Global Collaborative Network for Vaccine Safety Studies

“Les Pensières”
Fondation Mérieux Conference Centre
Veyrier-du-Lac - France
March 28-30, 2011

Steering Committee:

• Catherine DUTEL
• Hector IZURIETA
• Alena KHROMAVA
• Jacques LOUIS
• François SIMONDON
• Patrick ZUBER
Welcome Letter

March 28, 2011

Dear Participant,

It is our pleasure to welcome you to the symposium entitled:

‘Global Collaborative Network for Vaccine Safety Studies’

in Fondation Mérieux’s Conference Centre ‘Les Pensières’. We hope you will enjoy this meeting, which brings together some of the world’s foremost experts.

The format of the discussion is intended to generate discussion and interaction among participants and to foster the dissemination of new information on this topic. The conference will provide an opportunity for specialists to exchange their knowledge and experience through collaboration with researchers from around the world.

Over the next three days, the team at Les Pensières will be on hand to help you with any questions you may have and to make your stay and conference as comfortable and valuable as possible.

Benoît Miribel
Director General
Fondation Mérieux

For more information: www.fondation-merieux.org
Background and rationale

Pioneering vaccine safety analytic work by single countries such as Denmark and the USA (CDC’s Vaccine Safety Datalink) has been built on significant investments, long-term collaborations to enhance data quality, and dedicated investigators. Although similar abilities exist in a handful of other countries and settings, many areas of the world lack the ability to investigate in a timely fashion vaccine safety issues that may arise locally and affect vaccine acceptance and potentially also patients’ health. Inability to address vaccine safety issues rigorously and in a timely fashion can lead to loss of confidence in vaccines and consequently decreases in coverage, as were seen with pertussis vaccines in the 1980’s in some regions, and then subsequently with MMR vaccine in the UK. Concerns about vaccine safety have also adversely affected the drive to eradicate polio. As many vaccines used in low- and middle-income countries are not used in countries with effective analytic systems, it is important to explore how similar approaches could be developed so that some of the vaccines that are used in highest volumes can also benefit from modern safety monitoring.

Efforts are now underway in Europe to create the capacity and structure for multiple countries’ investigators and databases to be analytically joined to gain statistical power and geographic diversity. Such an effort requires close collaboration, funding, skilled and willing investigators, and important scientific-medical questions that are feasible to address. Such patient-based longitudinal database projects have also been undertaken in other countries. Like all such projects, they depend on the existence of computerized databases that include longitudinal data on patients health care experiences.

In the absence of computerized databases with high-quality information on patients, important vaccine safety questions can be addressed using alternative strategies. For example, hospital-based case-only study designs that evaluate quantitatively the temporal relationship (or lack of it) between vaccination and a serious adverse event can be used to assess a potential relationship between vaccination and that adverse event. Such a study design may be implemented in settings where resources are quite limited.

The objectives of this meeting are:

--to bring together investigators who have established or who aim to establish vaccine safety evaluation infrastructures, in countries ranging from the most to least wealthy.
--to share information, practical lessons and experiences related to technical and administrative/ organizational approaches that do and do not work.
--to create links that can allow more rapid communication and potential collaboration in the event that future vaccine safety concerns arise, whether or not these concerns are emergent.
--to delineate levels of evidence for vaccine safety from signal detection to refutation/confirmation, and to link attainable levels of evidence to infrastructure for a given adverse event.
--exploring regulatory implications of making improvements beyond the current infrastructure.
--describing and discovering synergies of a global collaborative vaccine safety network.
--identifying next steps to forward a global collaborative vaccine safety network after the end of this meeting.
## Scientific Programme

### Monday 28 March 2011

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### Tuesday 29 March 2011

#### Session 1

Case studies on how to evaluate vaccine safety, the potential benefit of a global collaborative network  
Chaired by François Simondon & Gabrielle Breuglemans

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<td>International infrastructure needed for vaccine safety signal strengthening and hypothesis testing</td>
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#### Session 2

**New initiatives and existing vaccine safety evaluation structures**
Chaired by Piotr Kramarz & Jan Boenhoffer

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**Wednesday 30 March 2011**

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### Session 3  
**09.05 - 17.00**  
The importance for a global collaborative network for vaccine safety  
Panel discussion  
Chaired by John Clemens and Robert Chen

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| 14.15 - 16.15 | Panel Discussion  
**What are the next steps to an optimal global collaborative network for vaccine safety studies?**  
*Items to be addressed during small groups discussion:*  
- How to structure the network organizationally to promote funding? With attention to conflicts of interest.  
- Appropriate coordination center for such network? Should it be located in a less developed country? What would be the role of each institution?  
- How would priorities be set?  
Patrick Zuber, Hector Izurieta, Steve Black, Robert Chen, John Clemens, the speakers and chairs from sessions I and II, Vincent Ahonkhai, Patricia Saddier and John Weil  
Moderators:  
Patrick ZUBER, Hector IZURIETA, John CLEMENS and Robert CHEN |
| 16.15 - 16.45 | Summary presentations by each group                                  |
| 16.45 - 17.00 | Concluding remarks and end of the meeting                           |
Keynote lecture

The potential significance of a global collaborative network for vaccine safety studies
The potential significance of a global collaborative network for vaccine safety studies

Barbara LAW
Centre for Immunization and Respiratory Infectious Diseases, Public Health Agency - Canada

Immunization is a proven public health intervention with an outstanding record that includes smallpox eradication, prolongation of life expectancy and significant reduction of morbidity and mortality due to over 20 vaccine preventable diseases. Yet no vaccine is 100% effective or 100% safe and the paradox remains that, the more effective vaccines are, the less apparent the need for them and the more vulnerable immunization programs become to issues that lead to loss of confidence. Experience with vaccine safety concerns, real and perceived, plausible and implausible, proven and theoretical, has taught many valuable lessons and led to improvements and innovations in vaccine safety monitoring, signal detection and validation, hypothesis testing and public risk communication. Nonetheless, to maximize current and future vaccine uptake and thereby effectiveness, there must be global effort and infrastructure to monitor safety and respond rapidly to emerging concerns. When it comes to vaccine preventable diseases and vaccine safety the world is a global village. Diseases, allegations and rumors cross borders with ease and the impact is far reaching. So too must be the efforts to respond, gather evidence and mitigate risk.

A global collaborative network for vaccine safety studies has enormous potential for increasing both local and global capacity to conduct vaccine pharmacovigilance in the broadest sense of the word. Given the limitations of what can be learned about safety prior to licensure, a global network could provide access to large diverse populations with the power to assess rare event causality, determine risk factors for adverse outcomes in specific groups, rapidly investigate new emerging concerns, maximize the power to study vaccines with limited distribution and add capacity to compare different products targeting the same disease. The global network could facilitate, strengthen and accelerate current efforts led by WHO and others to improve capacity for assessing post-licensure vaccine safety in low and middle income countries. High income countries lacking the capacity for large linked administrative database studies such as those done in the United States and Denmark may also benefit.
Suite

There are many synergies to be gained not only from the anticipated end result, once achieved, but also from the processes and collaboration needed to get there. These include but aren't limited to increased collegiality and ease of communication, harmonized language and methodology, shared best practices and innovations, increased opportunities for training and collaboration and enhanced knowledge translation. The application of standard methodologies throughout the vaccine life cycle may enable meta-analyses to better inform vaccine safety. The network could work to determine background rates along with the impact of age, genetics and geography on diseases likely to be temporally associated with vaccine administration. Preparedness to meet the next pandemic or other global challenge could be strengthened along with the capacity to investigate completely unexpected vaccine–event associations such as narcolepsy. Finally to the extent the network becomes publicly visible, identifying problems and seeking answers to questions, it will give testament to the readiness for all involved stakeholders to maintain vigilance regarding vaccine safety and never take the many benefits of vaccines and immunization for granted or become complacent about products that are safe but not 100% safe.
Session 1

Case studies on how to evaluate vaccine safety, the potential benefit of a global collaborative network
Introduction. What a global collaborative network for vaccine studies could contribute: the role of the meeting

Alena KHROMAVA
Global Pharmacovigilance and Epidemiology Department, Sanofi Pasteur - Canada

In the presentation, the meeting objectives will be reviewed. Global Vaccine Safety datalink is a part of WHO Global Vaccine Safety Blueprint. A brief overview will be given to what happened in vaccine safety field after the Global Vaccine DataNet meeting in September 2007. Some new vaccines will be introduced in low and middle income countries (LMIC). The need for vaccine safety infrastructure in LMIC will be reiterated.
Vaccine safety monitoring is increasingly being recognized as a key component of public health programs. The increasingly global introduction of new vaccines requires well coordinated and trusted international vaccine safety monitoring. Regulatory agencies need to be in the position of making well informed decisions. Public health authorities need to be in the position to respond to vaccine concerns before turning into large scale scares, reducing vaccine uptake, derailing immunization programs, and causing resurgence of disease.

Accurate and reliable vaccine product testing and monitoring requires high quality data and involves populations of 100 million and above depending on the frequency of the event, vaccine coverage, and the time pressure during which data need to be generated. This can be achieved most efficiently and indeed financed as part of post authorisation safety studies utilizing large linked population based databases of exposure (i.e., vaccine registries) and outcome data (i.e., hospitalization discharge databases or electronic medical record databases). The availability and type of databases varies greatly between regions and countries.

Effective international collaboration requires a shared infrastructure and harmonized methods. Consensus on a common language (e.g., mapping of codes, definitions of outcomes), harmonization of methods (e.g., study protocols, data management), and utilization of electronic tools (e.g., standardized data entry systems, distributed data model software, automatic classification tools) are hallmarks of an international framework meeting today’s requirements.

The US VSD is the best established system. Several recent developments have addressed issues of international collaboration. For example, the WHO sponsored international case series investigating the association between pandemic influenza vaccine and GBS, and the VAESCO network testing several hypotheses across European member states. The international federation of existing databases and capacity building at the national level with focus on low and low-medium income countries is a major opportunity to move vaccine safety monitoring to the next level.
The VAESCO Consortium of the EU: studies on H1N1 vaccination and GBS/Narcolepsy

Miriam STURKENBOOM
Nicoline van der Maas, Anders Hviid, Nick Andrews, Corinne de Vries, Terhi Kilpi, Par Sparen, Harald Heijbel, Jann Storstaetter, Brigitte Stanislawski, Carmela Santucci, Anne Castot, Daniel Weibel, Paco de Abajo, Piotr Kramarz, Kari Johansen, Jan Bonhoeffer
Erasmus MC - The Netherlands

The VAESCO consortium, which is funded by the European CDC (ECDC) and coordinated by the Brighton Collaboration aims at developing a European Vaccine Safety Datalink. Within months after its launch the pandemic started and the consortium was asked by ECDC to conduct studies on 1) Background rates of events of special interest (as defined by FDA/EMA); 2) the association between vaccination for the 2009 pandemic influenza A (H1N1v) virus and Guillain-Barré Syndrome. One year later a signal was raised on a potential association between the pandemic vaccine and narcolepsy and the VAESCO consortium was asked to rapidly respond to this issue. The capacity in Europe to conduct the required studies differs from country to country regarding the availability of population based registries capturing health outcomes, lag times in updating of these data and the availability of vaccination registries. VAESCO capitalized on EC investments into linking databases across the EU to monitor drug safety (EU-ADR project). In the EU-ADR project software tools were built for a distributed and harmonized approach for data extraction and manipulation. These tools allowed for a rapid assessment of the background rates of 12 events on an experience of 260 million person-years in 8 countries. Since many countries do not have vaccination registries linked to outcomes databases, a two tiered approach was used for association studies (narcolepsy and GBS) accommodating centers with registries/databases and those in need of field studies. Based on these approaches a case-control and self controlled case series analysis of the pandemic vaccination and GBS was conducted and a case-control study on the association with narcolepsy is ongoing.

VAESCO is breaking grounds by allowing for flexible high quality and harmonized data collection across countries while respecting local needs and requirements.
Safety issues related to oral poliovirus vaccines

Roland SUTTER
World Health Organization - Switzerland

Shortly after licensure of monovalent type 3 oral poliovirus vaccine (mOPV1) in the United States in 1961, vaccine-associated paralytic poliomyelitis (VAPP) cases were noticed, particularly in adults. Since 1963, the trivalent OPV (tOPV) has become the vaccine-of-choice for poliomyelitis control in the United States and most of the world. The risk of VAPP following tOPV has been well-characterized in the United States, the United Kingdom, and other countries, and is generally most elevated following the first dose of vaccine, and decreases with subsequent doses. Individuals with B-cell immunodeficiency disorders are at highest risk. In 1988, the World Health Assembly resolved to eradicate poliomyelitis globally by the year 2000, relying almost exclusively on tOPV. However, because the immunogenicity of OPV vaccines, particularly in Northern India, was much lower than elsewhere, the technical oversight committee of the global polio eradication initiative recommended in 2004 the development of more immunogenic OPVs. After an intensive development effort that brought together manufacturers, regulatory agencies and WHO, newly-formulated mOPV1 and mOPV3 vaccines were licensed in 2005, followed in 2009 by licensure of a bivalent (types 1 and 3) OPV (bOPV) vaccine. These vaccines were integrated into the eradication program immediately and used massively (>1 billion doses of mOPV1 used in the first calendar year of use) for supplemental immunization activities. We will present immunogenicity data for these newly-developed vaccines and discuss the risk of VAPP following administration of these vaccines.
Fever and febrile seizures in New Zealand children following administration of 2010 (H1N1-containing) inactivated influenza vaccines – findings and lessons

Helen PETOUSIS-HARRIS
Tracey Poole, Robert Booy and Nikki Turner
Immunisation Advisory Centre, University of Auckland - New Zealand

In 2010 Western Australia reported an increase in febrile convulsions in young children following administration of a single brand of influenza vaccine and the programme was suspended for children aged five years and younger. At the time it was not known if just one or more brands of vaccine were associated with the problem.

To urgently address this issue four retrospective surveys were undertaken in New Zealand including a large survey (FIIVa) evaluating 3176 doses of influenza vaccine. This presentation will include the findings for these studies which include data for 2892 infants aged 6 months of age through to adults aged 55 years, over a total of 4205 doses of vaccine. The FIIVa study found a relative risk of 3.28 (2.75–3.91) for fever within 24 hours following administration of Fluvax vaccine compared with Vaxigrip, and a RR of 39.5 (5.2-303.3) for admission to hospital for a febrile-related event in young children. Data on other major febrile events will be presented and the strengths and challenges of these studies will be discussed along with data from the NZ passive monitoring system for the same period and value of collaborating with Australia.
Investigation of possible association of GBS to meningococcal conjugate vaccine

Katherin YIH
Harvard Medical School and Harvard Pilgrim Health Care Institute
USA

Abstract not provided
Autism and thimerosal containing vaccines

Anders HVIID
Statens Serum Institut - Sweden

This presentation will highlight the strengths and weaknesses of the register-based Danish approach to vaccine safety research exemplified by how the suggested link between thimerosal and autism was evaluated. The presentation will finish with a discussion on if and how international collaboration could have added to the study.
Intussusception risk and health benefits of rotavirus vaccination in Mexico and Brazil

Manish PATEL
Centers for Disease Control and Prevention - USA

Because post-licensure surveillance identified that a previous rotavirus vaccine, Rotashield, caused intussusception among 1 in 10,000 recipients, we assessed the association of the new monovalent rotavirus vaccine (RV1) and intussusception after routine infant immunization in Mexico and Brazil. We used the case-series and case-control method to assess the association between RV1 and intussusception. In this study, RV1 was associated with a short-term intussusception risk of substantially lower magnitude than Rotashield. The absolute number of deaths and hospitalizations averted through vaccination in Mexico and Brazil far exceeded the number of intussusception cases associated with vaccination.
Session 2

New initiatives and existing vaccine safety evaluation structures
VAERS and VSD: new initiatives

Frank DESTEFANO
Immunization Safety Office, Centers for Disease Control and Prevention - USA

In the United States, the Vaccine Adverse Event Reporting System (VAERS) and the Vaccine Safety Datalink (VSD), provide the backbone for vaccine safety monitoring and research. VAERS is a spontaneous reporting system. It is national in scope and serves as the early warning system to detect signals of potential safety problems. VSD is a collaborative project between the Centers for Disease Control and Prevention (CDC) and 10 large U.S. managed care organizations. VSD has access to computerized healthcare databases for a population of over 9 million members, including immunization data and coded diagnoses of health care encounters, as well as access to detailed medical records information. Both VAERS and VSD have been in existence for over 20 years and both have made important contributions to identifying vaccine safety problems and also providing reassuring data on a number of vaccine safety concerns. Both systems have undergone modifications and improvements over the years. Current initiatives to enhance VAERS include application of Web-based and text-messaging technologies to make reporting easier and more accurate and also to enable more active follow-up of vaccinated individuals; incorporation of alerts into electronic medical record systems to improve reporting to VAERS; evaluation of text-mining software; and greater reliance on data mining for signal detection. The most far-reaching recent innovation in the VSD project has been the development of the technical and statistical methodologies to allow near real-time monitoring of safety of new vaccines or vaccines used in mass vaccination campaigns. Other current initiatives include the expansion of the project to increase the size of the population. Also, linkages with regional immunization registries have been explored and implemented at some sites. The diffusion of electronic health records and the capability to link records across data systems (such as large health insurance claims data bases and immunization registries) may allow the expansion of the population that could be included in post-licensure epidemiologic evaluations of vaccine safety such as is currently possible in VSD.
Feasibility of vaccination studies with the German pharmacoepidemiological research database

Edeltraut GARBE
Bremen Institute for Prevention Research and Social Medicine, University of Bremen - Germany

The German Pharmacoepidemiological Research Database (GePaRD) consists of claims data from 4 statutory health insurances in Germany and is currently being built by the Bremen Institute for Prevention Research and Social Medicine. The database contains data on 14 million insurance members covering all regions of Germany. Besides demographic information, the database includes data on outpatient care, hospitalizations and prescribed drug dispensations from pharmacies. Drugs are coded with a central pharmaceutical number (PZN). Since vaccines are often administered from office supplies of physicians in private practice, they are usually not recognizable by the PZN, however, they may be identified by data on reimbursement which physicians request for administering vaccines. This more cumbersome approach will be demonstrated in the context of a feasibility study on MMR/MMRV vaccines and febrile convulsions in the database.
Denmark – New Initiatives

Anders HVIID
Statens Serum Institut - Sweden

This presentation will focus on new approaches to the study of vaccine safety in Denmark using our national registries. This includes:

I) how to utilize our national registries for signal detection as a supplement to traditional spontaneous adverse event reports, and

II) studying vaccine safety in individuals and special populations.
Global initiative to develop a collaborative vaccine safety network: issues with the international study to evaluate the risk of GBS after flu vaccination

Hector IZURIETA
FDA - USA

To assure vaccine safety, countries should make efforts to develop the capability to detect, evaluate and confirm safety signals or concerns. This means developing a vaccine adverse event surveillance system with the technical capacity to strengthen and evaluate signal using quality checks, verification in other systems, outbreak investigations and confirmatory epidemiological studies. This usually includes a reporting system (passive or active), particularly for serious, rare adverse events, well trained and rapidly deployable outbreak investigation teams, and the availability of observational study sites able to perform epidemiological investigations as needed.

Many countries have limited infrastructure and technical capacity to perform complex observational epidemiological studies on their own. Others, which may have the necessary technical resources, do not have study populations large enough to provide the power for evaluating rare adverse events in reasonable time. Therefore, a collaborative approach is needed to monitor in a timely fashion potential serious vaccine reactions. To this effect, a participative approach has been proposed. Under this model, each country and study site engage into a collaboration, so that each country contributes a few study sites (e.g. national reference hospitals) to a WHO-led international vaccine adverse event investigation group built with technical support from international experts. This group should ideally have the capability to rapidly put together, at WHO’s and participant countries requests, the analytical resources of multiple partners to implement complex and/or large observational studies needed to assure vaccine safety globally.

This collaborative approach is being tested in a proof of concept study currently investigating the risks of GBS following administration of H1N1 influenza pandemic vaccines. The project is supported by WHO, the FDA and NVPO. Participants in this proof-of-concept study also include EMA, the Brighton Collaboration, the ECDC-sponsored VAESCO project, led by the University of Rotterdam (including data from sites in Finland, Denmark, United Kingdom, Italy, Norway, Sweden, Netherlands, France and Germany), as well as collaborating centers and hospital networks from Australia, Singapore, Hong Kong, Israel, Canada, Spain, Mexico and the U.S. (which includes data from the VSD, VA, CMS and DoD).
For this proof of concept, a protocol was developed to identify cases of GBS through clinical data sets, to classify such cases using a GBS case definition developed by the Brighton collaboration, and to utilize the case series methodology to analyze the risk of GBS following pandemic vaccine administration. The case series methodology was chosen because it provides the capacity to reliably study rare adverse events without the need to use population denominators (difficult to obtain, and often unreliable, particularly in middle and low income countries).

The purpose of this collaborative effort is to perform a scientific assessment of the risk of GBS following pandemic influenza vaccination as well as to demonstrate the feasibility of developing and adhering to a collaborative protocol, pooling data and performing a joint valid epidemiological analysis. Work on this effort is ongoing. An international team of experts is performing data simulations to select the most appropriate self controlled methodology, and WHO is gathering data from participating countries to develop the analysis dataset. Final results of this proof-of-concept study are expected for later this year.
Leveraging existing sentinel systems for monitoring safety and effectiveness of vaccines in resource-limited countries

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Abstract not provided
Background: Various viral vectors are being explored for use in vaccines against diseases such as HIV, TB, and malaria. The unexpected halt in 2008 of the “STEP” HIV vaccine trial highlights the importance of safety assessments of candidate vaccines. Safety parameters generally cannot be measured directly, but require indirect inference from the frequency of multiple adverse events (AEs). We seek harmonization of AE assessments to maximize their comparability and value across trials of multiple vaccine candidates.

Methods: The Brighton Collaboration (BC) was created to develop high quality information about vaccine safety; case definitions on 24 AEs have been published. The BC formed the Viral Vector Vaccines Safety Working Group (V3SWG) in October, 2008. The BC secretariat organizes and supports monthly conference calls.

Results: To date, the V3SWG has 1) recruited ~30 volunteers from stakeholders representing academia, industry, and government for balance between virology and safety expertise, 2) agreed on a standard template developed for collection of data on each vector and risk assessment framework, and 3) developed a workplan to harmonize assessment of the following issues: a) potential for vector recombination with wild type pathogenic strains, b) implications of prior infections on safety, c) genetic stability of replicating vaccine viruses in vivo, d) potential changes of vaccine viral tropism, e) tests for absence of reversion to virulence, f) absence of replication-competent virus when replication incompetent vectors are used, g) vaccine effects on innate immunity and on the induction of an immuno-suppressive window or immune-activation, h) length of time for monitoring AEs, i) inclusion of adventitious agents in cell culture, and j) possible secondary transmission of vaccine virus.

Conclusion: The BC has successfully launched the V3SWG as its first entrée into harmonization of pre-licensure safety assessments. The guidelines in development should improve our ability to prioritize vector selection and interpret safety data of viral vector vaccines. These efforts should in turn aid public acceptance of the eventual licensed vaccine.
Session 3

The importance for a global collaborative network for vaccine safety
Applying surveillance infrastructure to the assessment of vaccine safety and effectiveness in Kenya

Robert BREIMAN
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Background: the second decade of the twenty-first century will bring to Africa long-awaited vaccines to prevent the leading causes of severe pneumonia, diarrhea and meningitis in children. For years, these vaccines (or similar formulations) have been available for children in industrialized nations, where systems exist to document post-licensure effectiveness and to monitor for vaccine-associated adverse events. In contrast, most developing countries lack capacity to conduct surveillance which would adequately assess how vaccines perform following introduction. As a result, countries rely heavily on data from Phase III, double-blind, placebo-controlled trials to support introduction and to address questions about safety; however, pre-licensure data may not reflect real-world conditions and impact from vaccines and the numbers of participants in trials are often insufficient to detect important vaccine-associated adverse events.

Methods: documentation of public health impact and relative occurrence of adverse events can be critical towards sustaining vaccine use, especially as responsibility for vaccine purchase shifts from donors to governments, which often have limited available resources for public health prevention. Furthermore, risk-benefit ratios for the developed world are often quite different from Africa, where vaccine-preventable diseases are much more likely to result in severe illness and death; post-licensure data from the developed world, while inappropriate for assessing risk-benefit for African studies, are, nonetheless, relied upon with potential devastating impact on life-saving vaccine programs. CDC-KEMRI established active population-based infectious disease surveillance in rural and urban communities in Kenya (total population=55,000) to define burden of disease and priorities for disease prevention efforts. In addition, CDC-KEMRI operates a health and demographic surveillance system in rural western Kenya to monitor health trends, including mortality among 220,000 people.
Suite

Results: a variety of surveillance systems are available to assess direct and indirect effectiveness following vaccine introduction. These systems have the potential to monitor for and characterize incidence of adverse events following vaccine introduction or during demonstration projects prior to nationwide vaccine introduction. A study to assess adverse events associated with the 10-valent pneumococcal conjugate vaccine (PCV-10) is ongoing within our population-based surveillance sites.

Conclusions: while larger hospital-based data systems are under development, their utility will be limited by relatively low health utilization in many areas in Africa; strategically placing or adapting/utilizing population-based surveillance systems (using common methodologies) in Africa would be helpful during this decade of introduction of new childhood vaccines.
Evaluation of pharmacovigilance systems in developing countries: the role of an international collaborative network

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Since 1996, WHO has supported its member states in assessing their vaccine regulatory systems. Through more than 300 visits in over 100 countries, those systems have been regularly assessed against pre-established indicators and institutional development plans adjusted according to evaluation findings. Post-marketing surveillance (PMS) for adverse events following immunization (AEFI) is one of the six functions assessed. In recent years, this function included 8 main indicators and 25 sub-indicators. A systematic review of those indicators reveals that, although most industrialized countries and other vaccine producing countries have an effective PMS system in place, only a small number of countries that rely on United Nations procurement services have such a system in place.

An international effort, the Global Vaccine Safety Blueprint Project, is currently underway to propose a global plan for assisting low- and middle-income (LMIC) countries enhance their ability to conduct vaccine safety activities. A concept of minimal capacity is being proposed as a benchmark for countries to ensure that vaccine safety can be monitored and corrective action taken. As an increasing number of vaccine products are used exclusively in LMIC and promising newer products are underway, this capacity will be required for LMIC to monitor and respond to vaccine safety alert as a mechanism for ensuring that unwanted vaccine reactions are minimized and public confidence in vaccination is maintained.

In support of this effort, it is proposed that an international collaborative network collaborates with WHO in order to assist countries with a series of resources for: capacity building, harmonized standards and tools, systematic evaluation of surveillance data, availability of expert advice, conduct of vaccine safety studies and risk communication. Implementation of the Blueprint should ensure that national regulatory authorities and immunization programs are empowered for managing vaccine safety issues with adequate communication and information exchange across countries and with industry. A network of technical agencies, non-governmental organizations and multilaterals will provide the global backbone for implementing this Blueprint.
Rapid and routine detection of vaccine safety signals: methods challenges that impact collaboration

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The link found in 1999 between rotavirus vaccine and intussusception, along with the association observed later between rofecoxib and heart disease, substantially increased interest in developing ways to perform effective post-marketing safety surveillance for vaccines and drugs. This talk will provide a historical overview of the issues faced while trying to develop the means of performing rapid, yet routine monitoring for vaccines in the CDC Vaccine Safety Datalink project. At first, a major challenge arose simply in orienting the large amounts of data such that it could be prepared easily and shared routinely on a weekly basis. At the same time, the data needed to contain enough detail and specificity as to allow its use for multivariate modeling. Once the data became available for use in analyses, the original models used Sequential Probability Ratio Testing (SPRT) to test for vaccine safety signals. However, it soon became apparent that temporal trends in coding and in the completeness of data collection threatened the accuracy of the results. It was only after these secular trends were accurately controlled that the SPRT processes performed well, and were then used to assess the safety of both rotavirus vaccine and the new acellular pertussis-containing combination vaccines. Attempting to extend the use of SPRT to examine the safety of influenza vaccine, however, uncovered a fundamental limitation to this method, related to an excess dependence on prior knowledge of vaccine risk. Given that the level of the risk – for rare serious adverse events - of most vaccines are not well known before licensure, it was clear that there was the need to modify the SPRT process, leading to the development of the maximum likelihood estimate (maxSPRT). Currently maxSPRT is used by the VSD for performing surveillance on new vaccines licensed in the United States, while work continues on identifying the best ways to optimize the statistical approach to monitoring for vaccine safety. Other new methods under development will also be presented, including ‘case-based’ methods which reduce data requirements substantially; their strengths and limitations will be discussed. Ongoing challenges – such as how to decide which outcomes to screen for, and how to minimize ‘mission creep’ when performing surveillance – will be discussed using real-life examples.
How can Industry participate/assist in the development of a global collaborative network on vaccine safety studies?

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Abstract not provided
Lessons from the 2007 Global Vaccine DataNet meeting at Fondation Mérieux: what have we learned since then

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In 2007, a meeting of possible stakeholders, public health officials, investigators and pharmaceutical company representatives was held at this site to discuss the rationale for and the feasibility of a global vaccine safety datalink. At the meeting, there was a general consensus that such an effort would be both feasible and worthwhile. Since that time, many countries that attended the meeting have initiated vaccine safety studies utilizing clinical databases and collaborative efforts among countries, notably in Europe, have begun. In addition, the Global Vaccine Safety Datalink collaboration to evaluate the risk of GBS following the 2009 Influenza A H1N1 pandemic vaccines now includes more than 18 countries in the first truly global collaborative vaccine safety evaluation using clinical databases. However, the latter is a largely unfunded demonstration project and several datalink projects globally do not have sustainable funding. Having demonstrated the feasibility and worth of these efforts both at the national and international level, the challenge in the future will be to make these efforts sustainable and to expand their scope to include middle and lower income countries as well.
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