EXPERT REVIEWS

Global Vaccine Safety DataNet Meeting

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Steven Black
279 So South Street, Wilmington, OH 45177, USA
stevblack@gmail.com

Global Vaccine Safety DataNet Meeting

Annecy, France, 12–13 September 2007

An international meeting was held at the Merieux Foundation in Annecy, France, on 12–13 September 2007, to discuss the establishment of a Global Vaccine Safety DataNet. Invitations were extended to experts from developed and developing countries that currently, or will soon, collect computerized information on vaccine exposure and clinical outcomes, as well as representatives of public health agencies and pharmaceutical companies. The goals of the meeting included assessing current capabilities and interest in establishing a global vaccine safety data network, exploring the infrastructure and funding required to bring such a project to fruition and discussing the best approach to implementation.

Although vaccines are among the most effective of public-health interventions, in many cases, their very success has eradicated the public's memory of the diseases they were designed to prevent. As a consequence, fear of disease has been replaced by concern about vaccine safety. Although, these concerns are scientifically valid in some cases, more often they are based on rumor and unsubstantiated claims and, with the advent of the internet, these rumors can spread quickly. Unfortunately, while the scientific community is in the process of collecting data to support or refute these claims, vaccine uptake may decline with subsequent increases in disease morbidity and mortality, as has occurred with pertussis in Japan and measles in the UK and elsewhere. Similarly, a safety scare regarding oral polio vaccine significantly derailed the global eradication program for this disease.

Historically, most vaccines have been developed, produced and first introduced in countries (primarily in North America and Europe) with considerable resources for evaluating safety in clinical trials and with postmarketing surveillance. However, vaccine manufacturing is globalizing, with production in Brazil, India, Cuba and China, as well as other countries. An increasing number of new vaccines, wherever they are manufactured, will be introduced first in developing countries that have a limited infrastructure for monitoring safety. The most recent example of this is a rotavirus vaccine, which has been introduced into the developing world before introduction in the USA or Europe. The history of rotavirus vaccines and intussusception highlights the rarity of the events, the differences in background rates in different countries and the different balance of risk and benefit in countries with high and low mortality from diarrhea. The introduction of rotavirus vaccines has been accelerated in the developing world, where they have higher benefit, creating a high need for postmarketing surveillance in these regions. Future vaccines, such as those against HIV or malaria, will probably also make use of newer technologies, such as DNA vaccines, live virus vectors or new adjuvants, about which safety information is limited. Since these vaccines are likely to be introduced in the developing world first, intensive safety monitoring will be required.

For these reasons, there is a great need for a global approach to evaluating vaccine safety. Using computer databases for this evaluation is attractive because such databases allow rapid identification of possible cases and vaccine exposure information and, with appropriate standardization of definitions, allow for the comparison or combination of data across several sites. Several developed countries, such as the USA, UK and Denmark, already have linked electronic databases to track vaccinations and clinical outcomes within their countries. Computer databases and technology to utilize such databases exists in other countries that would allow the development of a Global Vaccine Safety

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DataNet (GVSD). This network would foster the standardization of procedures and definitions for performance of analyses of vaccine safety based upon computerized data within countries and could form the basis for collaborative studies across several countries should the need arise. Establishment of a GVSD would greatly expand the geographic scope of current capacity. It would also allow results obtained in one geographical area to be tested in different populations, and provide additional statistical power for identifying rare events. Furthermore, the development of data networks in locations that currently lack them will facilitate the local evaluation of safety issues or hypotheses in populations around the world. This will be critical for vaccines that are first introduced in the developing world that are unavailable in the developed world (such as malaria), but may also provide valuable information on the potential risk of adverse events, whose base rates differ by location or where the endemic rates of disease may affect the results of risk–benefit analyses. Global collaborations would also enable the experience and expertise of the developed world to be extended to the developing world.

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Perspectives on need

Representatives of the WHO, US FDA, European Centre for Disease Prevention and Control and vaccine manufactures all acknowledged that current methods of safety surveillance have limitations in addressing global vaccine safety issues. New infrastructure is needed to assure that vaccines are safe, including large databases that can respond to vaccine signals in many areas of the world. Current databases are not sufficiently diverse to address global safety issues because safety issues can be region specific (such as those relating to a malaria vaccine); and events of interest, such as Kawasaki's disease, can have very different background rates in different populations. Within the EU, there is an interest in improving the evaluation of vaccine safety and a current call for proposals to evaluate adverse events following immunization in Europe.

Data links have the potential to provide speed, comprehensiveness and flexibility to the design of safety studies. Their best use is to test hypotheses generated by surveillance, clinical studies or 'the rumor mill'. The past successes of the Vaccine Safety Datalink (VSD) in the USA, including the confirmation of links between the rotavirus vaccine, RotaShield®, and intussusception, as well as the lack of such an association for the currently licensed Rotateq®, illustrate the value of such systems. In Denmark, a fully integrated system represents a very attractive model. Many challenges remain, however, to increase timeliness and include a more diverse and larger population.

In order for any findings to be credible and actionable, a GVSD should be organized or monitored by institutions without any conflicts of interest. In addition, the investigators must be scientifically independent and the science rigorous. Development and administration of a single central database would not be desirable nor acceptable to many countries but rather individual databases should be created in each participating country or site, which could be queried to analyze a specific problem, either alone or, potentially, in collaboration with other countries within the GVSD. The latter would require *a priori* establishment of proper communication and coordination among sites regarding case definitions and data structure.

Existing infrastructure

Prior to the meeting, a survey of member participants regarding data sets currently available in their countries, or likely to be available in the future, was conducted. The national experience with the use of automated data to assess vaccine safety was also described. Capacity and experience varied widely, even between countries within a region (Box 1). Of note, the majority of countries present had computerized information on at least outcomes available on all or a subset of their populations. In all, this information was available for a surveillance population of over 70 million, based upon the survey of participating countries.

The UK Health Protection Agency (HPA) has extensive experience evaluating vaccine safety hypotheses using information in several types of databases, although, ethics reviews are required for this. The General Practice Research Database (GPRD) is a system that allows linkage of exposure and outcome data. Included are hospital admissions and outpatient care, although, only 3–4% of the outpatient diagnoses and treatments are coded, in contrast to hospital admissions, which are all coded. Vaccine data are contained in a separate database but are linked to the outcomes data.

In Denmark, data linkage for public health evaluation is encouraged, and extensive databases are available that include information on every resident of Denmark, which facilitates the analysis of complex questions, such as a recent analysis rejecting an association of thimerisal exposure and autism [1].

The VSD, which was established by the CDC in 1990, allows linkage of exposures and outcomes for approximately 11 million members of eight managed-care organizations. The VSD is used for studies on the safety of new vaccines, clinical disorders following vaccination and vaccine safety in special populations, such as those at high risk for adverse events. The data sets supporting the VSD are refreshed weekly, which

Table 1. Participants at the Global Vaccine Safety DataNet Meeting, Annecy, France.

Countries	Participants
Australia	Sarah Dugdale, Jim Buttery, Mike Gold
Bangladesh*	Abdullah Brooks
Belgium	Pierre Van Damme
Brazil*	Eduardo Hage Carmo
Canada	Barbara Law, Louis Barre
Chile*	Rosanna Lagos
China (Shanghai)	Genming Zhao
China (Hong Kong)	Susan Chiu
Costa Rica*	Maureen Salas
Denmark	Anders Hviid
Finland	Juhani Eskola, Tea Nieminen
Germany	Brigitte Keller-Stanislawski
Italy	Giovanna Zanoni
Mexico*	Vesta Richardson, Gomez Altamirano, Ariel Lopez
New Zealand	Diane Martin
Singapore	Chia Yin Chong
South Africa*	Shabir Madhi
Switzerland	Jan Bonhoeffer
UK	Nicolas Andrews, Julia Stowe, John Parkinson, Stephen Evans
USA‡	John Iskander, Jane Gidudu, Ned Lewis, Robert Chen
Vietnam*	Dang Duc Anh
Regulatory and public health agencies and international organizations	
WHO	Philippe Duclos, Patrick Zuber
US FDA	Miles Braun
European Centre for Disease Prevention and Control	Pierluigi Lopalco
International Vaccine Institute	Luis Jodar
Global Alliance for Vaccines and Immunization	Arnold Fang
PATH	Kathy Neuzil
Sponsoring pharmaceutical companies¶	
GlaxoSmithKline	Thomas Verstraeten
Sanofi Aventis	William Holden, Gillis Carrigan
Novartis	John Ferguson
Merck	Patricia Saddier, Guy Demol

*Considered to be a developing country for the purpose of this meeting.
‡The US CDC participated as the representative of the USA and is not listed separately as a public-health agency.
§Participants from public-health agencies paid their own way to the meeting.
¶Sponsorship of the meeting was through unrestricted donations. Representatives of sponsoring companies were also participants in the meeting.

Box 1. Survey results of currently available infrastructure by country.

Countries with regional or national data on immunization, demographics and hospital outcomes:

- Australia
- Belgium
- Brazil
- Canada
- China
- Costa Rica
- Denmark
- Italy
- Mexico
- New Zealand
- Singapore
- Thailand
- UK
- USA
- Vietnam

(total surveillance population >70 million people)

Countries with hospital outcomes data without immunization registries:

- Chile
- Finland
- Germany
- South Africa
- Switzerland

Countries with experience using computerized data for vaccine safety analyses:

- Australia
- Denmark
- New Zealand
- UK
- USA

Countries without current computerized outcomes or exposures:

- Bangladesh

enables almost real-time analysis. To date, more than 85 articles have been published using data from the VSD, and 75 studies are ongoing.

Recently, Vietnam set up one of the few data linkage projects in the developing world as a pilot project in the Khanh Hoa Province. The project showed that it is feasible to perform linked database studies for vaccine safety through linkage of medical events to vaccine histories. The feasibility of this approach was contingent upon reliable census data, diagnostic coding and the willingness of the community to participate. In the future, Vietnam might be able to increase the completeness of its system through the use of a health card for young children. The success of this effort should provide encouragement to other developing countries.

Approaches to infrastructure & data management

The focus of the effort would be to expand the number of countries with infrastructure capable of generating cohort analyzes in a large number of vaccinees followed in order to allow evaluating vaccine safety related to the occurrence of rare and chronic events. A global network would allow for conducting collaborative studies. One of the key features of the CDC-sponsored VSD provides a possible model for such collaborative studies within a GVSD through its use of distributed data. For this, source data at sites participating in a collaborative study would continue to reside exclusively at the participating sites and not at any central location. These data sources are then queried at the site when a specific collaborative project is undertaken using standardized definitions and programs across the sites. Then, only an abstracted, de-identified analysis dataset is sent to one location for analysis. Thus, locally based infrastructure would allow total local control, with priority setting and the conduct of most studies at the local level and increasing local credibility of investigators. For collaborative studies, this design preserves patient privacy and confidentiality and does not require extensive (and expensive) central infrastructure, while still facilitating collaborative studies that can be conducted with appropriate data security. Although within the US VSD, the disseminated data model is used for almost all studies, for a GVSD, this type of approach would only be warranted for collaborative studies. Using this model for collaborative studies, each site would have the option of participating or not participating in a given study and would have to approve the data extraction for each study. Only the data required to answer a specific question would be sent to the central site and only for collaborative studies. For studies within a country, or collaborative studies between two countries, an even simpler approach might be taken. The importance of protecting private information is also illustrated by the Manitoba Center for Health Policy, Canada, where a wide range of linked data sets are used to study vaccine safety and other issues in the entire population of the province, scrambled identifiers preserve confidentiality, and no one database contains both study data and personally identifiable information.

Although the potential for collaborative multicountry studies does not require specific computer architecture, it requires that each site use standard data definitions, such as those developed by the Brighton Collaboration [101]. The proposed standardized data structure keeps the focus on high-quality data rather than complicated computer systems. In other words, this amounts to asking the right questions and taking just the data needed to answer them. Simple data sets for analysis can be created from large amounts of data using modern databasing tools, such as SQL and an exposure/event tracking system. In addition to allowing analyses of data sets from systems of different architecture to be merged for central analysis, it facilitates data-mining and hypothesis-strengthening analyses.

Data analysis

If asking the right question is critical, it is also critical to design studies carefully in order to provide the most robust answers to safety questions as quickly as possible. Several approaches to data analysis were discussed, including traditional cohort and case–control studies. One method that appears particularly attractive for a GVSD is the self-controlled case series (SCCS) design [2] In a SCCS analysis, a specific risk period after vaccination is identified as the period of risk for a given event being studied. For example, the risk period for idiopathic thrombocytopenic purpura after measles–mumps–rubella vaccination is 6 weeks, and for febrile seizures after measles vaccination is 6–11 days. For each case, the event will have occurred within the risk period or outside of it. Relative risks can be calculated in a way similar to that for a cohort analysis but using a conditional Poisson regression. Since the data are not aggregated over many individuals, the analysis can be performed with information from a limited number of cases, rather than needing data on a large cohort. This is also a useful technique when the majority of the population has been exposed, as might occur with a routine vaccination program, which would limit the number of unexposed controls available for inclusion.

Criteria for participation & phased implementation

A group discussion on possible resource models highlighted that different sites currently have different capacities and will, therefore, require varying levels of support to establish the necessary infrastructure for a GVSD. One approach would be to have a phased implementation, in which a core set of countries with established support from their scientific and public health communities would form the initial network. These initial participants would already have the necessary infrastructure or the potential to develop it, access to at least a minimum set of data on vaccine exposure and clinical outcomes, and local expertise in data management, analysis and epidemiology. In addition, geographic diversity and a range of probable vaccine exposures will be important in site selection. Additional sites could contribute to discussions while ramping up their local resources for full participation. The global need could be met by first establishing vaccine safety datalink infrastructure within individual countries, while working to assure that procedures for data management and analyses are standardized. Established sites within a region could, eventually, act as regional centers to mentor other sites in the same geographic area to eventually expand the scope of the GVSD. These regional alliances could also more readily address regional issues. In terms of questions that might be addressed within the network, it was suggested that the WHO Global Advisory Committee on Vaccine Safety, as well as local agencies or experts and investigators, would need to influence the research agenda.

Although some concerns were expressed about accepting manufacturer support, most participants recognized that such support is routine for prelicensure studies and for many postmarketing studies already, and that establishing ties with manufacturers in many countries, including developing countries, could improve vaccine safety surveillance in those countries.

Several speakers suggested that influenza vaccine could provide a timely and practical demonstration project. Awareness of the potential for an influenza pandemic has grown in recent years, and funds to prepare for such a pandemic have become available. Therefore, it may be possible to obtain initial funding from existing initiatives to prepare for pandemic influenza. The GVSD could be initially tested on routine influenza vaccines, which are administered worldwide. In addition to providing information on current vaccines, this approach would ensure that a system would be in place to quickly identify any safety concerns that might arise if influenza vaccine were distributed widely over a short time in the event of an influenza pandemic.

Challenges

A GVSD is likely to face some of the same challenges that are inherent in all database research on adverse events, including inaccuracies in coding, variations in case definitions, recall bias or missing information, particularly with regards to date of vaccination. Global standards for case definitions, as developed by the Brighton Collaboration, and the ability to review patient charts, may help resolve some of these issues, although it will always be necessary to be aware of potential confounders as in any observational study. Furthermore, there are some safety issues that a GVSD would not be able to address, such as local contamination or misuse. Achieving wide geographical representation will be an issue as the GVSD develops, and the best balance between real-time signal detection and carefully executed studies will also have to be determined so that rare events can be detected in a timely manner without sacrificing scientific rigor. Finally, it will be necessary to develop the infrastructure within each participating site so that it serves the needs of that individual country with the goal of building infrastructure that becomes integrated into each country's public-health infrastructure and is, thus, sustainable.

Next steps

It was the general consensus of the group that the establishment of a GVSD is both desirable and feasible. Immediate next steps will be to disseminate the information derived from the meeting (of which this article is a part) and to identify which countries would form the initial core group for the development of the GVSD by performing on-site surveys of potential candidates. It was the consensus of the group that the WHO should take a leadership role in coordinating the development of a GVSD. In addition, detailed site assessments of possible participants would be conducted to determine capacity, as well as resource needs.

This information would be used to develop a prospectus to obtain funding, especially for sites in developing countries that currently lack infrastructure.

Vaccines are increasingly developed, manufactured and introduced worldwide, and manufacturers, regulatory agencies, academics and local and international public-health agencies have recognized the need for globally coordinated studies utilizing computerized data on exposure and safety. At the same time, computer and internet technology has developed to the point of making a GVSD feasible. A GVSD would increase our ability to both identify real safety problems and to quickly quash unfounded concerns, a meaningful step toward providing the safe vaccines and the confidence in vaccination programs that are necessary to protect against infectious diseases worldwide.

Financial & competing interests disclosure

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References

1 Hviid A, Stellfeld M, Wohlfahrt J, Melbye M. Association between thimerisal containing vaccines and autism. *JAMA* 290, 1763–1766 (2003).

2 Farrington CP, Nash J, Miller E. Case series analysis of adverse reactions to vaccines: a comparative evaluation. *Am. J. Epidemiol.* 147(1), 93 (1998).

Website

101 The Brighton Collaboration. Setting standards in vaccine safety. www.brightoncollaboration.org

Affiliations

• Steven Black, MD
Professor in the Center for Global Child Health at Cincinnati Children's Hospital in Cincinnati, OH, USA
stevblack@gmail.com