Adverse Events Following Immunization in the South-East Asia Region 2008-2010

Report on WHO support to training programmes

World Health Organization
Regional Office for South-East Asia

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Acronyms

AEFI	adverse event following immunization
ATT	Access To Technology
AIIMS	All India Institute of Medical Sciences
CHD	Child Health Division
DCGI	Drugs Controller-General of India
DDA	Directorate of Drugs Administration
DGDA	Directorate-General of Drugs Administration
DPRK	Democratic People's Republic of Korea
DTP-HepB-Hib	Diphteria-Tetanus-Pertusis-HepatitisB- Hemophilus Influenza Type B vaccine.
EPI	Expanded Programme of Immunization
FDA	Food and Drugs Administration
GAVI	Global Alliance for Vaccine Initiative
GTN	Global Training Network
HCW	health care worker
HHE	hypotonic-hyporesponsive episode
ICMR	Indian Council of Medical Research
IDP	institutional development plan
IEC	information, education communication
INCLEN	International Clinical Epidemiology Network
IVD	Immunization and Vaccine Development
JE	Japanese Encephalitis
LMD	Logistics Management Department
MOH	ministry of health
NCL	national control laboratory
NICD	National Institue of Communicable Diseases
NIP	national immunization programme
NPSP	national programme for surveillance of poliomyelitis

NRA	national regulatory authority
NUV	new and under-utilized vaccine
QSS	quality safety and standards
SEA	South-East Asia
SEARO	South-East Asia Regional Office
SIA	supplementary immunization activities
SII	Serum Institute of India
SOP	standard operating procedure
USAID	United States Agency for Interantional Development
VPD	vaccine preventable diseases
VSQ	vaccine supply and quality
WCO	WHO Country Office

Executive summary

Immunization is one of the most cost effective public health interventions. In the last decade more vaccines have become available for the national immunization programmes in developing countries. In 2000 The Global Alliance for Vaccines and Immunization (GAVI) made funds available for the introduction of HepB vaccine and later for combination vaccines, including DTP-HepB and DTP-HepB-Hib vaccines. The introduction of new vaccines, although beneficial for the programmes as more vaccines are administered with less injection, poses regulatory challenges for the national regulatory authority and the national immunization programme of a country. There are limited immunogenicity and long-term safety data available for the new vaccines compared to the six traditional EPI vaccines. Furthermore, the addition of more vaccines in combination in a single vial increases the complexity for the national regulatory authority to assess safety quality and efficacy for the market authorization of the vaccine. With technical support from WHO for the national regulatory authority and the national immunization programme, most countries in the Region have made significant progress in monitoring adverse event following immunization (AEFI). Consequently, more AEFI cases are reported leading to an apparent increase in the number of AEFI that raised public concerns about vaccine safety.

WHO has a long history of technical support to build national regulatory authority capacity and to improve monitoring of AEFI through the EPI reporting system. To address these new challenges with introduction of vaccines WHO revised the training material to better fit country needs especially, to address the need of the members of the national AEFI committee. During 2008-2010 the training material was updated and tested in Bangladesh, Bhutan, India, Indonesia, Nepal, and Sri Lanka. There are now two sets of training material available. The first set addresses training needs for countries that want to establish an AEFI monitoring system and a second set for countries that have an established monitoring system with a national AEFI committee but need to improve investigation and causality assessment.

Through this process of revising WHO training material on AEFI and conducting training workshops, countries have gained capacity to detect, to manage and to analyse AEFI reports. However, as serious AEFI cases are very rare events it is critical that all training programmes for medical doctors, nurses, midwives and primary health care workers involved in immunization include a session on AEFI monitoring to expand and sustain knowledge on Adverse events following immunization. Because of the high level of sensitivity involved in case of serious AEFI it is also very important that all national immunization programmes establish a national AEFI committee to conduct analysis and to scientifically determine the causality of the event with the vaccine. This national AEFI committee will also have the responsibility to advise the Ministry of Health and the national immunization programme on activities to improve the vaccine safety surveillance system.

1. Background

It is well recognized that vaccines have had an unparalleled success in reducing the morbidity and mortality due to vaccine preventable diseases and are undoubtedly one of the most effective and safest of all public health interventions[1]. Nevertheless, implementation of national immunization programmes (NIP) faces many challenges. One challenge is to ensure immunization safety and monitor adverse events following immunization (AEFI)[2]. The incidence of vaccine preventable diseases (VPD) has been reduced or is even close to be eliminated due to high routine immunization coverage[3], supplementary immunization activities (SIA) and the use of very effective vaccine of assured quality. On the other hand, better surveillance systems able to detect and report AEFI - which earlier went unnoticed have generated an apparent increase in AEFI and, in the absence of VPD, led to increased public concerns about vaccine safety.

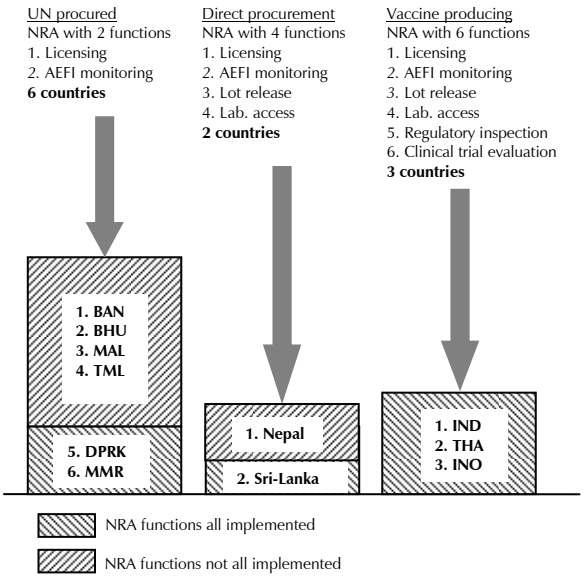
All countries in the South-East Asia (SEA) region could see their NIP achievements swept away by false allegations of vaccine safety as they have limited pharmacovigilance capacity to regulate vaccine including systems to monitor and respond to AEFI. The monitoring of post-vaccination adverse events had received little attention in developing countries. Traditional Expanded Programme of Immunization (EPI) vaccines[1] used in the NIP for decades have very well documented vaccine safety profiles which facilitated AEFI causality assessment. However, this paradigm has changed with the introduction of new and under-utilized vaccines (NUV) in developing countries. Most of the NUV are developed specifically for developing countries either by manufacturers in a developing country or developed country and some are not widely used in the producing countries. In addition, some are very new and do not have sufficient post-marketing surveillance data for thorough causality assessment. WHO, in consultation with the ministry of health in countries of the Region has supported formal assessments of the vaccine regulatory systems, developed and implemented institutional development plans to build the capacity of the national regulatory authority (NRA) to regulate and monitor safety, quality and efficacy of vaccines used in the NIP.

[1] Traditional EPI vaccines include BCG, DTP, OPV and measles vaccines

2. Vaccine Regulatory Systems

In South-East Asia, all the NRAs except in Timor-Leste have conducted formal assessments of their regulatory systems using the standardized WHO assessment tools. Institutional development plans (IDP) were developed and implemented with technical and training support from WHO. Since 2008, NRAs in India and in Thailand have become functional which along with Indonesia make all the NRAs in SEA vaccine producing countries functional. The other countries used either the government procurement agencies to import vaccines e.g.: Sri Lanka and Nepal or for the others UNICEF procurement agencies as they have only a limited NRA capacity to regulate vaccines. Figure 1 illustrates the procurement policy and NRA functions required to regulate vaccine safety, quality and efficacy.

Figure 1: ***Procurement policy and NRA functions required to regulate vaccine***



Post-marketing surveillance and AEFI monitoring are functions that all NRAs have to establish regardless of the procurement policy i.e.; vaccine locally manufactured, vaccine directly imported or imported through UN procurement agencies. This function, established post-licensure to monitor the safety and quality of vaccine once they are in use in the public sector, is

however implemented with variable level of enforcement across countries in the Region. Table 1 displays funding sources to supply vaccines to NIP, availability of local production of vaccines and vaccine procurement policy in each country of the Region.

Table 1: *Funding sources to supply vaccines to NIPs, local vaccine production and procurement policy in countries of SEA Region.*

Country	Self-financing	Local vaccine production	EPI Procurement policy
Bangladesh	Yes	Yes	UN procurement
Bhutan	No	No	UN procurement
DPRK	No	Yes*	UN procurement
India	Yes	Yes	Nat'l proc. Agency
Indonesia	Yes	Yes	Nat'l proc. Agency
Maldives	No	No	UN procurement
Myanmar	No	Yes**	UN procurement
Nepal	Yes	No	Nat'l proc. Agency
Sri Lanka	Yes	No	Nat'l proc. Agency
Thailand	Yes	Yes	Nat'l proc. Agency
Timor-Leste	No	No	UN procurement

* DPRK produces EPI vaccines but they are not used for the NIP to vaccinate children under one year old. The vaccines for the NIP are supplied by UNICEF.

** Myanmar has a production of Hep vaccine (plasma derived and recombinant) but they are not used for the NIP to vaccinate children under one year of age. Vaccines for the NIP are supplied by UNICEF.

The challenge to establish AEFI monitoring is to ensure the synergy between the manufacturers, the NRA, the national control laboratory (NCL) and the EPI programme to detect, manage, report, analyze and conduct scientific causality assessment in order to identify true AEFI and avoid public loss of confidence in immunization. Because of this it is critical to have specific terms of reference and standard operating procedures (SOP) for each EPI stakeholder involved in the vaccine safety post-marketing surveillance and AEFI monitoring.

3. Adverse Events Following Immunization Monitoring

3.1 New vaccines and AEFI

Starting 2008, under-utilized DTP-HepB-Hib vaccine was introduced in SEA[4] Region and Sri Lanka in January 2008, Bangladesh in January 2009, Nepal in April 2009 and Bhutan in September 2009. New vaccines were introduced as well including pandemic flu vaccine H1N1 in Maldives (March 2010), in Bangladesh (May 2010) and in Thailand (March 2010). Bhutan, Democratic People's Republic of Korea (DPRK), Sri Lanka and Timor-Leste also used the pandemic flu vaccines received through WHO. Finally, HPV vaccine was introduced nationwide in Bhutan in May 2010.

AEFI were reported with DTP-HepB-Hib vaccine introduction in Sri Lanka with reports of apparent increase of hypotonic-hyporesponsive episode (HHE) cases. Bhutan reported temporally associated deaths with DTP-HepB-Hib vaccine but when the AEFI cases were investigated they were found to be unlikely related to the vaccine. In Thailand the introduction of seasonal H1N1 vaccine represented a communication challenge when several foetal deaths occurred among pregnant women after H1N1 vaccination[5, 6].

Dealing with AEFI associated with new vaccine or/and vaccine that have never been used on a large scale in the Region was very challenging for the Ministry of Health (MoH). These vaccines had a very high public expectation with regard to safety because prior to the vaccine introduction MoHs conducted Information, Education and Communication (IEC) campaigns to inform the public about the usefulness and safety of the new vaccine. Health care workers attended training workshops on AEFI and thus, their awareness was increased about risks of side effects. They started reporting minor side effects not reported previously with other traditional EPI vaccines. This was the case in Sri Lanka with DTP-hepB-Hib vaccine temporally associated with an increasing number of hypotonic-hyporesponsive episode[7] (HHE) cases that stopped the programme for several months.

3.2 Country capacity to monitor and to respond to AEFI

Although all the countries except Timor-Leste have published guidelines to monitor AEFI, its enforcement varies widely from country to country. Table 2 shows NRA indicators for the assessment of post-marketing functions of the NRA and the status in South-East Asia. Most countries detect serious AEFI with deaths and hospitalization. Only two countries, namely Bangladesh and Sri Lanka in the Region monitor mild cases of AEFI through passive post-marketing surveillance systems. Following WHO's formal assessment of NRAs, IDP were developed and implemented to establish post-marketing surveillance systems for vaccine safety quality and efficacy. In-depth reviews of AEFI monitoring systems were conducted in Bangladesh, Myanmar, Nepal and Thailand and in two states of India.

As part of their IDP, countries established national AEFI committees to analyze and investigate AEFI. These committees contributed to improve AEFI detection and reporting by advising the MOHs on priority interventions. However, national committees could be operational because the budget for AEFI monitoring was funded with donor support. Support from donors, mostly from the Global Alliance for Vaccine Initiative (GAVI) was provided for introduction of Hib containing vaccine and for the measles campaigns to ensure and monitor injection safety. The United States Agency for International Development (USAID) also provided financial support for AEFI monitoring for the vaccination campaigns against seasonal and pandemic flu.

3.3 AEFI crisis management

In the SEA Region the MoHs had to temporally suspend immunization services following clusters of deaths temporally associated with AEFI e.g.: with the use of measles vaccine in India in 2008 and 2010 and, with rubella vaccine in Sri Lanka in 2009[8]. The formal causality assessments when conducted by MoH, with the technical assistance of WHO, demonstrated that the quality of the vaccine was not an issue related to the cause of the deaths.

National AEFI committees in the Region were challenged to respond appropriately to AEFI cases and public concerns with new and under-utilized vaccines without post-licensure vaccine safety data. Pentavalent

DTP-HepB-Hib, seasonal and pandemic flu vaccines have never been used on a large scale in the Region.

Table 2: *NRA indicators for post-marketing and AEFI monitoring and their status in SEA in 2010*

Main indicators related to AEFI	SEA status
(1) Guidelines and procedures for the monitoring and management of AEFI at national and peripheral levels	**Met.**
(2) Roles and responsibilities of the key players (immunization staff, NRA, NCL, surveillance staff, etc.) clearly defined and documented	**Met**: AEFI expert committee in place with TOR in 9 out of 11 Member States .
(3) Routine training/information on AEFI monitoring and management provided to health staff	**Partly met:** in-country training with WHO but limited national training capacity
(4) Routine and functional system for regular review of safety and efficacy for regulatory action, including a process to review and share relevant data between key players	**Partly met:** Lack of expertise in causality assessment and limited access to expertise
(5) System for providing feedback on AEFI from national to all levels	**Not met:** only Sri Lanka has a feedback system
(6) Demonstrated capacity to detect and investigate significant vaccine safety issues	**Partly met**: Poor data quality
(7) Documented process for action to be taken regarding vaccine performance	**Partly met:** Lack of expertise
(8) Provision for post-marketing safety monitoring in the marketing authorization (MA) process	**Partly met:** Constraints in vaccine producing countries that do not use their production in the NIP.

The response to AEFI temporally associated with these new vaccines varied widely from country to country. Some countries are still very reluctant to share the information with immunization stakeholders including WHO or even with their national AEFI committees resulting in a crisis situation with the media reporting all sorts of allegations about vaccine sub-quality. In some countries it even evolved in to a political crisis with

opposition parties along with anti-vaccination groups trying to undermine the credibility of the minister of health and its team.

WHO support to training on post-marketing surveillance and AEFI monitoring in the Region evolved to respond to ever more complex vaccine formulation and its regulation, to build on strengthened surveillance systems and to maintain public confidence in immunization once the disease fades away from public memory.

4. WHO AEFI Training Programme in Sea Region

4.1 Strategy and methodology

WHO has a long history of technical and financial support to build national capacity of Member States to monitor AEFI. The WHO Global Training Network (GTN) on Vaccine Quality was established by the Access To Technologies (ATT) team in WHO Headquarter in 1996[9]. The GTN includes several training centres across the world which are coordinated by WHO. The overall objective of the GTN/VQ is to provide training courses on vaccine quality to NRAs and NCLs in developing countries. The GTN is a cost-effective mechanism to train NRA/NCL personnel who are usually scarce, to work on vaccine regulation in their respective countries.

In 2003, WHO-SEARO established a Global Training Network (GTN) centre in Colombo, Sri Lanka to provide training on AEFI monitoring to SEA Member States and to other WHO regions as well including the Western Pacific Region, the East Mediterranean Region and the African Region. Initially the course content focused on AEFI due to programmatic errors and systems for early detection of serious AEFI cases and their management. By 2005, all candidates from countries in the Region had attended the GTN training and as NRAs were strengthening their capacity to regulate vaccines there was a need to further expand the course in order to train more people.

AEFI monitoring and vaccine post-marketing surveillance requires the involvement of all immunization stakeholders including vaccinators, EPI managers at districts, provincial and central levels, hospital pediatricians, NRA and NCL technicians, representatives from medical institutes and manufacturers. Since it was not cost effective to send many people for

training outside the country in a WHO GTN centre IVD instead opted for an in-country training strategy enabling training of all EPI stakeholders involved in AEFI monitoring in each country at a reasonable cost.

The course content was revised to cater to the need of national AEFI committees as they were being established by NRAs/NCLs with pharmacists, experts in allergies, forensic specialists, professors in immunology, etc. who were not always knowledgeable about their national vaccine safety surveillance system. Country AEFI data and recent AEFI reports were used to develop case studies and drills for group work - sessions on investigation and causality assessments.

In April 2009, the Quality Safety and Standards (QSS) unit in WHQ/Hq organized a meeting of focal points on AEFI from WHO Regions to review the training material and update the content to respond to the needs of national committee members. SEARO sent two persons from the IVD unit to participate in this meeting. There are now two sets of training materials for AEFI. The first course focuses on AEFI monitoring to address the specific needs of countries that do not report AEFI but need to establish the system and a second more advanced course for countries with an established system to monitor AEFI and a national AEFI committee that needs training to conduct investigation and, causality assessment to advise the NRA and EPI on priority issues and to strengthen capacity to detect and report AEFI.

4.2 Implementation of AEFI training in South-East Asia

In 2008, with financial support from GAVI, the WHO Regional Office for South-East Asia (SEARO) started to use the advanced course to address the training needs of national AEFI committee members in selected countries. Although the WHO course material for AEFI investigation and causality assessment was used from 2008 to 2010 its implementation was adapted to country specificities. Below is a summary of these AEFI training workshops in each selected Member State.

Bangladesh

A facility-based surveillance system on AEFI was introduced in Bangladesh in 2003 and at present the 825 health facilities are functioning as AEFI surveillance sites in the country. In 2006, the AEFI surveillance was expanded to the community. Although the AEFI monitoring system detect

and reports around 2000 cases each year, AEFI is still not integrated into the immunization programme and no funds are allocated to the national AEFI committee to conduct vaccine post-licensure studies and to conduct periodic meetings for causality assessment and feedback reporting. The role of the NRA together with the NCL to oversee the safety, quality and efficacy of the vaccine is not well understood.

In 2008, the government requested WHO support to strengthen the Department of Drugs Administration (DDA), the NRA in Dhaka to regulate vaccine in order to comply with the national plan to produce vaccines. An international team of vaccine regulatory experts visited Bangladesh in October 2009 to conduct formal assessment of the DDA, using the WHO standard methodology for NRA assessment. At the end of the assessment the mission held a meeting with the Minister of Health and other senior staff in the MoH to discuss recommendations and follow-up. During this meeting the Ministry of Health acknowledged the need to strengthen capacity of the national AEFI committee members to improve sensitivity and specificity of the vaccine safety surveillance system in the country. The MoH requested WHO assistance to implement a training workshop on AEFI investigation and causality assessment.

The training workshop on AEFI monitoring, investigation and causality assessment was conducted in Cox's Bazar from 10-14 October 2010. Prior to the workshop facilitators reviewed the training material, especially case studies that were adapted to include serious AEFI cases that occurred in the past five years. The workshop was attended by 23 persons from EPI at the national level, Directorate-General, Drugs Administration, Directorate-General of Health Services, representatives of medical colleges, institutes of public health and representatives of the NCL. During the working group sessions several areas of the AEFI surveillance system were identified for improvement. At the end of the training workshop brainstorming sessions were held to identify priorities as follows:

- Finalize list of members in the national AEFI committee.
- Review the AEFI monitoring form and field investigation forms.
- Institutionalize AEFI function within the DGDA (the DDA was upgraded in 2010 to become Directorate-General of Drugs Administration) in Dhaka.

- Review of the AEFI monitoring system in selected districts to identify constraints and barriers for reporting.
- Conduct a formal causality assessment review with the support of an international causality expert.

Bhutan

Bhutan has a small population - 690000 inhabitants and a birth cohort of 13500 infants. There is a well developed public health service. There are 20 health districts, 31 district hospitals, two referral hospitals, 181 basic health units and approximately 1,200 village health workers. The primary challenge for the country is the geographical isolation of the communities and how this affects health delivery and surveillance.

In September 2009, the Ministry of Health introduced into the national immunization programme the DTwP-HepB-Hib (pentavalent) EasyFive™ vaccine, a fully liquid pentavalent vaccine manufactured in India, to replace the tetravalent vaccine comprising DTP-HepB. Hib vaccine was not provided in the NIP before introducing the pentavalent. In October 2009, the national health authorities were notified about five serious AEFIs, including four deaths among infants hospitalized in Thimphu national referral hospital from 10 September to 23 October 2009. Based on this information, the Ministry of Health suspended use of the vaccine.

It appears that until the reports of death following the pentavalent vaccine there was widespread public trust in vaccination. There was little concern regarding vaccine safety. Although there was prominent media coverage of the event it is still not known how widespread the current community concern is. Clearly, amongst the more educated population and those with media access this issue is likely to be of greater concern. Nevertheless, this event exposed the weakness of AEFI surveillance and monitoring in the country and highlighted the need for strengthening.

The characteristics of the current AEFI system is one of a low number of AEFI reports – with three reports in 2009 of one abscess, one convulsion and, one HHE case. The strength of the programme is the availability of expertise within the country and the willingness of all sections of the health system to work towards the common goal of AEFI monitoring and surveillance.

In the course of this unfortunate incident, the Ministry of Health acknowledged the need to strengthen capacity of the national AEFI committee members to improve sensitivity and specificity of the vaccine safety surveillance system. The MoH thus, requested WHO assistance to implement a training workshop on AEFI monitoring, investigation and causality assessment.

The training workshop using the WHO training package on AEFI investigation and causality assessment was held in Paro, from 27 September to 1 October 2010. The 21 participants included senior paediatricians and medical specialists from Jigmi Dorji Wangchuk national referral hospital in Thimphu and Lungtenphu Hospital, Royal Bhutan Army, Thimphu; Medical officers from district hospitals including Mangar, Damphu, Riserboo, Trongsa, Samtse, Lhuntshi; the Head Research and Epidemiological Unit and Chief Programme Officer, Communicable Disease Division and EPI Programme Officer in the Ministry of Health; director and professors from the Royal Institute of Health Science in Thimphu; the Chief Procurement Officer, pharmacists and representative of the NRA.

During the last session of the training workshop participants were requested to develop priority activities for 2010-2011. The list below captures the main features of this activity plan:

- To finalize terms of reference and list of representatives of the national AEFI committee.
- To review the national AEFI guideline.
- To train community health care workers on what to report, when and to whom using mobile telephone network and to immediately detect and manage serious AEFI.
- To prepare training material to be included in training curricula for PHC workers and other post-graduate training for heath care workers (HCW) involved in immunization.

India

India is a major vaccine producing country in the Region and globally. However, progress in implementing a vaccine safety surveillance system including monitoring of AEFI has been slow. India reported less than 300 AEFI cases temporally associated with vaccines in 2009, mostly

hospitalization and deaths. The national AEFI committee was established in January 2008 and its members met the first time on 25 July 2008 with the Joint Secretary, Health, and WHO for a one-day orientation. During this meeting the committee members requested WHO support to implement recommendations emanating from the NRA assessment which was conducted in January 2008 with priority given to conduct a five-day training workshop on AEFI investigation and causality assessment.

The training workshop on AEFI monitoring investigation and causality assessment was conducted from 3 - 7 August 2009 in Manessar, New Delhi. The training workshop was attended by 28 participants. In addition to the eight AEFI committee members, the participants included representative of the Drugs Controller-General of India (DCGI), the CDL Kasauli, State EPI Officers (Jharkhand, Kerala, Madhya Pradesh, Karnataka, Gujarat) and representatives from the Indian Council of Medical Research (ICMR), professors from the All India Institute of Medical Sciences (AIIMS) and medical colleges, epidemiologists from the National Institute of Communicable Diseases (NICD) and the International Clinical Epidemiology Network (INCLEN) in India as well as drugs reaction specialists from the pharmacovigilance system based in Mumbai. The WHO National Programme for the Surveillance of Poliomyelitis (NPSP), India, actively participated in the workshop. WHO/Hq provided facilitators and the local participants were funded by WHO-SEARO (Immunization and Vaccine Development (IVD)).

At the end of the workshop panel discussions were conducted, chaired by the Chairman of the Indian national AEFI committee. During the panel discussions, issues were identified and presented to the Joint Secretary, Health, who attended the closing ceremony. The main constraint to improve AEFI reporting is the lack of a budget to support the national AEFI committee. It was proposed that a secretariat be created and clear roles and responsibilities for investigation at central and peripheral levels defined. The first task of the AEFI committee will be to review the current AEFI guidelines to update procedures in light of the centralization of vaccine licensing procedure implemented by DCGI.

It was also proposed to the Joint Secretary, Health, to identify a state in India to implement the AEFI monitoring pilot project. This pilot state would be designated to join the WHO Global Network for post-marketing surveillance (GPMS) of vaccine safety which is a global initiative of WHO/Hq supported by the Bill and Melinda Gates Foundation. Currently,

10 countries are included in this network with Sri Lanka from the SEA Region. The Joint Secretary, Health, suggested the state of Maharashtra which has an established system to detect and report AEFI.

Indonesia

Indonesia is the second most populated country in the SEA Region with 230 million inhabitants. It is also the largest archipelago in the world with more than 17,000 islands representing a geographical challenge to report to the central level. The health infrastructure is fairly decentralized which requires a different approach to meet the country needs for AEFI training. Three training sessions were conducted from 2008 to 2010.

The first session conducted from 20 to 23 October 2008 included central level staff, mostly members of the national AEFI committee, EPI, the Food and Drug Administration (FDA), and the NRA. Out of 29 participants, five were representatives of the regional AEFI committee including East, West, Central Java, West Sumatra and DKI Jakarta.

As the training programme was adopting a more decentralized approach to deliver the course to provinces it became necessary to translate the content in the local language. During this October 2008 session 10 participants were identified to facilitate the course in the local language at the provincial level. The training material was then translated by the EPI staff and WHO provided two international facilitators to conduct training of trainers from 16 - 18 April 2009 with the selected facilitators.

The 10 facilitators then conducted the second session in Jakarta in the local language from 30 April - 3 May 2009 with 35 participants including representatives from the following provinces: West, South, East and Central Kalimantan, West and East Nusa Tenggara, Bali, East, West, and central Java and Banten.

The third and last session of this series of AEFI workshops was conducted in the local language from 8 - 11 October 2009 in Jakarta and included 26 participants from Jakarta Pusat, Jawa Barat, Sumatra Barat, Jawa Timur, Gorontalo, Sulawesi (Selatan, Tenggara, Utara, Barat and Tengah), Maluku Utara and Papua.

These training workshops on AEFI monitoring, investigation and causality assessment in Indonesia provided knowledge and skills to 90 EPI

and NRA technicians. In addition technical staff from UNICEF Indonesia and the WHO Country Office (WCO) participated in the training workshops.

Nepal

The AEFI monitoring system in Nepal is not yet well established to enable early case detection and investigation of all serious AEFIs. Non-serious AEFI cases are currently not reported to the central level. Aware of the need to strengthen AEFI monitoring especially in the context of japanese encephalitis (JE) vaccination and introduction of new vaccine, the MoH through the WHO country office in Kathmandu requested technical assistance to train members of the national AEFI committee on AEFI investigation and causality assessment. The four-day training workshop was attended by 23 persons including the six members of the national AEFI committee, representatives of the child health division (CHD), the logistics and management division (LMD), paediatricians from major hospitals, President of the Paediatric Association, Nepal and four WHO Immunization preventable diseases (IPD) field officers and the WHO Immunization coordinator.

Several working group sessions were organized to alternate with presentations and plenary discussions. The priorities identified during the plenary discussions were to improve investigation and data quality for serious case reporting and to establish tally sheets in the vaccination sessions to collect non-serious AEFI events and introduce line listing at the district level to compile non-serious and serious AEFI (case-based, subject to investigation but very rare) and report to the central level.

The Director of CHD participated in the last day of the workshop to discuss the activity plan developed by the participants. As immediate action the group indentified the need to review and update guidelines and, prepare simple SOP for grassroot health care workers to know what, when, and where to report AEFI including non-serious cases. This activity plan was later finalized and officially endorsed by CHD to initiate WHO technical support for AEFI monitoring for the next two years as part of the wider objective of NRA capacity building to regulate vaccine safety and quality in Nepal.

Sri Lanka

The AEFI surveillance system in countries of the Region was first introduced in Sri Lanka in 1995. The Ministry of Health established the system gradually starting with sentinel hospitals at district level and then in 2000 it was expanded to all health facilities providing immunization services. Today, Sri Lanka reports between 5000 and 6000 AEFI cases per year including serious and mild cases.

Currently, all reported AEFI cases are expected to be investigated. The health officers investigate the AEFI select cases depending on the severity and magnitude of the AEFI. Mild AEFI are investigated by the field staff, moderate by district level staff and severe by the district and / or national team. Case investigation reports and monthly reports (including "Nil" reports) are sent by the investigators and medical officers of health to the Central Epidemiology Unit. Monthly reports from the Medical Officers of Health are routed through the Deputy Provincial Director of Health Services/ Regional Epidemiologist to the Epidemiological unit in Colombo. Feedback is provided through the Weekly Epidemiological Report and the Quarterly Epidemiological Bulletin[10].

In April 2008, the Government of Sri Lanka withdrew a DTwP-HepB-Hib (fully liquid) pentavalent vaccine (Quinvaxem®) produced by Berna Biotech Korea Corporation from its national immunization programme as a precautionary measure following reports of serious AEFIs. Subsequent investigation of the reported AEFIs and a review of the vaccine quality by WHO concluded that there was no evidence of an increased safety risk associated with Quinvaxem®. Quinvaxem® vaccine thus remained on the list of WHO prequalified vaccines and WHO has not recommended at any time a general withdrawal of the vaccine.

In March 2009, the MoH in Colombo reported a cluster of serious AEFIs with one death temporally linked to the WHO pre-qualified monovalent rubella vaccine produced by the Serum Institute of India (SII). The event occurred on 19 March during school vaccination of girls in grade VIII at Matara town in South Sri Lanka. Investigations by a team from WHO and MoH revealed that the very same batch of rubella vaccine from SII that produced the AEFI was used safely in six other countries. The SII vaccine was prequalifed by WHO and used in the national immunization programme in several countries since 1992. The team concluded that the event was unlikely to be caused by the vaccine.

In view of the serious AEFIs reported, the MoH Sri Lanka requested WHO through its country office to conduct a training workshop to strengthen AEFI monitoring, investigation and causality assessment. This was conducted in Colombo between 28 September and 2 October 2009. There were 18 participants including the chief consultant judicial medical officer, three senior professors of paediatrics from the Faculty of Medicine, Colombo and the University of Jayawardanapura, consultant virologist and vaccinologist, histopathologist and forensic histopathologist from the Medical Research Institute, Colombo. The chief epidemiologist and her team from the Epidemiology Unit, Colombo also participated, Three resource persons from WHO/Hq, SEARO and the professor of paediatrics, Dalhousie University, Halifax, Canada, provided technical support.

Among the topics that were discussed by working groups and during plenary sessions were issues around causality assessment especially how to rely less on vaccine testing and more on procedures for optimal causality assessment especially autopsy protocols in the context of Sri Lanka. The participants agreed that the epidemiology unit will be responsible for forming a small working group to finalize an action plan to strengthen the AEFI system by fine tuning the preliminary elements identified at the workshop. The elements of the preliminary action plan included the following broad points.

- Existing AEFI forms to be revised and completeness and quality of reporting reviewed (a working group to be given the responsibility).
- SOPs for physical and verbal autopsies to be developed, as well as plans for training, implementation and monitoring.
- A review/analysis of AEFI data - including at regional levels - and feedback to be carried out for routine and new vaccines.
- Steps to be undertaken to improve reporting and quality of reports from the private sector, including legal requirements for reporting and investigation of serious AEFIs.
- A communication plan to be elaborated.

4.3 Lessons learned

Rumours affecting vaccine coverage performance

In 2010, several countries received donations of pandemic flu vaccine and Thailand purchased the vaccine with its own budget to vaccinate selected population at risk. The pandemic vaccine was used first in industrialized countries with the population not well informed about the risk benefit of this vaccination campaign. Consequently, low coverage was reported across most of these countries and anti-vaccination groups seized this opportunity to fill the internet with false statements about vaccine safety and its benefits. These rumours spread across developing countries which resulted in public concern and low coverage. The Member States need to prepare adequately and promptly to respond to these rumours. The most effective way to do this would be by developing country-specific risk communication plans. IVD/SEARO aims to assist countries to fulfil this task during 2011-2012.

Training

Serious AEFIs are very rare events which may not occur for several years especially in countries with a relatively small population e.g.: Bhutan and Maldives. As cases are not reported for a long period of time, the health workers lose interest or forget about appropriate procedures to manage AEFI cases. AEFI training must be included in all refresher immunization training including in medical institutes that train nurses, auxiliaries and other primary health care workers involved in immunization.

Institutional support

AEFI monitoring is still not integrated into the immunization programme in many countries and no funds are allocated by many MoHs to the national AEFI committee to conduct vaccine post-licensure studies or to conduct periodic meetings for causality assessment and feedback reporting. National AEFI committees should include a secretariat and have a budget to fulfil their duties and responsibilities. The role of the vaccine industry in AEFI surveillance is limited by perceived conflicts of interest, generating a lack of credibility. However, in Thailand a local manufacturer provided financial support to the NRA/NCL to implement a routine AEFI monitoring system. As the manufacturer did not lay down specific conditions and funds were not used for staff salary the support was free of conflict of interest.

Opportunities for financial support from manufacturers should be further explored to pilot test improved vaccine surveillance systems in the Region without manufacturers' interfering with the decision making process either directly or indirectly.

Role of the NRA/NCL in the context of AEFI

The role of the National regulatory authority together with the National control laboratory to oversee the safety, quality and efficacy of the vaccines is not well understood especially in the countries that do not produce vaccines. The role of the NRA/NCL should be established from the moment the vaccine specifications are developed and tenders are issued for the procurement. Then the NRA must be involved while receiving the vaccine to check compliance with specifications and release the lot for use in the NIPs. When AEFI occurs the role of the NRA is critical to contact manufacturers to verify if similar incidents occurred in other countries where the vaccine was distributed and also to conduct testing procedures that manufacturers may be asked to undertake to verify vaccine causality hypothesis. WHO developed a guideline for fast-track licensing[11] that includes simple procedures to be undertaken by the NRA when WHO pre-qualified vaccines are delivered to the country.

5. WHO Priorities in the Sea Region to Strengthen AEFI Monitoring and Vaccine Safety Surveillance

Countries have established procedures to respond to serious AEFI cases. WHO will provide technical support to strengthen these procedures through empowering the national AEFI committee and through advocating greater involvement of the NRA/NCL in the investigation. In this connection, in the country importing vaccine, WHO will support the implementation of the WHO guideline, "Procedure for Expedited Review of Imported Prequalified Vaccines for Use in National immunization programmes". The procedure is based on the review of Summary Lot Protocols, labels and inserts and the appearance of the vaccine samples. This simple checking conducted by the NRA upon vaccine arrival will allow detecting any abnormality before sending the vaccine to the field and thus avoiding unnecessary delay to use the vaccine due to health care workers' questions about appearance or labelling of the vaccine which are difficult issues to address once the vaccine is distributed throughout the health care infrastructure.

In 2009, countries started to implement WHO's training programme on AEFI investigation and causality assessment. The course content was revised and updated in 2010 to better suit country specificities by using for example existing data on AEFI that are available at country level for working group sessions. This course therefore is dedicated to countries which have an established system to monitor AEFI and an established national AEFI committee with terms of reference. The course will be conducted in Myanmar and India (Maharashtra state as part of the WHO GPMS project) in 2011-2012. In the countries which received training on AEFI investigation and causality assessment the follow-up activities include the revision of the national guideline. WHO will provide priority technical assistance to vaccine-producing countries. India completed the revision of the guideline and it will be published in 2011. In Indonesia the MoH has plans to implement a pilot project in a selected state to field test new reporting forms that will preclude an updated version of their guideline. The system will include a notification form for rapid notification of serious AEFI to trigger investigation within 24 hours. For the field investigation a form to collect data will be developed and tested. In addition and to address the needs to report selected minor AEFI e.g.: fever, inconsolable (prolonged) screaming, HHE, nodule (pronounced local reaction), abscesses, etc. a form to collect aggregate data at district level will be developed and tested as well. In Thailand similar work is planned to be initiated in 2011.

The search for a causal relation between an AEFI and the vaccine is complex[12] and requires a high level of expertise which is not always available at country level. To strengthen causality assessment WHO has a two-pronged strategy:

(1) **Strengthening networking of AEFI experts in the Region:** WHO-SEARO with WHO/HQ have a extensive experience to establish a network of experts to conduct NRA assessments and to share and discuss findings. All AEFI experts who were involved in NRA assessments for the function of post-marketing surveillance and AEFI monitoring have access to a share point server currently managed by WHO/Hq. This represents a large data bank of expertise that is continuously updated. This network will be extended to create working plate-forms where AEFI experts will be able to debate and share data on AEFI and also to work on specific tasks. In the first quarter of 2011, a forum of the NRAs in the Region will be held in a SEA country of the Region to present current regulatory challenges and make propositions to work together on specific priority issues to address those challenges.

(2) **Streamlining and standardizing investigation procedures on two fronts:**

(a) For the field investigation when a team of investigators are sent to collect data about the case and the vaccines. Completeness and timeliness of this investigation is not yet up to standard although preliminary data collected through the routine AEFI reporting system showed, in several countries, that investigations are conducted in most cases within 24 hours following the notification of serious AEFI.

(b) Laboratory investigation is an important component of the investigation of serious AEFI. However, in many instances the MoHs requested the vaccine vial to be tested before field investigation is completed. Vaccine testing by an independent laboratory is very costly and needs to be specific and requested during the complete case review by the national AEFI committee which may require a laboratory investigation to verify causal hypothesis. A post-mortem investigation when it can be undertaken is usually more useful to verify an hypothesis. WHO, with national AEFI members will support the development of a regional guideline for clinical post-mortem investigation in the context of AEFI. Some countries have expertise in post-mortem investigation and members of the AEFI committee have started working on country-specific guideline. WHO will help this process by preparing a regional guideline.

The SEARO/IVD/VSQ strategy to strengthen surveillance of vaccine safety is in line with WHO's global strategy that promotes cross-country cooperation and establishment of a network. In this connection WHO established the global network for post-marketing surveillance of newly pre-qualified vaccine in which Sri Lanka and one state of India are participating. Through this network countries will have access to vaccine regulatory experts from 10 different Member States of the global PMS network, gain experience in conducting AEFI investigation and causality assessment, develop and field test a model to establish a system for post-marketing safety surveillance of vaccines.

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Most of the new and under-utilized vaccines have never been used in countries of the SEA Region in large population groups e.g: seasonal flu vaccine and Hib vaccine as monovalent vaccine and/or delivered along with DTP and HepB as a single combination vaccine. Serious Adverse Events Following Immunization are very rare. Vaccines are given to healthy children below five years of age, which is a very vulnerable age group in developing countries. Other coincidental cause of death can be easily miss-interpreted as vaccine reactions without proper investigation and causality analysis procedures. It is therefore critical for national regulatory authority (NRA) and national immunization programme (NIP) managers to monitor AEFI and establish a vaccine safety surveillance system within their countries. Because of the high level of sensitivity involved in case of serious AEFI it is also very important that all national immunization programmes establish a national AEFI committee to conduct analysis and to scientifically determine the causality of the event with the vaccine. This national AEFI committee will also have the responsibility to advise the Ministry of Health and the national immunization programme on activities to improve the vaccine safety surveillance system.

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