

Review

Effective vaccine safety systems in all countries: A challenge for more equitable access to immunization

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ABSTRACT

Serious vaccine-associated adverse events are rare. To further minimize their occurrence and to provide adequate care to those affected, careful monitoring of immunization programs and case management is required. Unfounded vaccine safety concerns have the potential of seriously derailing effective immunization activities. To address these issues, vaccine pharmacovigilance systems have been developed in many industrialized countries. As new vaccine products become available to prevent new diseases in various parts of the world, the demand for effective pharmacovigilance systems in low- and middle-income countries (LMIC) is increasing.

To help establish such systems in all countries, WHO developed the Global Vaccine Safety Blueprint in 2011. This strategic plan is based on an in-depth analysis of the vaccine safety landscape that involved many stakeholders. This analysis reviewed existing systems and international vaccine safety activities and assessed the financial resources required to operate them. The Blueprint sets three main strategic goals to optimize the safety of vaccines through effective use of pharmacovigilance principles and methods: to ensure minimal vaccine safety capacity in all countries; to provide enhanced capacity for specific circumstances; and to establish a global support network to assist national authorities with capacity building and crisis management.

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In early 2012, the Global Vaccine Safety Initiative (GVSII) was launched to bring together and explore synergies among on-going vaccine safety activities. The Global Vaccine Action Plan has identified the Blueprint as its vaccine safety strategy. There is an enormous opportunity to raise awareness for vaccine safety in LMIC and to garner support from a large number of stakeholders for the GVSII between now and 2020. Synergies and resource mobilization opportunities presented by the Decade of Vaccines can enhance monitoring and response to vaccine safety issues, thereby leading to more equitable delivery of vaccines worldwide.

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1. Background

Each year, vaccines prevent more than 2.5 million child deaths globally [1]. New vaccines against more diseases are becoming available, substantially increasing the number and segments of vaccinated people throughout the world. Historically, by the time vaccines were introduced in low- and middle-income countries (LMIC) experience had been made over decades helping to understand the safety profile of those vaccines from countries with developed pharmacovigilance systems. As a result of concerted support for new vaccine introduction new vaccines become available sooner in LMIC and joint international efforts are also required on pharmacovigilance to compensate for the gap in safety intelligence. Increased number of vaccines offers protection against many more diseases, in particular severe and life-threatening conditions. As a preventive measure, vaccines are usually administered to healthy individuals making recipients of vaccines especially aware of their safety profile. Even though vaccines are designed to be safe, untoward events may occur following vaccination. Most observed events are either minor reactions resolving spontaneously (e.g. reactions at injection site) or their observation is coincidental with no causal association. However, although serious reactions are rare, they may lead to significant health problems. As diseases prevented by vaccination disappear, public attention is increasingly shifting toward the rare undesirable effects of vaccines, be they real or perceived [2].

The safety of vaccines is first assessed during their clinical development and subsequently during the post-licensure stages. Typically, by the time a product is submitted for licensure to regulatory authorities, several thousands of study subjects would have received it in clinical trials and the most frequent reactions were documented. However, due to limited sample sizes of clinical trials, rare events (<1:1000 doses administered) will only be identified after a vaccine has been made available for general use in a larger number of people [3]. Likewise, possible risks among populations with particular health characteristics such as immunocompromised individuals or pregnant and lactating women would not have been adequately assessed before licensure [4]. Many of the new vaccines will likely be developed using more complex technologies (e.g., recombinant viral vectors) which may require not only scaling up of clinical trials sample size but also increased monitoring once a vaccine is entering the market. Thus there is need for effective post-licensure pharmacovigilance to obtain

evidence of the safety of vaccines among the general population and populations with particular health characteristics under real-life conditions.

Pharmacovigilance systems for monitoring vaccines after licensure have been developed in many countries. The general principles of these surveillance systems are similar. Approaches may differ depending on the organizational structure of immunization services and the amount of resources available in a given country. The steering role of health authorities in ensuring the quality of medicines and biologicals has long been established [5]. Since 1992, the PAHO Directing Council, the World Health Assembly, and the Executive Board of the World Health Organization (WHO) have adopted a number of resolutions [6–9] to strengthen health authorities at all levels.

To be effective, national surveillance of adverse events following immunization (AEFI) should be carried out by the national immunization programme working in close collaboration with the national regulatory authority (NRA), an AEFI review committee, technical agencies, and academic institutions. NRAs are usually mandated to ensure that all medicines, including vaccines, used within the country are safe, effective, and of good quality. The WHO program for strengthening the capacity of national regulatory authorities, launched in 1996, supports countries by assessing the performance of six regulatory functions, including vaccine pharmacovigilance after licensure [10]. This capacity-building program relies on a 5-step quality management process, during which benchmarks are developed and regularly updated, national system performance regularly assessed based on these indicators, and institutional development plans generated to identify and meet needs for further improvement.

The analysis of data collected through WHO NRA assessments [10] in over 100 countries provides a strong evidence base about the status of vaccine pharmacovigilance systems in LMIC and insights about the areas that need the most attention. It confirms that most industrialized countries have implemented the critical indicators for vaccine safety. However, most LMIC still need to strengthen their vaccine safety functions. This situation reflects a strong inequity in the way vaccines are monitored throughout the world and requires energetic action.

Having effective programs in LMIC is now critical because vaccines used in these countries increasingly differ from those used in industrialized countries because of market segmentation. New products have been developed which specifically target the needs

of LMIC such as meningitis A conjugate vaccine [11], or are currently being developed, such as malaria and dengue vaccines. Consequently, introductions of new and sometimes complex vaccines, targeting diseases which are prevalent in LMIC, will increasingly take place in countries with limited pharmacovigilance capacity. Thus, the first LMIC that introduce a novel vaccine need to have the ability to detect and investigate possible reactions as early as possible.

Several important vaccine safety initiatives are already ongoing [10]. They provide harmonized methods and tools, training resources, data exchange and analysis, investigation capacity and advice from the global or regional perspective. However, the impact of these initiatives in LMIC is currently limited. In spite of its recognized importance, vaccine pharmacovigilance often competes for resources with other public health activities. Several reasons can be identified that include inefficient mechanisms for developing and disseminating the outputs from those initiatives. In the area of vaccine safety monitoring, such as signal detection, signal validation, and hypothesis testing, as well as in risk communication, limited coordination between those initiatives (e.g. lack of health data, low involvement of LMIC, lack of standard operating procedure), suboptimal collaboration between pharmacovigilance, NRAs, and vaccine safety initiatives and insufficient or unstable resources jeopardize the effective conduct of their mission [4,10].

2. Developing the global vaccine safety blueprint

To address those challenges, a collaborative group of vaccine safety experts set out to develop a global strategic plan for strengthening vaccine safety activities in LMIC [18]. The aim of this project was to place capacity building in LMIC in the center of a global support system that would include: harmonized tools, product monitoring, signal detection, evaluation, analysis and response. A participative development process for a Global Vaccine Safety Blueprint strategy was developed (Fig. 1).

An initial landscape analysis was conducted to provide an overview of existing structures, activities, and needs of vaccine safety stakeholders and initiatives at national and international levels [10]. To ensure that the analysis captured all aspects and opinions of vaccine safety stakeholders, a web-based consultative mechanism was put into place. Through this mechanism, key stakeholders could review and advise on all elements of this landscape analysis. Eventually, more than 60 experts from regulatory agencies, national immunization programs, procurement agencies, technical agencies, donor agencies, vaccine manufacturers as well as other WHO-partner organizations had access to a web-based

Table 1
Definition of vaccine pharmacovigilance.

Vaccine pharmacovigilance is defined as the science and activities relating to the detection, assessment, understanding and communication of adverse events following immunization and other vaccine- or immunization-related issues, and to the prevention of untoward effects of the vaccine or immunization.

platform providing them with protocols and reports from the landscape analysis for review. The landscape analysis was completed in 2010.

During 2011, a first draft strategic plan was produced through a series of Collaborative Group retreats and reviews through the web-based consultative mechanism. The development of the Blueprint was undertaken as an inclusive process, actively seeking the inputs and ensuring consensus of experts and practitioners worldwide. The Blueprint development process took into account the synergies of currently on-going activities and captured the benefits of coordinating vaccine safety efforts at international and national levels, which had previously also been identified in the landscape analysis. In June 2011, the Global Advisory Committee on Vaccine Safety (GACVS) provided a first review and suggested several important elements to be included in the Blueprint: (1) to design a monitoring system for vaccine safety to detect potential safety problems and respond to them rapidly; (2) to create and coordinate capacity for appropriate epidemiological investigations to be undertaken in response to potential safety signals at country or inter-country level—GACVS also highlighted the existence of several networks with the relevant capacities and the critical role that WHO could play in convening and coordinating these groups; (3) to establish a code of conduct to be followed during interactions with the pharmaceutical industry; (4) to ensure that a proportion of national budgets for vaccines include funding for assessing and investigating safety to sustain the development of safety systems; and (5) to implement regulations on data protection that will allow for secondary use of health-care data for public health purposes, including the sharing of data among countries [12].

In September 2011, the draft plan was subsequently presented to a significant number of vaccine safety stakeholders at the Global Vaccine Safety meeting at WHO Geneva. On this occasion each strategic objective was reviewed by different work groups. The recommendations from the global forum were incorporated into the subsequent version that was presented to WHO's Strategic Advisory Group of Experts (SAGE) at its November 2011 meeting. SAGE endorsed the vision and strategic goals of the Blueprint. SAGE also emphasized that vaccine pharmacovigilance (Table 1) [13] is a critical component in global immunization activities that requires

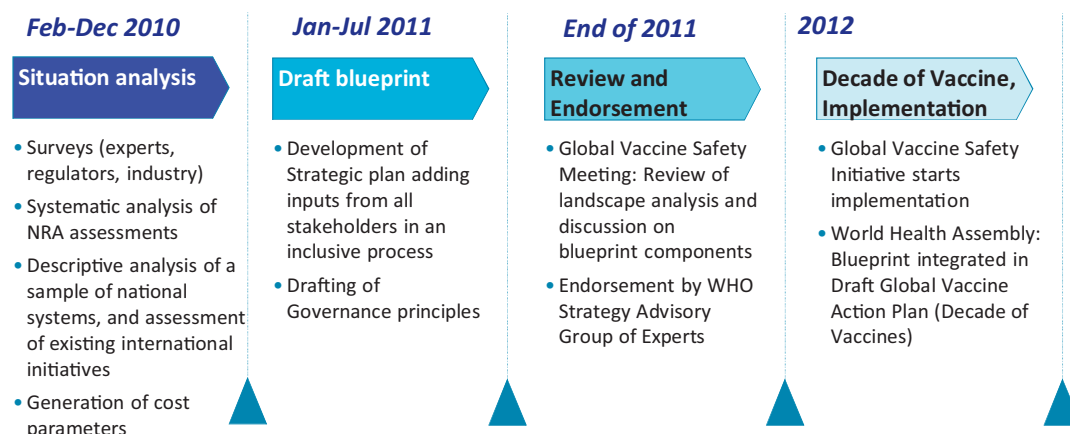


Fig. 1. Time line of the Blueprint strategy development process.

further strengthening. Another important request of SAGE was to focus on country needs during the implementation of the Blueprint in particular to help enhance national ownership in monitoring vaccine safety and respond to safety concerns [14].

Subsequent to SAGE recommendations, GACVS addressed the implementation of the Blueprint at its December 2011 meeting. Given the complexities involved with setting-up a global pharmacovigilance system, the Committee highlighted the need for step-wise approaches and prioritization. GACVS also acknowledged the terms of reference for a Global Vaccine Safety Initiative (GVS), which shall serve as mechanism to implement the Blueprint. GACVS suggested that as guiding principle, the GVS should be aligned with other related WHO capacity-building efforts such as the strengthening of immunization programs and national regulatory authorities, together with the development of national expert advisory bodies [15] that reflect expertise in specific fields such as pediatrics, immunology and infectious diseases. The Blueprint was further endorsed, as it was included as the vaccine safety strategy in the Decade of Vaccines Global Vaccine Action Plan (GVAP) [16].

3. Main findings from the landscape analysis

Besides data resulting from the WHO assessment of national regulatory authorities, the landscape analysis looked at six additional dimensions related to global vaccine pharmacovigilance. Among these were three stakeholder surveys (*vaccine safety experts*, *vaccine manufacturers*, and *regulators*), two other systems analyzes (*existing international vaccine safety initiatives* and *vaccine pharmacovigilance infrastructure in a sample of eleven low- and middle-income countries*) and one financial analysis to assess the cost of implementing the Blueprint strategies [10].

The three stakeholder surveys provided consistent views about the need for strengthening the capacity for vaccine safety activities at all levels. *International vaccine safety experts* highlighted the increased needs of more active vaccine safety monitoring and called for building expertise by training and knowledge transfer. They further highlighted the need for standardized terms and definitions, as well as harmonized approaches, which should be used by everyone contributing to a globally integrated vaccine safety monitoring system. Importantly, the capacity for active signal detection and hypothesis testing by utilizing health care databases was identified as an urgent gap to be addressed. Finally, there was a strong agreement about the importance of information sharing and risk communication as well as the need for a more coordinated international support structure, which was requested by 93% of responding professionals coming from 26 LMIC.

Vaccine manufacturers placed great emphasis on the need for harmonization in signal detection and reporting, and evaluation of AEFI. Areas requiring harmonization include data collection, AEFI definitions, medical review and report management, patient's vaccination history, reported event terms, vaccine dictionaries, and causality assessment. They also proposed priorities for developing global pharmacovigilance and identified active surveillance utilizing health care databases as a most important priority. Concerning capacity at country level, the availability of qualified staff was deemed of great importance. Manufacturers emphasized the need for personnel training, use of information technologies and communication, strengthening spontaneous reports, and establishing well-maintained databases in countries. The establishment of sentinel sites or centers for monitoring and coordinating pharmacovigilance activities was proposed as a possible approach for improving vaccine safety surveillance.

The survey of *regulators* concluded that there was an essential need for a coordinated system to standardize and communicate AEFI data to all relevant vaccine safety stakeholders in countries. Such a system should be supported by sufficient infrastructure

and resources strengthening capacity for functional vaccine safety systems in LMIC. Regulators identified in particular the need for standardized and readily accessible AEFI reporting forms, improved spontaneous and active surveillance mechanisms, adequate vaccine safety expertise and training, coordinated exchange of vaccine safety information between national regulatory agencies and public health agencies, as well as shared access to vaccine safety data and the political will to establish, sustain or resource regulatory authorities [17].

The analysis of existing International Vaccine Safety Initiatives (IVSA) demonstrated that all areas of vaccine safety monitoring are already addressed by at least one initiative—but with little coordination among themselves. The greatest attention is being paid to detecting and validating vaccine safety signals. To address the next step of reliably testing hypotheses generated through those signals, a global strategy to build population based health care databases and immunization information systems and to coordinate utilization for vaccine safety research is needed. This will require specifically coordinating know-how and human, technical, and financial resources. In addition, an integrated strategy for communication between regulatory and public health agencies, countries, and other stakeholders should be developed and implemented. The analysis confirmed the high commitment to capacity building, innovation and development. Finally, as for all areas in vaccine pharmacovigilance the limited resources available require a judicious use of person time in addressing current shortcomings and issues specific to LMIC.

The review of *pharmacovigilance infrastructures in a sample of eleven low- and middle-income countries* described countries, mainly relying on spontaneous reporting systems that have put the strengthening of their vaccine safety capacity as a priority. This analysis was therefore not representative of LMIC but rather an illustration of the elements that are available in countries where vaccine pharmacovigilance has been identified as an important activity. This analysis provided models for structuring and managing spontaneous AEFI reporting systems, building and maintaining capacity as well as communicating vaccine safety issues. Based on this analysis, a costing of existing systems was also conducted, providing parameters for costing the implementation of the Blueprint strategies.

4. Mission vision, strategic goals and objectives for the Global Vaccine Safety Blueprint

The Global Vaccine Safety Blueprint was designed and updated in an iterative process to best address the needs identified in the landscape analysis and the comments received during the open web-based consultation process. The mission statement of the Blueprint sets the optimization of the safety of vaccines through effective use of state of the art pharmacovigilance principles and methods as the main aim of the strategy. The Blueprint further envisions that effective vaccine pharmacovigilance systems are established in all countries.

To achieve this overarching aim, the Blueprint suggests three strategic goals that distinguish between three areas of work to respond to needs at different levels. The first goal is to ensure minimal capacity in all countries, the second goal looks at providing enhanced capacity for specific circumstances and the third goal aims to establish a global support network (Table 2). From this generic framework, eight strategic objectives have been derived to describe how to best support the implementation process to reach the three main goals. The first four strategic objectives outline direct improvements of the actual vaccine pharmacovigilance activities (definition see Table 1), whereas the second four objectives relate to supporting elements ensuring the effectiveness and sustainability of vaccine safety systems.

Table 2
Global Vaccine Safety Blueprint mission, vision and strategic goals.

Mission
To optimize the safety of vaccines through effective use of pharmacovigilance principles and methods.
Vision
Effective vaccine pharmacovigilance systems are established in all countries.
Strategic goals
(1) To assist low and middle income countries to have at least minimal capacity for vaccine safety activities.
(2) To enhance capacity for vaccine safety assessment in countries that introduce newly-developed vaccines, that introduce vaccines in settings with novel characteristics, or that both manufacture and use prequalified vaccines.
(3) To establish a global vaccine safety support structure.

The strategic objectives provide the basis for planning of activities as illustrated by its high level targets (Table 3). Each target identified in Table 3 corresponds to practical outcomes that could be facilitated by the Blueprint implementation. They provide the basis for further work planning. As an example of the Blueprint's practical implementation, an illustrative work plan and budget were developed and presented at the September 2011 Global Vaccine Safety meeting. Estimates of the illustrative work plan foresaw that implementing the Blueprint by 2020 would require at least US \$10 million per year to operate a global support network and to provide countries with seed money to establish minimal capacity.

5. Minimal capacity and enhanced capacity

The Global Vaccine Safety Blueprint proposes two main concepts of national capacity for vaccine pharmacovigilance [18]. The concept of a *minimal capacity* should be ubiquitously available in countries, and the concept of an *enhanced capacity* expands the scope of the Blueprint to countries that manufacture vaccines or introduce newly developed vaccines. These two concepts are complementary, ensuring that possible safety issues of vaccines can be promptly detected among any population to which vaccines are

administered. They provide the necessary dimensions for building a globally equitable vaccine safety system that can adapt to the rapidly evolving landscape of solutions aiming at safe use of vaccines.

Minimal capacity includes a series of structural and managerial elements (Table 4). The structural elements are very closely aligned with the pharmacovigilance capacity concept promoted by WHO for all pharmaceuticals [19]. The managerial elements reflect the continuous capacity building principles that support WHO's national regulatory authorities strengthening program. Ensuring minimal capacity for countries should among others take into account continued and regular training of staff engaged in vaccine safety reporting since new vaccines may present unique features and characteristics.

Enhanced capacity corresponds to the implementation of advanced vaccine pharmacovigilance methodologies in LMIC settings in order to respond to the evolving landscape of vaccine products and taking advantage of rapid progress in implementing advanced epidemiology in LMIC as well as the potential of modern information technologies. It aims at both the ability to carry out active surveillance rather than relying solely on spontaneous reporting of AEFI for the purpose of signal detection, and the ability to carry out epidemiological studies to test hypotheses generated from active or passive signal detection methods. In addition, for new vaccines, passive surveillance for signal detection should be supplemented by active surveillance since spontaneous reporting systems may fail to identify or overestimate a vaccine safety signal because of the under- or selective reporting to spontaneous reporting systems. Enhanced capacity also targets a rapid and adequate assessment of and response to vaccine safety signals, which spontaneous reporting systems may be insufficient to address. Rapid responses to safety signals are particularly important for minimizing the impact of vaccine scares due to false signals, and of actual adverse reactions on the public confidence in the safety of vaccines. In particular, countries introducing newly-developed vaccines or manufacturing and using prequalified vaccines are in need of this increased level of vaccine safety capacity. An example for the use of enhanced capacity was the recent safety monitoring of meningitis A conjugate vaccine introduction in West Africa [20,21].

Table 3
Global Vaccine Safety Blueprint strategic objectives and high-level targets.

Strategic objective	High-level targets
1. To strengthen vaccine safety monitoring in all countries	<ul style="list-style-type: none"> • Effective spontaneous reporting of AEFI in all countries.
2. To strengthen the ability of countries to evaluate vaccine safety signals	<ul style="list-style-type: none"> • Enhanced capacity for vaccine pharmacovigilance in countries that manufacture vaccines and countries where newly available vaccines are being introduced • Countries have the ability to verify vaccine safety signals and initiate appropriate public health action • Countries have the ability to investigate a potential public health risk
3. To develop vaccine safety communication plans at country level to promote awareness of vaccine risks and benefits, understand perceptions of risks, and prepare for managing any adverse events and concerns about vaccine safety promptly	<ul style="list-style-type: none"> • A global collaborative mechanism is available for concerted public health action • To develop or strengthen the ability of countries to have ongoing communication with local communities, health care workers and decision-makers about important vaccine safety issues
4. To develop internationally harmonized tools and methods to support country vaccine safety activities	<ul style="list-style-type: none"> • Vaccine safety rumors will be detected and investigated promptly and communications strategies put in place • Standard procedures and methodologies will be available for analyzing and investigating vaccine safety issues
5. To promote a legal, regulatory and administrative framework for the safety of vaccines at national, regional and international levels	<ul style="list-style-type: none"> • Harmonized tools will be available to facilitate vaccine pharmacovigilance • All countries have provisions for establishing vaccine pharmacovigilance, including lines of accountability
6. To strengthen regional and global technical support platforms that meet countries' expressed needs	<ul style="list-style-type: none"> • Vaccine pharmacovigilance is established as an international responsibility
7. To provide expert advice on vaccine safety issues at national, regional and international levels	<ul style="list-style-type: none"> • Global access to learning for the development of national vaccine pharmacovigilance • Global access to technical response support for vaccine safety issues
8. To put in place systems for appropriate interaction between national governments, multilateral agencies, and manufacturers at national, regional and international levels	<ul style="list-style-type: none"> • National, regional and global advisory bodies maintain the global safety profile of all vaccines and advise on investigating vaccine safety signals of global importance • Efficient information exchange mechanisms are in place between public and private sectors, including the use of harmonized tools and methods

Table 4
Minimal capacity for vaccine pharmacovigilance.

Structural elements	<ul style="list-style-type: none"> • A national dedicated vaccine pharmacovigilance capacity, with designated staff for this purpose, stable basic funding, clear mandates, well defined structures and roles, collaborating with the WHO Programme for International Drug Monitoring. • Health-care workers and others encouraged to report vaccine safety issues. • A reporting form for individual case safety reports (i.e. a national reporting form for AEFI). • A national database or system for collating, managing and retrieving AEFI reports. • A national AEFI expert review committee (ARC) that is able to provide technical assistance on causality assessment of serious AEFI and clusters of AEFI so that unwanted risk can be managed • A clear strategy for risk communication that identifies risks and benefits to prepare health professionals, caregivers and the public for possible vaccine reactions, explaining possible coincidental events, encouraging the monitoring of AEFI by all concerned, and with preparedness plans in place to address vaccine safety crises (risk communication is dynamic and needs a feedback loop to all relevant stakeholders). • Harmonized methods and tools for the monitoring and investigation of AEFI implemented.
Managerial elements	<ul style="list-style-type: none"> • A regulatory framework is in place that defines the provisions for monitoring and management of AEFI. • Clear lines of accountability have been identified for the conduct of vaccine safety work. • An institutional development plan is in place for implementation of activities and development of performance indicators. • The institutional development plan is periodically evaluated and revised in order to ensure continuous quality improvement in the conduct of national vaccine safety activities. • There is a commitment to sharing information on vaccine safety with other countries.

6. Global vaccine safety initiative

GVSI was set up to provide WHO and partners with a network to implement the Blueprint. The GVSI was launched in early 2012 through the constitution of a Planning Group. The Initiative is administered by WHO and steered by the Planning Group, which is composed of representatives from intergovernmental organizations, international non-governmental organizations academic institutions and regulatory authorities.

In its initial phase, the Planning Group is looking at strengthening the global support structure by bringing together and exploring synergies among existing IIVSA and mapping those which contribute to vaccine safety identifying short term deliverables for the biennium 2012/2013. Worldwide, numerous ongoing projects of IVSA address one or more of the Blueprint strategic objectives. Identifying those projects and providing their sponsors with opportunities for synergies, helping disseminate their products and experiences is among the top agenda items for the Initiative. An inventory of ongoing projects is being assembled to help all stakeholders interested in joining forces around the common purpose of increased harmonization, standardization and information exchange in vaccine pharmacovigilance. As country capacity development is the main guiding principle for the Initiative, every opportunity to link these projects with actual piloting or demonstration in countries that participate in the GVSI network will be sought.

Another aspect of the GVSI is to conduct advanced vaccine pharmacovigilance around the introduction of new vaccines. For example, intussusception studies in Latin America [22] have provided

models that can now be emulated in the first African countries to introduce rotavirus vaccines. Meningitis A conjugate vaccine introduction in West Africa provided opportunities to develop active surveillance approaches that are adapted to the clinical practices of those countries. During the 2009 pandemic influenza vaccination campaigns a global collaborative study of Guillain-Barre Syndrome was developed as a demonstration of the feasibility of combining experience from different sites across the globe for the common purpose of monitoring rare vaccine reactions [23]. Lessons from these early experiences will be used to build a stronger approach for the many important vaccines currently in development, such as those against malaria [24] or dengue [25] among others. Countries with emerging vaccine manufacturers also benefit from coordinated support to enhance their vaccine pharmacovigilance systems with the help of many experts from established regulatory agencies, pharmacovigilance centers and academic institutions.

A network of 11 countries has piloted the possibility of sharing experiences in improving the detection and investigation of AEFI in spontaneous reporting systems [26]. Those countries and the WHO Collaborating Center for International Drug Monitoring [27] have recently provided the rationale for a harmonized set of core variables that have been endorsed by GACVS for the surveillance of AEFI [28]. One main benefit of this proposed reporting format is that it will allow the development of a web-based, and harmonized interface through which countries will have the possibility of maintaining their own AEFI data base and exchange relevant information internationally. This system will also include standardized terminologies and a vaccine dictionary thereby ensuring the comparability of the reports recorded. For the purpose of analyzing AEFI, the Brighton Collaboration case definitions [29] are piloted for use in LMIC settings. New definitions are also continuously developed to adapt to the evolving spectrum of conditions of interest for different vaccines, such as the definition of adverse events by Council for International Organizations of Medical Sciences (CIOMS) [13]. Through its network of experts, the Brighton Collaboration also provides a powerful means for developing and evaluating new approaches and tools. As new tools become available, the WHO Collaborating Center for Advocacy and Training in Pharmacovigilance will provide a global repository for their dissemination on the model of their pharmacovigilance toolkit [30].

Industry is a key player to ensure the improvement of global vaccine pharmacovigilance. Through their own networks of vaccine safety monitoring, pharmaceutical companies have accumulated considerable knowledge. Making sure that vaccine manufacturers inform the development of harmonized tools will provide another way of optimizing their soundness and relevance and will ensure that they will also be adopted by the private sector. Enhancing information exchange between public and private sectors has been identified as a priority by all stakeholders during the landscape analysis.

Beyond the early steps described above, enhanced efforts to improve worldwide ability for monitoring and assessing the safety profile of all vaccines should also benefit from more sophisticated methodologies. Providing access to computerized medical records is one of the longer term goals of the GVSI [31]. To that end, criteria should be proposed for involving health care data bases into a collaborative network that will allow for testing of hypotheses in computerized medical data. For multi-center studies, the use of existing sentinel sites such as the Demography and Health Surveillance Sites (DHSS) of the INDEPTH network [32] are also being explored with pilot projects. Communication technologies could help detect vaccine safety signals. Their possible use will be reviewed in the early stages of the Initiative. Finally, with respect to communicating about vaccine safety, innovative approaches to research on the component of public trust in vaccines are urgently needed [33] and can play a significant role.

The Decade of Vaccines undoubtedly presents an enormous opportunity for moving forward the global vaccine safety agenda. It may increase interest in vaccine safety from many players in LMIC and garner support from a large number of stakeholders for the Global Vaccine Safety Blueprint strategies. Stable funding support for vaccine safety is critical to garner a sufficient range of activities ensuring a minimal capacity in countries in the envisaged time period. The timeline of the Blueprint implementation has been matched to the timeline of the Decade of Vaccines. Accordingly, it envisions a broad plan of action covering activities starting in 2012 and running until 2020. Additional resources should be raised to further develop and implement Blueprint activities and to help accelerate progress in strengthening vaccine pharmacovigilance. As a result, vaccines will be administered anywhere in the world in a more equitable way, benefitting from improved monitoring and response to safety issues.

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References

- [1] World Health Organization, United Nations Children's Fund (UNICEF), World Bank. State of the world's vaccines and immunization. 3rd ed. Geneva: WHO; 2009.
- [2] Chen RT, Rastogi SC, Mullen JR, et al. The vaccine adverse event reporting system (VAERS). *Vaccine* 1994;12:542–50.
- [3] Ellenberg SS, Foulkes MA, Midthun K, Goldenthal KL. Evaluating the safety of new vaccines: summary of a workshop. *American Journal of Public Health* 2005;95(May (5)):800–7.
- [4] GACVS and WHO secretariat. Global safety of vaccines: strengthening systems for monitoring, management and the role of GACVS. *Expert Review of Vaccines* 2009;8:705–16.
- [5] Lilienfeld DE. The first pharmacoepidemiologic investigations: national drug safety policy in the United States, 1901–1902. *Perspectives in Biology and Medicine* 2008;51(Spring (2)):188–98.
- [6] Pan American Health Organization. Essential public health functions (document CD42/15) [online]. In: 42nd Directing Council, 52nd Session of the Regional Committee of the World Health Organization for the Americas. Washington DC: PAHO; 2000.
- [7] World Health Organization. Immunization and vaccine quality (resolution WHA45.17). In: 45th World Health Assembly. Geneva: WHO; 1992.
- [8] World Health Organization. Implementation of WHO's Revised Drug Strategy: Safety, efficacy, and quality of pharmaceuticals (Resolution WHA47.17). In: 47th World Health Assembly. Geneva: WHO; 1994.
- [9] World Health Organization. Quality and safety of medicines, including of blood products (document EB113/10). In: 113th Session of the Executive Board of the World Health Organization. Geneva: WHO; 2004.
- [10] World Health Organization. Global vaccine safety blueprint—the landscape analysis. *WHO IVB* 12.04; 2012.
- [11] Djingarey MH, Barry R, Bonkoungou M, et al. Effectively introducing a new meningococcal A conjugate vaccine in Africa: the Burkina Faso experience. *Vaccine* 2012;30(Suppl. 2):B40–5.
- [12] World Health Organization. GACVS report: preparing for vaccine introduction in Africa and Asia. *The Weekly Epidemiological Record* 2011;86:323–4.
- [13] CIOMS/WHO Report on Vaccine Pharmacovigilance (see also http://www.cioms.ch/frame.vaccine_pharmacovigilance.htm (last visited: July 2012)).
- [14] World Health Organization. Meeting of the Strategic Advisory Group of Experts on Immunization, November 2011—conclusions and Recommendations. *The Weekly Epidemiological Record* 2012;87:9–10.
- [15] World Health Organization. GACVS: implementing the Global Vaccine Safety Blueprint. *The Weekly Epidemiological Record* 2012;87:58–9.
- [16] Decade of Vaccines Collaboration. Global Vaccine Action Plan. *Vaccine* 2013;31:B5–31.
- [17] Graham JE, Borda-Rodriguez A, Huzair F, Zinck E. Capacity for a global vaccine safety system: the perspective of national regulatory authorities. *Vaccine* 2012;30(July (33)):4953–9 [Epub 2012 May 30].
- [18] World Health Organization. Global vaccine safety blueprint (2012). *WHO/IVB/12.07*; 2012.
- [19] World Health Organization. http://www.who.int/medicines/areas/quality_safety/safety_efficiency/pharmvigi/en/index.html (last visited: July 2012).
- [20] Ouandaogo CR, Yaméogo TM, Diomandé FV, et al. Adverse events following immunization during mass vaccination campaigns at first introduction of a meningococcal A conjugate vaccine in Burkina Faso. *Vaccine* 2010;30(Suppl. 2):B46–51.
- [21] Chaibou MS, Bako H, Salisou L, et al. Monitoring adverse events following immunization with a new conjugate vaccine against group A meningococcus in Niger, September 2010. *Vaccine* 2012;30(June):5229–34.
- [22] Patel MM, López-Collada VR, Bulhões MM, et al. Intussusception risk and health benefits of rotavirus vaccination in Mexico and Brazil. *The New England Journal of Medicine* 2011;364:2283–92.
- [23] Dodd CN, Izurieta HS, Zuber P, Romio S, Sturkenboom M, Hua W, Bonhoeffer J, Weibel D, Black S, The Global H1N1-GBS Working Group. International Collaborative Case Series Safety Monitoring for Pandemic 2009 H1N1 Vaccines: Estimation of the Risk of Guillain-Barre Syndrome. Poster 778. In: 27th International Conference on Pharmacoepidemiology & Therapeutic Risk Management. 2012.
- [24] Bairwa M, Rajput M, Khanna P, Rohilla R, Verma R, Chawla S. Malaria vaccine: a bright prospect for elimination of malaria. *Human Vaccines & Immunotherapeutics* 2012;8(June (60)) [Epub ahead of print].
- [25] Konishi E. Issues related to recent dengue vaccine development. *Tropical Medicine and Health* 2011;39(December (Suppl. 4)):63–71 [Epub 2011 Aug 6].
- [26] WHO, GACVS. Global network for postmarketing surveillance and AEFI monitoring. *The Weekly Epidemiological Record* 2012;87:57–8.
- [27] Uppsala Monitoring Centre. <http://www.who-umc.org/> (last visited: July 2012).
- [28] World Health Organization. GACVS report. *The Weekly Epidemiological Record* 2012;87:281–828.
- [29] Brighton Collaboration. <https://brightoncollaboration.org/public/what-we-do/standards/case-definitions.html> (last visited: July 2012).
- [30] WHO Collaborating Centre for Advocacy and Training in Pharmacovigilance. <http://pvtoolkit.org/> (last visited: July 2012).
- [31] Black S, Zuber PLF. Global trends and challenges in vaccine safety. *Pediatric Health* 2009;3(August (4)):329–35.
- [32] INDEPTH network <http://www.indepth-network.org/> (last visited: July 2012).
- [33] Larson H, et al. Addressing the vaccine confidence gap. *Lancet* 2011;378(9790):526–35.