

**Report of the Second Meeting of the Global Vaccine Safety Initiative
19-20 November 2013
New Delhi, India**

The second Global Vaccine Safety meeting took place in New Delhi, India on 19-20 November 2013. This general meeting guides the Global Vaccine Safety Initiative (GVSU), which is the implementation mechanism for the Global Vaccine Safety Blueprint.

During two days, immunization programme managers and national regulatory authorities pharmacovigilance staff from twenty one 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 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 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 first year of implementation of the GVSU
- Discuss needs and opportunities at country level for strengthening their vaccine pharmacovigilance system
- Explore mechanisms to further strengthen collaboration in support of GVSU

The expected outcomes of the meeting were to:

- Identify effective models for implementing the Global Vaccine Safety Blueprint objectives
- Strengthen the collaborative mechanisms in support of GVSU
- Provide recommendations to develop and finance the GVSU portfolio of activities

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

DAY 1 - MEETING CHAIR: PR. NK. ARORA

Global Vaccine Safety Initiative first year implementation report of the Global Vaccine Safety Planning Group - Pr A. Dadoo

Summary

The GVSI spearheads the implementation of the mission and the vision outlined in the global vaccine safety (GVS) Blueprint with the participation of all stakeholders on vaccine safety. Since inception in March 2012, the GVSI has been instrumental in particularly supporting low and middle income countries to have functional vaccine safety systems in place.

Main discussion points

- The GVSI Planning Group oversees the implementation of activities planned under each of the 8 strategic objectives identified in the GVS Blueprint. Activities are implemented by stakeholders and monitored to identify progress through a transparent mechanism.
- A GVSI portfolio has been created with over 90 activities listed based on a set of criteria which includes impact, geographic relevance, feasibility, usefulness, sustainability and guidance.
- Some of the activities completed by the various GVSI stakeholders include the PV toolkit developed by the University of Ghana Medical School, tools developed by the Brighton Collaboration for case definitions, AEFI data maintained by the UMC, the web based and offline tools for AEFI data management by IVI and the tools developed by the WHO such as the training tools, AEFI surveillance guidelines, manual on causality assessment, AEFI core variables and standard form for reporting AEFI, information sheets on known vaccine AEFI rates and the GVSI bulletin.
- Some of the activities that are in the pipeline include, active surveillance for new vaccines (rotavirus; MenA conjugate in pregnancy); hypothesis testing for rare AEFI through multi-country collaboration of sentinel sites; and translation of training and other reference materials (UN languages and others).
- A set of rules of engagement that outlines the operational structure and processes, funding, intellectual property of participants, conflicts of interest, public-private interaction and first year of operation have been prepared and the manuscript submitted for publication in the WHO Bulletin.
- The challenges facing the GVSI include the development of new products – ideas, partners, strategies and resources, disseminating information and utilization of developed products, expansion of GVSI network and funding.

Conclusions

The GVSI Blueprint document provides the guiding principles. It outlines shared responsibilities and shared solutions towards reaching out to a better world. It is necessary to focus on achieving short and long term goals to ensure the achievement of targets described in the Decade of Vaccines (DOV).

Evolving Global Vaccine Pharmacovigilance in developing and developed countries : the key role of clinical databases- Pr S. Black

Summary

There are multiple modalities to evaluate safety in the post-licensure settings. Active surveillance yields better information than passive surveillance. It is feasible even in developing countries. Without active surveillance, safety issues can be missed and inability to respond to a concern can jeopardize good programs. Global collaborations can increase efficiency and capacity and assure our populations receive safe and effective vaccines.

Main discussion points

- In developing and developed countries there is the need for active surveillance and passive reporting.
- Active surveillance studies in developing countries are important with increased vaccine uptake, vaccines are being introduced earlier or exclusively into developing countries with incomplete safety profiles.
- Passive surveillance yields information only about cases among vaccinated as a result, relative and attributable risk cannot be determined.
- Case series using outcome data with clear need to identify cases in an unbiased manner is a good method to assess risk and causality.
- Background rates of adverse events are particularly important in the context of active population based surveillance.
- In developing countries, passive surveillance alone is inadequate as it cannot identify safety signals in special populations such as HIV infected, malnourished persons or people with malaria.
- Both active and passive surveillance are possible in developing countries. In Burkina Faso, when Meningitis A vaccine was introduced in December 2010, it was found that active surveillance was almost 200 times more sensitive than passive surveillance in identifying cases of convulsions and allowed rate comparisons. However, it is not easy to establish active surveillance and sustainable infrastructure is needed to make this practical.
- Collaborative mechanisms have demonstrated that analyses of risk can be performed. Some examples are the global collaborative evaluation of the risk of Guillain-Barré Syndrome, the PREVENT pilot (as an example of testing infrastructure capacity) and the recent GVSI intussusception data collection exercise.

Conclusions

Public expectation is for a rapid response to possible concerns or signals that may arise due to chance alone. Surveillance systems should be tailor made to provide essential information to detect signals and respond quickly.

Systemic approach to safety concerns: managing the pentavalent vaccine safety challenges in India - Pr NK. Arora

Summary

There has been significant progress in improving AEFI surveillance in India in recent years. Key stakeholders have initiated a series of activities that improved reporting of AEFI considerably. However there is still substantial room for progress. New vaccines including the liquid pentavalent vaccine have been introduced into the program accompanied by enhanced reporting and media attention to both fatal and non-fatal serious AEFIs. There is lack of information on the background rates of several AEFI. A study is being planned to address this gap.

Main discussion points

- In India, the recent efforts to enhance AEFI surveillance and reporting include:
 - Establishment of AEFI Secretariat at Immunization Technical Support Unit (ITSU), constitution of AEFI Committees and developing benchmarks for reporting.
 - National AEFI Committee has taken steps to establish partnership with Indian Academy of Pediatrics to report AEFIs and identify medical institutions for developing AEFI Technical Collaborating Centre. First such centre is Lady Hardinge Medical College (LHMC), New Delhi.
 - Establishment of AEFI cells in Central Drugs Standard Control Organization (CDSCO) headquarters and all zonal offices.
 - Greater coordination between NRA and EPI.
 - National AEFI guidelines and SOPs developed and disseminated.
 - Autopsy protocols for investigation of AEFI deaths and protocols for verbal autopsy being developed.
 - Preparation of pharmacovigilance guidelines for Marketing Authorization Holders and an AEFI Edition of Pharmacovigilance program newsletter.
 - Review of AEFI reports from pharmacovigilance program and vaccine regulators.
 - Basic trainings for about 71,000 accredited social health activist workers, Medical officers, District immunization officers and state EPI officers and causality assessment trainings for experts completed.
 - In preparation to Pentavalent vaccine introduction, communication guidelines for handling AEFIs, media engagement strategy and FAQs were developed.
- The impact of these efforts include:
 - Progressive improvement in the reporting of serious and non-serious AEFI.
 - Since the introduction of the Liquid Pentavalent Vaccine (LPV) in December 2011, 176 Serious AEFIs including 54 deaths and 122 hospitalizations reported after 11,428,907 doses.
 - System is now better equipped to handle media issues and voices raised by anti-vaccine groups through a coordinated mechanism and involvement of communication experts at ITSU.

- Pentavalent vaccine safety challenges:
 - The lack of existing literature or reports of Sudden Infants Death Syndrome (SIDS) among infant deaths results in attribution of all post vaccination deaths as vaccine related.
 - Heterogeneous reporting and management of AEFIs across states and differences in quality of care at hospitals and homes affecting the outcome of serious AEFIs.
 - Some expected AEFIs became serious medical conditions due to lack of timely and appropriate care.
- Response to Pentavalent vaccine safety challenges
 - A large study to characterize events as serious AEFI in 6-24 weeks old infants in the context of Universal Immunization Program (UIP) in Kerala and Tamil Nadu has been developed.

Conclusions

India has made substantial progress in AEFI surveillance and response. There is still room for improvement. This progress accompanied by new vaccine (such as pentavalent vaccine) introduction has resulted in enhanced reporting of AEFI. The absence of background rates for the events reported has been identified as an important gap that the country is planning to address through a special study.

Pentavalent Vaccine and Infant mortality: analysis of public confidence as an integral part of comprehensive safety monitoring – Pr M. Sturkenboom, Pr J. Bonhoeffer

Summary

A new set of tools have been developed to evaluate public confidence in vaccination. Vaccine safety concerns account for only 22% of all negative media content on vaccine globally. There are standard sequence of events and pattern of responses that lead to and follow vaccine safety crisis. To monitor and respond to public perception, suitable tools are needed to review the huge volume of information available in the public domain. An algorithm has been developed by the Vaccine Confidence Project which could be used to pick up information from social networking sites. Machine learning approaches are newer tools that help program managers to extract information from large volumes of data.

Main discussion points

- A new set of tools determine public confidence in vaccination include case based approaches and population based approaches.
- Data from Vaccine Confidence Project of London School of Hygiene and Tropical Medicine indicates that vaccine safety concerns accounted for only 22% of all negative report content on vaccine in media globally for all vaccines.
- It is important to have contextual information available and monitor the public opinion and sentiment during vaccine safety crisis. In the example of DTP-HepB-Hib and sudden deaths in India:

- A standard pattern was observed: Introduction of Vaccine - Infant deaths observed - signal raised - vaccine suspension discussed - public concern increased - coverage waned - confidence restored or vaccination stops completely.
- Inadequate safety and effectiveness studies prior to vaccine introduction accompanied by rumors resulted in litigation by professionals.
- Analysis of positive, neutral and negative mainstream media reports from India indicate peaks in positive reporting when reduction in pentavalent vaccine price was announced and when pentavalent vaccine was launched. Negative reporting was observed when there were litigations.
- Simple Google searches yield several hundreds of thousands of results that cannot be easily reviewed and a mechanism is necessary to quickly evaluate the same.
- To monitor the media faster, an algorithm has been developed by Vaccine Confidence Project using manual annotation to pick up information in social networks (Facebook, Twitter and Google+) that will alert program managers of impending vaccine safety issues.
- Machine learning approaches such as NaiveBayes, Support Vector Machine, Ripper using automated annotation of media reports can give an idea on the polarity (negative, neutral or positive) and the priority (red, yellow or green)

Conclusions

Monitoring public sentiment is possible and feasible in LMIC in social media, through automated detection. With greater awareness and social interaction, for the Immunization program, it is essential to gauge the public perception and respond appropriately.

Breakout session: Improving AEFI reporting

Using case studies, the participants explored the challenges and provided suggestions on increasing AEFI in countries ravaged by war with poor health infrastructure, in countries with evolving system with multiple priorities, and in countries with excellent infrastructure challenges with new disease and new vaccine.

Challenges foreseen in AEFI detection and reporting:

- Non-functional NRA; lack of resources
- No pharmacovigilance systems; inadequate health care systems
- Pharmacovigilance might not be considered a priority
- Underreporting as a result of inherent inadequacies in the National AEFI reporting system
- NRA may require a post-marketing safety study (phase IV)
- Importance to collect baseline data on the disease and other endemic diseases in the region prior the introduction of new vaccine
- Increase HR to analyze all data sent to central level through internet.

Guidance and strategy to ensure reporting of AEFI

- Encourage reporting , look for known AEs
- Ensure SOPs for reporting and update forms, web etc.
- Ensure practical mechanisms for reporting are instituted
- Validate the AEs once they are reported
- Ensure that the quality of data report
- Provide feedback to the reporters and acknowledge them
- Monitor the immunization coverage
- Report the quality issues (important to differentiate the AEFIs from Quality complaints)
- Focus should be to prevent AEFIs (the real meaning of "Pharmacovigilance vs. Pharmacodiligence")
- Establish baseline background rates for the provinces that are not vaccinated
- Establish Expected rates of AEFI in the communities
- Keep the National committees updated
- Establish communication plan
- Provide regular trainings
- Encourage use of modern technology to report AEFI e.g.: cell phone.
- Identify regions/districts with low capacity to detect and report to establish stimulated surveillance system
- Issue letter from EPI to encourage reporting without fear of punishment
- Establish call centers to inform on vaccine safety.
- Establish indicators of the AEFI functionality

Support requested from the government

- Political commitment
- Stakeholder Alignment via awareness workshops, consultations, press releases, expectation setting etc.
- Institute systems, policies and processes
- Communication plan and campaign: communicating with vaccinees, parents, communities etc.
- Crisis management Plan
- Resources: manpower, pharmacovigilance systems, AEFI SOPs, training.
- Training of immunization providers on AEFI and AEFI cases management
- Revitalize AEFI committee to enable them to respond to AEFI reports

Support requested from international agencies

- Access to international expertise.
- Establish international platform to share experience and AEFI data.
- Alert system to inform countries about serious/unusual AEFI cases
- Support investigation e.g. laboratory investigation, forensic investigation.
- Financial support
- Sharing global experience
- Training programs

- SOPs/Data collection forms/Guidelines
- Access to global safety database
- Regional collaboration (alliance)
- Independent oversight

Breakout session: increasing collaboration between EPI and NRA

Participants were divided in working groups to discuss the main challenges faced for collaboration between EPI and NRA on vaccine safety, the respective roles and responsibilities of EPI and NRA. Examples of best practices of collaboration were sought.

Main challenges identified:

- There is no systematic formal structure / platform / meetings that link NRA / EPI
- No formal reporting / legal documentation that binds both NRA and EPI to communicate or share data
- No compatibility in reporting formats of AEFI and adverse drug reactions to facilitate exchange of data
- NRA staff are commonly at national and sometimes regional levels. No formal linkages with EPI at lower levels.
- Lack of capacity – Skilled personnel in NRA for vaccine safety evaluation.
- EPI considers AEFIs largely as programmatic errors and has less interest in reporting to NRA.
- Focus of EPI is on immunization coverage while NRA focuses on quality, efficacy and safety.
- When vaccines are supplied through UN agency, the NRA is not systematically involved nor informed. The NRA is then in a difficult position to evaluate the vaccine benefit risk, having not access to the vaccine registry file.
- Little resources are allocated to vaccine safety / monitoring & investigation of AEFIs

Examples of best practices:

- Joint planning for
 - Assessing vaccine products
 - Immunization activities in particular campaign
 - AEFI Guidelines development
 - Institutional Development. Plan (IDP)
 - Involvement in Advisory Committees: NITAG; AEFI review committee

Suggestions for NRA/EPI collaboration improvement :

- A National AEFI Committee, composed of all stakeholders to investigate the events.
- EPI can detect and report but can't investigate (conflict of interest).
- Multiples sources of information but unique database. Need for an unified data management tool or compatible tool to facilitate exchange of information.
- Need for an official guidance to clarify EPI vs NRA roles and responsibilities
- NRA to work independently from the MOH
- Put in place licensing guidelines (a way to force dialogue between NRA and EPI)

DAY 2 - MEETING CHAIR: PR. S. BLACK

Vaccine Adverse Events Information Management System – Dr AP. Singh

Summary

The Vaccine Adverse Events Information Management System (VAEIMS) is a software that has been developed by International Vaccine Institute (IVI) in technical collaboration with WHO to transfer AEFI data using the AEFI core variables from the periphery of the health care system, efficiently and effectively into a central national database for processing and conversion of raw data to information for action. VAEIMS is currently an offline desktop based application which due to its small size can be simply emailed to users. It enables AEFI data sharing from reporting entities from the care provider to the national level. Users at grass root levels send email alerts to the district level, upon which they will be invited to download the tool and enter the data.

VAEIMS incorporates the notification form that has been designed locally by the country, is easy to fill out, and includes mandatory and optional fields. Data transfer from VAEMS is E2B compliant. Cases can be searched, analyzed and mapped by time, event, vaccine, place and performance. The database is being piloted in Sri Lanka and is proposed for piloting in North Korea.

Main discussion points

- Any change to data entered into VAIMS at any level requires repeated uploading.
- Duplicate uploads have to be corrected manually.
- Larger databases (more than 100,000 reports) cannot be handled by the software.
- Data loss can occur due to machine issues.
- The analysis tool can only be used for own or reported data. Finally, the database can only be manually linked to global databases.

Conclusion

To respond to some of the requirements by end users, a web-based version of VAEIMS is planned for the second quarter of 2014. The online version includes the possibility of creating backups. Furthermore, android and SMS based applications are planned for 2014 which may enable SMS based reporting.

Addressing the challenges of AEFI data gathering and analysis: Brazil experience – Dr S. Deotti

Summary

The specificities of Brazil and the structure of the Ministry of Health, of which ANVISA forms part, were introduced. The National Immunization Programme (NIP) of Brazil has an annual budget of 1.2 million US dollars. Among others, it recommends immunization calendars for children and makes vaccine available in 35,000 public vaccination rooms. Brazil has 14 vaccines in their routine immunization

schedule. ANVISA works closely together with the NRA in sharing information of reported AEFIs and providing them to the national AEFI review committee (created in 2008).

Brazil is making considerable progress in strengthening its vaccine pharmacovigilance system: for example, the third edition of the AEFI manual is being published. It includes AEFI concept types, Brighton Collaboration case definitions and other tools supporting the monitoring and evaluation of AEFI. AEFI investigation forms have been updated to include the WHO 22 core variables. Furthermore, an online information system for AEFI reporting (SIPNI) is being developed that aims to synchronize the existing 5 NIP registry systems and to allow for more effective data management and analysis, using E2B format. NOTIVISA is worth mentioning as it is an existing NRA notification system that is primarily used by private vaccination rooms and manufacturers.

Main discussion points

- Increased political commitment necessary to strengthen the reporting of AEFI.
- Increased capacity required for lab investigation, communication and risk evaluation.
- Issue of concern: reporting of AEFI by the private sector. This system seems currently limited as it is not sufficiently connected to the public data gathering systems and seems to miss denominators and quality oversight.

Conclusion

Brazil has made significant progress towards the implementation of its AEFI reporting system and the establishment of a national AEFI Review committee. Tools in form of manuals and IT based reporting systems are underway and promise to further increase the reporting and analysis of AEFI.

Recent innovations from UMC and the WHO Programme for International Drug Monitoring – S. Olsson.

Summary

117 countries are contributing to the WHO Programme for International Drug Monitoring. Development of the new system for direct patient reporting was part of the Monitoring Medicines project, funded by the FP 7 programme of the European Commission. It aims to collect Individual Cases Safety Reports (ICSR) directly from the general public.

The UMC's new data analysis tool is called Vigilyze. It is more graphical and interactive than previous search facilities and aims to offer easier access to the global database VigiBase to countries. Data can be searched by drug name, adverse reaction and be filtered by country, sex, age, and time window. Results can be listed and graphically displayed. Currently VigiBase includes 8.4 million ICSR, which can be searched progressively using filters in Vigilyze. Online trainings are available to support the use of Vigilyze.

Main discussion points

- Reporting of AEFI to VigiBase: currently, this global ICSR database includes a total of 800,000 AEFI. A lot of this data is coming from Europe, North America, Australia and New Zealand. The lack of exchange of data between the NRA and the NIP in developing countries is of concern to UMC. Some countries are quite good at reporting, but the majority is rather limited in providing AEFIs.

Conclusion

UMC offers a broad range of information products. To meet effectively countries expectations, UMC welcomes the formation of the new WHO department of Safety and Vigilance. The merging of drug and vaccine safety units provide for UMC with an increased opportunity to collaborate with WHO in an integrated manner.

Monitoring the safety of live attenuated JE vaccine in China – Dr P. Zuber for Dr L. Dawei

Summary

Monitoring by the National Immunization Programme in China has dramatically evolved over time. Most vaccines used in China are manufactured by local Chinese companies.

The epidemiology of Japanese Encephalitis (JE) in China shows that its prevalence was much more important in the 60s and 70s following which an inactivated product was introduced. Live attenuated vaccine became available in 1989. At this time the incidence had already been greatly reduced. It is therefore not clear in how far disease control is a true reaction to the effect of vaccination. In 2005, JE vaccination was introduced to the national schedule. It is offered at 8 months of age and at 2 years of age. So far, five different products have been used in the Chinese National Immunization Programme with 30 million doses of live attenuated vaccine being administered each year.

Monitoring in China is mainly based on passive surveillance with county, prefecture, provinces, and national levels. AEFI reporting has steadily increased over the last years. In 2006, China was getting just a few 1000 AEFI reports every year compared to 2011 where more than 100,000 reports were registered. From the AEFI reported, only a limited number of serious events occurred and very few deaths were registered following JE immunization.

Main discussion points

- With 30 million doses administered annually, only very few serious adverse events were registered through passive surveillance, which did not detect any particular signal with the use of the vaccine. The use of active surveillance to understand further the actual rate of adverse events following immunization may provide the basis for the estimation of reaction rates to JE vaccine in China.

Conclusion

With the volume of information available, colleagues in China have the opportunity to manage the systematic analysis of adverse events making use of passive and active surveillance.

Malaria vaccines: what do national authorities need to know? - Dr V. Moorthy

Summary

Over 660,000 deaths annually are caused by Malaria, which is the single highest cause of mortality among children in Africa. The Strategic Advisory Group of Expert of WHO in April 2013 accordingly stated that Malaria Vaccine Development remains a global public health imperative.

- The only phase III trial, currently underway by GSK, is on Malaria vaccine RTS,S, which targets Malaria in the sporozoite/hepatocyte stage. This vaccine forms virus like particles, and includes AS01. Eleven countries participated in the phase III trial which took place in Africa.
- No data on efficacy of RTS,S exist outside of Africa.
- Efficacy data available is in the context of broad use of Insecticide Treated Bed nets (ITB) during the clinical trial (75 – 86%). So any protection observed is in addition to the ITN use. Evaluation of the use of RTS,S/AS01 is in addition to malaria preventive, diagnostic and treatment measures, and not in replacement to bed nets.
- The statistically valid endpoint for malaria vaccine efficacy studies is the reduction of total numbers of malaria episodes. So the percentage efficacy for clinical malaria means reducing total numbers of malaria episodes. Appropriate communication with community, mothers and all stakeholders to use available malaria control measures, seek diagnosis and treatment of malaria after RTS,S vaccination is critical.
- Efficacy in 5-17 month olds was confirmed in all 11 sites at 40%-77% reduction of malaria episodes. Pooled across all sites, there is statistically significant efficacy against clinical malaria (46%), severe malaria (35.5%), malaria hospitalizations (41%) and all-cause hospitalization (19%) over 18 months in 5-17 month age group. While efficacy over 18 month period has demonstrated a significant protective effect, there is evidence that efficacy is waning over time. Therefore data from the booster dose (study ongoing) will be important.
- In the younger age group (6-14 week of age), results are less favorable, with clinical malaria efficacy 27% over 18 months and no significant efficacy over 18 months for severe malaria and malaria hospitalizations.
- The incidence of generalized convulsive seizure within seven days of vaccination (according to the Brighton Collaboration diagnostic certainty level of 1 to 3) was higher in the RTS,S/AS01 group than in the control group: 1.04 per 1 000 doses in the RTS,S/AS01 group (95% CI: 0.62 to 1.64) and 0.57 per 1 000 doses in the rabies vaccine control group (95% CI: 0.19 to 1.34) for a risk ratio of 1.8 (95% CI: 0.6 to 4.9)
- Numerical imbalance observed, with more meningitis of multiple etiologies occurring in the vaccine compared to the control group. An assessment by the IDMC revealed that these occurrences seem not temporally associated to the vaccine and that there is a low biological

plausibility. It is therefore neither confirmed nor excluded if these cases are caused by vaccine RTS,S.

Main discussion points

- Any initial indication and recommendation for use will be in children <17 months of age in sub-Saharan Africa
- No pharmacovigilance datasets will become available from high income countries
- Strengthened pharmacovigilance with active surveillance will be needed as part of any initial introductions
- It is time to start planning for this, bearing in mind there are still several steps to go before any possible introductions. 2017 possible date for 1 or 2 country introductions.
- Baseline surveillance of meningitis will be important using the same surveillance system to render post-introduction data interpretable
- Following the clinical trial phase, there is need to plan post registration datasets.
- WHO guidance on best practice for generation of post registry safety and effectiveness data would be beneficial (development of such guidance is underway accordingly).
- In the ensuing discussion, the need was flagged to increase pharmacovigilance and to generate data for the introduction of new vaccines not only for Malaria vaccine but in general.

Conclusion

RTS,S might (or might not) receive licensure, prequalification and policy recommendation for use in children <17 months in some African settings by 2016. It is time to start planning for strengthened pharmacovigilance and effectiveness data collection as part of any initial country introductions from 2017 onwards.

Development status and safety profile of dengue vaccine – Dr K Vannice.

Summary

Following a short introduction on the characteristics of dengue virus and the corresponding vaccines, challenges for dengue virus development were identified and the reason to develop tetravalent formulations was given.

Hypothetical safety concerns of the dengue vaccine include dengue infection associated to vaccination as well as viscerotropic or neurotropic disease. Live tetravalent vaccines are currently being tested in phase I up to phase III clinical trials. The most advanced vaccine candidate is CYD-TDV. It is being evaluated in Phase III trial in Latin America and Asia. A WHO technical advisory group is advising on safety issues on clinical trials and includes former and current members of the Global Advisory Committee on Vaccine Safety (GACVS).

Main discussion points

- Continued careful assessment of clinical trial data is recommended.

- Capacity has to be built to enable NRAs to review registration applications and risk management plans.
- Early and coordinated planning for post licensure safety assessments should be undertaken

Conclusion

GACVS reviewed the CYD-TDV candidate in December 2012 and reaffirmed the 2008 WHO recommendations related to safety ('Guidelines for the clinical evaluation of dengue vaccines in Endemic countries') and recommended approaches for designing safety studies. Most other vaccine candidates are still in early stages of evaluation and safety data are not yet published. A Phase I study of TV003 showed no vaccine related severe adverse events.

Breakout session: vaccine risk communication, identification and prioritization of challenges and overview of resources.

A presentation on Vaccine Safety Risk Communication highlighted the importance of preparedness of national officials to conduct risk communication. The impact of several vaccine safety communication crises was outlined and research findings were presented to highlight the challenges to reach to populations most in need of vaccination.

In working groups, participants identified main issues related to vaccine safety communication and provided suggestions to the Global Vaccine Safety Initiative's future course of action.

Communicator

- Political situation and political will
- Commitment of Stakeholders
- Budget allocation for crisis management

Confounding factors

- Vaccine should save lives (evidence base messages)
- Language barriers in communication
- Literacy levels vary and thus very limited knowledge about the disease and the vaccine
- Needs advanced risk communication (emotional as children are affected, pronounced perception of risks)
- Media liberalism different from country to country

Audience

- Interpretation of vaccine benefits
- Media interpretation based on limited knowledge + rumor mongering (Government censorship on media -not trusted in some countries-) alternative: social media
- Negative propaganda by community leaders (religious belief and social norms)

Expected support from GVSI

- Encourage sustained media, civil society and parliamentarians engagement program (country specific)

- Prepare guidelines for media engagement
- Toolkit for training the stakeholders & shareholders (multilingual)
- Regular updates to stakeholders with regards to new evidence generated on safety
- Prepare guidelines for stakeholders engagement

Breakout session: National Regulatory Authorities strengthening : enabling factors

The National Regulatory Authorities (NRAs) responsibility in ensuring quality, safety and efficacy of medicinal products was introduced. Among the essential functions of a NRA, as defined by WHO's Expert Committee on Biological Standardization (ECBS), the one dedicated to the surveillance of vaccine field performance (safety and efficacy), named "vaccine pharmacovigilance" was detailed. The global status of this function as assessed by WHO was provided per region and per vaccine source (locally manufacturing, self-procured, UN agency procured).

In working groups, participants identified enabling factors for NRA to increase scope and capacity in vaccine pharmacovigilance, and provided suggestions for a GVSI support.

Institutional regulations and guidelines for PMS including monitoring and management of AEFI

- Regulatory process to establish role and responsibilities of all stakeholders

Roles and responsibilities of key players

- EPI responsible for immunization programme management; NRA responsible for quality, safety and efficacy of vaccines, and related process and procedures.
- Ensure complete and timely sharing of information between stakeholders; AEFI database management of information
- Guidelines for PQ vaccines to go through expedited NRA review
- For PQ vaccines, marketing authorization holder (MAH) to share safety information with NRA

Quality Management system (Completeness of AEFI/PSUR, Timelines, SOPs)

- Mutual Accreditation between NRA - (GVSI)
- WHO technical support (technical) - (GVSI)
- Internal audit
- Training (GVSI)

Human Resource Management

- Political commitment for resources allocation
- MAH Registration fees should include cost related to PV work
- Regular training (GVSI). Online courses and seminars in multiple languages.
- Incentives salaries to recruit and keep qualified staff

Routine and functional system for regular review of Safety Information

- To empower NRA with Statutory Provision
- Mandatory Information from Manufacturer
- Health care provider sensitization

- Timely information sharing in multiple language through networks (GVSI)

Capacity to detect/investigate safety issues

- Reporting system : Phone, fax (for general public, media, institution etc.)
- Internal capacity to detect (training, manpower)
- Centralized data base for reports
- Outside laboratory support for open vial (GVSI)
- Overseas/outside inspection, if required (GVSI)

Regulatory outcome on vaccine performance

- Mandatory registration by NRA, irrespective of prequalification status
- PMS/PSUR/Phase IV provision

Meeting conclusion and next steps

Dr Patrick Zuber concluded the meeting by thanking the participants for their interest and meaningful inputs allowing identification of effective models for implementing the Global Vaccine Safety Blueprint and shaping up collaborative mechanisms in support of GVSI.

The meeting recommendations will feed the GVSI planning group work plan and ultimately be reflected in the GVSI portfolio of activities, for effective vaccine pharmacovigilance systems in all countries.