies, routine analysis, evidence based decision making etc...
- Impact of manufacturing practices, lot release procedures, storage and handling of the product on vaccine safety is not sufficiently characterized.
- The importance of understanding the magnitude of local variations in assessing cases as those have a strong impact on the eventual study findings.
- Inventories of local population characteristics and clinical practice patterns are needed to assess the comparability of study data.
- The financial aspects of hypothesis testing studies should be quantified.

Strategic Objective 3: Vaccine safety communication

MODERATOR - DR HOUDA LANGAR

Synopsis of the presentations made for objective 3

Management of a crisis in Uganda during the introduction of HPV vaccine

- Human Papilloma Virus (HPV) vaccine was licensed in Uganda in 2007. Based on the successful pilot vaccine introduction in two districts, the Ministry Of Health scaled it up in 2012 to 12 districts preceding a planned nationwide introduction. In September 2012 MoH was requested to suspend the scale up following anonymous allegations of safety concerns. Media assisted with countering rumors by promoting benefits from vaccination. Among the lessons learned,

the need for preparing crisis management has been well identified. A risk management plan may be required for the future. HPV demonstration mobilized communities well. WHO information sheets were regarded as helpful support for communication.

Vaccine confidence gaps

- Vaccine confidence should be addressed beyond the fear of vaccines, as fear may not be the only driver of adverse events (example: MMR coverage drop in England). Impact of waning confidence can take months to manifest in vaccine refusals and VPD outbreaks. A diagnostic tool recently developed by the London School of Hygiene and Tropical Medicines may help to map out the different reasons for people to reject vaccines, and to assess level of confidence. The LSHTM detection tools may be helpful to understand additional components behind adverse events.

Gaps identified

- Communication should be started before introduction of vaccine.
- The critical role of health workers in vaccine safety communication needs to be understood further and approaches to improve upon it proposed.
- Modern communication technologies should be used increasingly.
- Schematic approach should be developed to help policy makers take decisions on how responding to a specific communication crisis.
- Studies on vaccine hesitation, questionnaire needed.
- Communication strategy and communication guidance documents adapted to the audience are needed, in particular: in preparation of vaccine introduction (risk communication); for crisis management (risk management)
- Transparency should guide risk communication where appropriate.

DAY 2 - MEETING CHAIR: DR S. DEOTTI CARVALHO

Strategic Objective 4: Harmonized tools and methods

MODERATOR - DR JAN BONHOEFFER

Synopsis of the presentations made for objective 4

GVSI tools and methods resources

- All tools currently in the GVSI portfolio were presented and intricate details on each tool and its implementing organization were provided to the audience.

A vaccine specific web-based Individual Case Safety Report management system

- UMC tools, such as VigiFlow, Vigibase and the drug dictionary were introduced in terms of methodology, use in practice and opportunities for implementation. The paucity of AEFI data was mentioned. Country specific requirements for communicating data to UMC is diverse. The software features most frequently used was identified to allow prioritization of features and streamlining software to needs.

An automatic case classification tool aimed to facilitate signal verification

- Presentation introduced methodology for automated case classification. The automatic case classification tool uses computer databases to classify the degrees of diagnostic certainty. Participants were asked to share information about other existing tools to enable synergies.

Gaps identified

- Background incidence should be available in the case classification tool as it would support the analysis. This should be included in a matrix combining resources such as information sheets and other products to provide an overview of information available.
- Available harmonized guidelines should be identified and reviewed with all data available including data from industry.
- Feedback from countries on the issues encountered in using VigiFlow for AEFI reporting should be captured and reviewed.
- Solution to facilitate the transfer from national database to UMC global database should be identified to avoid double data entry.
- AEFI SOPs/guidelines should include feedback on submitted reports to the reporters.

Strategic objective 5: promoting a legal, regulatory and administrative framework

MODERATOR - MR STÉPHANE GUICHARD

Synopsis of the presentations made for objective 5

WHO National Regulatory Authority assessment indicators have been developed and are regularly updated through consultative process with regulators from all regions. The review of the vaccine pharmacovigilance function of WHO NRA assessment goes beyond the NRA; it includes a review of the EPI program and all levels of the health system.

Senegal

- The country produces yellow fever vaccine, that has been prequalified in 2001. The functionality of its national regulatory authority has been regularly assessed by WHO since then, using the WHO NRA assessment tool. The country progressively developed its vaccine pharmacovigilance system and efforts are still ongoing to further strengthen it, based on WHO recommendations.

Indonesia

- The country is a major producer of prequalified vaccines. It went through regular WHO NRA assessment since 2005, the last having been conducted in June 2012. The WHO NRA assessment tool used for those assessment has evolved over time to adapt to stringent requirements. These regular assessments constitute a driving force for the country to continuously improves its national vaccine PV system, based on the institutional development plan developed and regularly updated in this context.

PAHO

- An overview of national regulatory authorities and pharmacovigilance activities in the Americas was presented : organization and outputs of the Pan American Network for Drug Regulatory Harmonization including the Good Pharmacovigilance Practices for the Americas publication and the web based community of practices. The NRA reference assessment is now done in the region using a common tool for medicine and vaccine pharmacovigilance, including 300 indicators (85 % being critical indicators). WHO/PAHO NRA assessment process support the development of countries national PV system. PAHO tool covers both medicines and vaccines pharmacovigilance.

Gap identified

- Need for harmonization between different pharmacovigilance assessment tools.

Strategic Objective 6: Regional and global technical support platforms

MODERATOR - DR CARLOS CASTILLO

Synopsis of the presentations made for objective 6

Regional and global technical support to training started with a presentation on GVSI products and services and capacity building products developed by WHO. Philipp Lambach, presented among others the Global Vaccine Safety Resource Centre, a capacity building platform developed by WHO, including training packages, a trainer database, and an E-learning course on Vaccine Safety.

At this session, the CD Rom version of the online training on Vaccine Safety was officially launched.

In a second presentation, Ajit Pal Singh summarized the current activities and services provided by the International Vaccine Institute (IVI).

GVSI resources available to strengthen capacity in countries

- Landscape analysis revealed that additional training resources are critically needed. Blueprint prioritizes access, technical support and global and regional infrastructure. Global resources examples as identified in the GVSI portfolio currently include:

- WHO GVS Resource Centre that provides solution to diverse requirements from a broad spectrum of stakeholders (vaccination staff, programme officials, AEFI Review committee members). The E-learning course CD ROM was launched.
- Pharmacovigilance toolkit from University of Ghana.
- IVI vaccinology course and trainings.
- 2-week training on Pharmacovigilance at Uppsala Monitoring Centre.
- Vaccine safety fellowship (quoted as example for a GVSI induced planned collaboration between University of Ghana, Brighton Collaboration and UMC).

Regional implementation is coordinated by WHO regional offices which support training activities, institution capacity building and piloting evaluations. The first GVSI portfolio draft indicates that Strategic Objective 6 currently receives the most funding compared to any other objective, which points at the importance of training/capacity strengthening perceived by donors and countries.

International Vaccine Institute (IVI) regional training center

- The IVI was described in terms of its organization, vision, mission and disease priorities and vaccine research activities. Research priority areas are cholera, typhoid and dengue fever vaccine. IVI also operates the SIVAC initiative for the region in support of national technical advisory committees. Training and symposia are conducted in-house and in many countries for all categories of research activities including basic and translational research.. A vaccinology course conducted on multiple aspects of vaccine safety caters to variety of participants from different countries, manufacturers and academia. IVI also has in-house capability to develop and design platform and repository for clinical safety data as currently being done for data capturing and management of studies conducted at IVI and its collaborators. IVI envisages several collaborations such as synergies with UMC course, creation of a pool of trainers and accreditation. Regional and country workshops are proposed for NRA, EPI programs and pharmacovigilance centers. This could take the form of regional centers for training collaborations, consortium of countries doing similar research.

Gaps identified

- A holistic approach is required to align different products available. Ideally, learning and capacity building resources should be interlinked with other products (e.g. e-learning and University of Ghana's pharmacovigilance toolkit).
- Existing awareness gaps have to be countered by effective communication on the available capacity building products. This was also seen as rationale of the GVSI which should not only promote synergies but also as communication platform informing stakeholders on new/upcoming products.
- The GVSI training resource center platform is critical to support sharing of information and experiences. Further opportunities should be identified to ensure a continuous information exchange by stakeholders (e.g. GVSI training newsletter).

- Training courses should not only be available in English but other important languages should also be available.
- Funding for each clinical trial is variable as IVI has resources making it an independent funder.
- Training material on communication to improve knowledge and communication skills of health care providers is needed.
- Contraindications to vaccination should be included in training for vaccinators to improve their knowledge.

Strategic objective 7: Expert scientific advice at national, regional and international levels

MODERATOR - DR MUTALE MUMBA

Synopsis of the presentations made for objective 7

Albania

- The presentation covered the experience of establishing national AEFI committee including the committee composition, roles and responsibilities. The presentation also addressed the procedures for handling and reporting AEFI, including transmission through Vigiflow, as well as strengths and weaknesses of the system. The country benefits from a very motivated staff. However, there is low reporting from hospitals, AEFI reports are not yet shared between NRA and EPI program.

EMRO

- The regional advisor presented EMRO efforts to strengthen pharmacovigilance of vaccines in EMR countries including information on the first regional meeting for strengthening pharmacovigilance of vaccines in Eastern Mediterranean organized by EMRO in November 2012 and attended by 17 countries from the region. One of the goals of WHO/EMRO is to create a platform for sharing experiences on vaccine safety that has led to the establishment of a regional network for vaccine pharmacovigilance. The presentation also covered requests made by countries at the first regional meetings on pharmacovigilance and sharing of the Brighton Collaboration case definitions.

PAHO

- This presentation addressed the establishment of a Pan-American Advisory Committee on Vaccine Safety (PACVS). Vaccines are procured through a rigorous quality control process and are handled in collaboration with many programs. The regional vaccine safety system was described and some highlights of the work of the national ESAVI (AEFI) committee were presented. The presentation concluded by describing the need for PAHO to have a regional vaccine safety committee, highlighting the proposed composition of PACVS and its relationship with the regional Technical Advisory Committee.

Gaps identified

- Need for sharing AEFI reports between all stakeholders.
- Need to introduce the revised causality assessment classification.
- Need for regional expert advice in order to help strengthen vaccine pharmacovigilance.
- Need to establish mechanism of country network in regions.
- Growing need to successfully communicate the strong body of evidence about the safety of vaccine and known untoward reactions .
- Need to develop business intelligence strategies for mapping the vaccine market.

Strategic objective 8: Promoting information exchange between regulators, manufacturers and multilateral agencies

MODERATOR - DR AJIT SINGH

Synopsis of the presentations made for objective 8

The CIOMS working group on vaccine safety

- CIOMS is an international, non-governmental, non-profit organization established jointly by WHO and UNESCO in 1949. Over the years it has produced many publications on norms and standards related to drug development. In 2012 it published general terms and definitions for vaccine safety surveillance. In support of the GVSI, CIOMS proposes to launch a new working group on vaccine safety to address harmonization of methodological aspects in vaccine pharmacovigilance that would be relevant to industry and regulators from industrialized and emerging countries. Anticipated tasks for the working group would be to elaborate systems for early exchange of data, explore tools for enhanced communication, endorse common methodologies and minimize duplication and overlap of efforts between both sectors. Proposals for the structure and operations of the group, currently under discussion with proposed members were described.

Vaccine-GRID

- This organization aims at allowing manufacturers, regulators, public health agencies and academia to collaborate on vaccine benefits and risks assessment. One of its purposes is to generate a platform where many international initiatives can collaborate together. Its vision is to have timely and high quality information on vaccine effects. It involves a network of partners established by the Brighton Collaboration Foundation. Vaccine-GRID proposes an IT platform for accessing to a network of local data bases do remote investigators can conduct hypothesis testing studies (funded and non-funded). A code of conduct based on European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) will be followed for interactions with manufacturers.

Gaps identified

- Clarification on funding sources for the CIOMS working group to be defined.

- Mechanism for sharing AEFI information with manufacturers need to be established.
- Define the time frame for the CIOMS working group on vaccine safety (alignment with GVSI is recommended).
- Contribution of industry to Vaccine-GRID, role in its governance should be defined.