



Capacity for a global vaccine safety system: The perspective of national regulatory authorities

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ABSTRACT

Confidence in vaccine safety is critical to national immunization strategies and to global public health. To meet the Millennium Development Goals, and buoyed by the success of new vaccines produced in developing countries, the World Health Organization has been developing a strategy to establish a global system for effective vaccine pharmacovigilance in all countries. This paper reports the findings of a qualitative survey, conducted for the WHO Global Vaccine Safety Blueprint project, on the perspectives of national regulatory authorities responsible for vaccine safety in manufacturing and procuring countries. Capacity and capabilities of detecting, reporting and responding to adverse events following immunization (AEFI), and expectations of minimum capacity necessary for vaccine pharmacovigilance were explored. Key barriers to establishing a functional national vaccine safety system in developing countries were identified. The lack of infrastructure, information technology for stable communications and data exchange, and human resources affect vaccine safety monitoring in developing countries. A persistent “fear of reporting” in several low and middle income countries due to insufficient training and insecure employment underlies a perceived lack of political will in many governments for vaccine pharmacovigilance. Regulators recommended standardized and internationally harmonized safety reporting forms, improved surveillance mechanisms, and a global network for access and exchange of safety data independent of industry.

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1. Introduction

Confidence in the safety of vaccines is critical to national immunization strategies and to global public health [1]. A complex array of obstacles, however, continues to threaten this confidence and challenge the implementation of effective vaccine safety systems, especially in low and middle income countries (LMIC) where hundreds of millions of vaccine doses are administered every year. Infectious diseases continue to exact a disproportionate toll [2] in countries where poverty and socio-political disruptions exacerbate the capacity and capability for effective safety surveillance and response. Efforts to address some of these challenges began in 1981, when the World Health Organization (WHO)'s Expert Committee on Biological Standardization recommended that all countries have a national regulatory authority (NRA) to monitor vaccine efficacy, safety, and quality. Still, by 1997, only 37 of WHO's 190 (19%) Member States, including 20 of the 52 (38%) vaccine producing countries, had a reliable NRA. In 1999, WHO's Immunization

Safety Priority Project targeted strengthening country capacity [3]. By 2008, this initiative was gaining ground. Fifty-eight of the then 193 (30%) Member States, including 33 of 48 (69%) vaccine producing countries, had reliable, fully functioning NRA. Yet despite these significant improvements, still only about one quarter of LMIC have a reliable NRA with sufficient human and material resources to assess and monitor vaccine quality [4] and broadly based, real-time active surveillance for AEFI remains an ideal, even in well-resourced countries [5,6]. Detecting, monitoring, responding and reporting AEFI remains of concern to manufacturers, regulators, health care providers, and the public [7].

That many countries are still without functional vaccine safety monitoring systems remains a global challenge demanding a coordinated international response to ensure vaccines are safe for everyone. LMIC continue to experience poor uptake of standardized safety protocol and practices (e.g. International Classification of Diseases [8], Brighton Collaboration [9], Uppsala Monitoring Centre [10]) and have modest capacity for the detection of adverse events following immunization (AEFI) that remain under-reported and under-investigated [11–14]. People in these countries must often travel long distances to immunization sites and are lost to follow-up [15]; they are challenged by undetected co-morbidities, and the systems for collating and managing data are complicated by inadequate information technology and lack of resources.

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With a growing number of high quality vaccine producers and functional regulatory authorities in LMIC, and the success of strategies such as product development partnerships to develop and produce low cost safe vaccines for developing countries, as demonstrated with the meningococcal A conjugate vaccine in sub Saharan Africa in 2010 [16–19], we can expect many more new vaccines to be manufactured, launched in, and exported from LMIC through mechanisms such as WHO prequalification [20].

The 2010 announcement of the Decade of Vaccines by the Bill and Melinda Gates Foundation set a number of new initiatives in motion. Still with no harmonized global vaccine safety system (GVSS) to govern, guide, and institutionally support the pharmacovigilance work of NRA across the diverse geographical and socio-political range of low, middle and high income countries [21–24], the WHO established the Global Vaccine Safety Blueprint (GVSBS) project as a way forward to solve these problems. The goal of the GVSBS is to develop a strategy to ensure safe vaccines for everyone everywhere [25]. The WHO commissioned a comprehensive series of baseline studies and landscape analyses to evaluate the capacity and capabilities of NRA and manufacturers to ensure safe immunization. Activities focused on assessing country post-market vaccine safety monitoring, an analysis of strengths, weaknesses, opportunities and threats in international vaccine safety activities, surveys of regulators and of manufacturers, assessment of the countries involved in WHO Global Post-marketing Surveillance Network, and a financial assessment of costs and funding.

This paper reports the results of the GVSBS survey of regulators, a qualitative study conducted between September and December 2010 to determine the challenges faced in implementing vaccine safety systems by NRA in a range of vaccine manufacturing and procuring countries. Our survey probed regulators for what they see as the key issues concerning vaccine safety, collecting descriptive data from regulators on the challenges of national AEFI reporting and post market surveillance. The current and future capacities and capabilities for ensuring vaccine safety were assessed, as well as relationships among regulatory authorities and with the private sector. Additionally, we examined the expectations of regulatory authorities regarding a GVSS, including their suggestions about how NRA might improve their own vaccine safety systems. This paper is a first attempt to broadly assess the status of vaccine safety monitoring on a global level from the perspective of NRA.

2. Methods

2.1. Qualitative survey method

Qualitative methods are especially well suited to explore complex phenomena, especially everyday practices, negotiations, and meanings [26,27]. They provide an important, necessary and widely accepted augmentation to quantitative approaches, being ideally suited to the documentation and analysis of motivations, explanations and activities not limited to known, predetermined or necessarily predictable factors. Qualitative methods include, for example, observation, unstructured or semi-structured interviews and open-ended surveys. This project required investigation of systems and practices around vaccine adverse event reporting that had as yet been neither described nor quantified. In consultation with the WHO GVSBS Advisory Committee, a web-based electronic survey was designed to qualitatively capture unanticipated responses while assessing the knowledge, attitudes and practices of a sample of regulatory licensing authorities concerning their national vaccine safety system (Appendix 1, Survey Questions). Specific questions were directed to countries that (i) manufacture, (ii) procure, and (iii) both manufacture and procure vaccines. The regulators were asked open-ended questions

that allowed them to identify and elaborate on issues that a closed, structured quantitative survey might well have missed [28]. This inductive approach [29–33] involved probing the regulators about what they considered were major challenges to vaccine safety in their countries, and for suggestions to build future capacity and capabilities for a global vaccine safety system. In accord with these methods, survey responses were coded and analysed using a constant-comparative and concept-development approach [34–36] that identified, compared, and refined the concepts and events into themes distinguished as important by the regulators [37,38].

2.2. Sampling frame

To create a meaningful representative sample with the diverse range of country geographies, politics, economics, population sizes, etc. is impractical. Many LIC do not have the resources to carry out regulation or to complete surveys. We built our data collection methodology, therefore, upon a series of strategic choices known in qualitative research as *purposive sampling*, where potential respondents are selected because they meet certain contextual characteristics of interest to the study objectives [39]. Purposive sampling enabled obtaining responses from NRA in a range of countries, while recognizing that their unique circumstances might present a variety of challenges that would affect their ability to participate in such a survey. Purposive sampling techniques allowed us to select a sample of exemplary countries with a variety of socio-economic contexts and population sizes, while intentionally over-sampling LMIC to better apprehend their needs for a global vaccine safety system according to the goals of the Blueprint. In consultation with the GVSBS Advisory Committee, we selected 32 NRA that together met the range of criteria of relevance to an assessment of global vaccine safety. Criteria for selection included:

- i. Countries that manufacture, procure, and both manufacture and procure vaccines;
- ii. Representation from all WHO Regions, African (AFRO), European (EURO), Eastern Mediterranean (EMRO), Americas (PAHO), South-East Asia (SEARO), and Western Pacific (WPRO);
- iii. Representation from the 3 economic categories recognized by the World Bank: low, middle and high income countries (respectively, LIC, MIC, and HIC) [40];
- iv. Representation from a range of populations sizes, categorized as: less than 40 million; between 40 and 80 million, and over 80 million.

Applying a wider sampling frame was constrained by the number of available countries. For example, a limited number of countries produce vaccines; once classified into high, middle and low income, then further classified as small, medium or large in terms of population, and then grouped according to WHO region, we struggled to find sufficient representation. Further, to respond to the survey, the NRA had to be experienced, functional and responsive. We sampled as many countries as possible and available and we were guided by the GVSBS Advisory committee that held experience and knowledge of which NRAs would respond and in a timely way. The gaps in our complex matrix of criteria were therefore filled by suggestions from the GVSBS Advisory committee eliminating the need for us to select.

2.3. Recruitment

WHO nominated key regulators from each of the selected countries. Using a modified Delphi technique to improve response [41], an introductory e-mail was sent from the WHO official leading the GVSBS, familiar to the regulators. The e-mail introduced the survey

and emphasized its importance to the Blueprint strategic plan. An e-mail followed with a hyperlink to the on-line survey. Follow-up reminders to complete the survey began 2 weeks after the initial survey was sent out and continued after the official deadline date. Several reminders were sent to non-responders. Countries who had not responded within 2 months were sent a reminder from the WHO GVSBS office. For purposes of an internal audit to triangulate findings for reliability and credibility [42], we also recruited the European Medicines Agency (EMA).

3. Results

Our sample frame targeted 4 of 35 LIC, 20 of 110 MIC and 8 of 70 HIC from the 215 economies recognized by the World Bank. A total of 19 of the 32 (59.4%) country NRA contacted completed the survey, including 3 LIC, 10 MIC, and 6 HIC contacted (Table 1). This 59.4% survey response amounts to 9% representation from each of the targeted World Bank categories. Three AFRO, 3 EURO, 3 SEARO, 2 WPRO, 2 EMRO and 6 PAHO countries responded. Our original sample frame contained 18 countries with less than 40 million people, 4 countries with populations between 40 and 80 million, and 10 countries with populations over 80 million, and included a wide range of countries with populations at different points on a continuous scale. We achieved representation from all targeted categories with the exception of a low income, medium sized population.

3.1. Requirements of a global vaccine safety system

The regulators identified a series of key barriers and made recommendations that together underline the essential role of a coordinated system for standardization and communication of AEFI data supported by sufficient infrastructure and resources to enable capacity and capabilities in LMIC for a functional vaccine safety system. Specifically, regulators disclosed the need for: (i) standardized and readily accessible AEFI forms; (ii) improved surveillance mechanisms; (iii) adequate expertise and training; (iv) coordinated exchange and access to safety data; and (v) the political will to build, sustain and enforce regulatory authority. We elaborate on these findings below, with emphasis on the accounts from LMIC.

3.1.1. Standardized and accessible AEFI forms

Several barriers to implementing AEFI reporting standards were identified. Insufficient infrastructure, equipment, information technology and technical resources undermine AEFI reporting in LIC, which relied primarily on the Expanded Programme on Immunization (EPI) preventable disease notification forms [43]. The EPI was established in 1974 through a World Health Assembly resolution to provide universal access to all relevant vaccines for all at risk. The goal of the EPI programme is to control disease and achieve better health for all, particularly the most vulnerable. While AEFI guidelines and a variety of forms including those developed by the Council for International Organizations of Medical Sciences (CIOMS) [44] were readily accessible electronically in MIC, with hardcopies distributed across regional and local offices, this was not the case for LIC. In these countries, in many instances forms were available in paper draft solely for staff involved in AEFI reporting, although a wide range of health care workers and citizens can report, in principle. The Brighton Collaboration standard case definitions [45] remain widely underused.

3.1.2. Improved surveillance mechanisms

NRA perform a central role in collecting, monitoring and assessing all safety related information submitted by the manufacturers. While NRA in HIC provide expert advice on weight of evidence of signals detected through the monitoring system, there was wide

recognition of the central need for improved surveillance mechanisms in LMIC countries to detect adverse events, which relied principally on the EPI notification of events from the field. Additional efforts to detect non-adverse events were also flagged by MIC as a challenge of “underreporting of minor events”. Most AEFI, even in HIC, are identified via passive surveillance through public health authorities, health care workers, as well as consumers. AEFI reporting remains challenged by the quality and completeness of the passive surveillance reporting practices. The health and co-morbidity of vaccine recipients goes largely undocumented. Lack of contact information often prohibited follow up. Only a few countries had some level of active surveillance (e.g. U.S. Vaccine Safety Datalink (VSD) [46] and Canada’s paediatric hospital-based national active surveillance network for adverse events following immunization in children, Immunization Monitoring Program ACTIVE (IMPACT)) [47]. Regulators recognized, however, that active surveillance that provides systematic assessment and more accurate estimates of incidence requires significant resources to detect and follow-up both serious and non-serious adverse events, making it an ideal rather than a necessary requirement of a functional GVSS. Without detracting from the optimal goal of collecting all adverse events, in resource-challenged areas it remains a fundamental priority to improve the collection and review of serious adverse events.

3.1.3. Expertise and training

All countries responding to our survey, regardless of economic status, had a national adverse event review committee and access to clinical experts nationally and internationally, although LMIC reported a lack of qualified personnel. While LIC regulators did not express a consistent view as to what would constitute minimal requirements for personnel for a national vaccine safety system, they recognized that the central role of a NRA should involve AEFI surveillance, registration and licensing of vaccines, and training of personnel. National experts were based at universities and in clinical practice. International experts were accessible through regional pharmacovigilance networks and WHO and could be called upon when new vaccines were registered and when national experts were unable to identify or analyse AEFI. Our data indicate, though, that expert advice is difficult to implement due to infrastructural and institutional factors. External experts are contacted when new vaccines are registered and when deaths occur. One MIC expressed concern about confidentiality among experts. These NRA tend to prefer to consult with EMA, FDA [48], EuCDC [49] and WHO for expert advice.

While HIC rarely need external experts, they can be called upon a case-by-case basis. LIC often relied upon manufacturers to meet training and expertise gaps in specific circumstances, such as: (i) when the government testing laboratory was unable to conduct a special test due to unavoidable unexpected situations or shortage of reference standard and equipment; and (ii) when developing an AEFI surveillance system for a vaccine campaign. These represented two types of industry-NRA collaboration: the first adopted the form of technical and material support, i.e., computers, books and invitations to conferences, while the second was specifically for training, improved communication and information exchange.

MIC also relied on training support from manufacturers in the form of courses, conference travel, joint inspections and information exchange when developing new guidelines, requesting safety data from manufacturers and investigating AEFI cases, and clarifying complaints related to specific products. MIC, several of which were manufacturing as well as procuring countries, had systems in place for providing and receiving feedback on safety, such as targeted publications (e.g. warning letters and bulletins). An emerging MIC noted that these industry-academic collaborations had

Table 1
Country NRA response to survey.

	Population < 40 m	Population 40–80 m	Population > 80 m
High income country	1 Procuring 1 Manufacturing 2 Manufacturing and procuring	1 Manufacturing	1 Manufacturing and procuring
Middle income country	3 Procuring 1 Manufacturing and procuring	2 Manufacturing and procuring	1 Procuring 3 Manufacturing and procuring
Low income country	2 Procuring	0	1 Procuring

translated into ongoing funding for product development that brought vaccine manufacturing to their country.

A serious gap in health care worker training with notable consequences was reported by several LMIC. They described “the fear of reporting” as a major barrier to AEFI reporting and surveillance in the LMIC surveyed. Regulators framed this fear in different ways. They suggested vaccinators often lack cultural sensitivity and have a “culture of fear” surrounding being blamed or punished if they report AEFI. They stated that insecure employment and inadequate training and knowledge of case definition and causality assessment undermined the confidence of vaccinators and officials alike and resulted in high turnover of personnel, fear of accusation of wrongdoing, punishment from superiors and hence, underreporting.

3.1.4. Co-ordinated exchange and access to safety data

Manufacturers are encouraged to meet with the NRA prior to filing a new vaccine submission to enable the manufacturer to obtain advice on product development and submission, and allowed the NRA to prepare for forthcoming submissions. Circumstances that prompted a post-market meeting with manufacturers in HIC included: (i) the manufacturer wanted to discuss product manufacturing or facility changes, clinical study plan, new indications and information from post-marketing safety evaluations; (ii) the cost/benefit ratio of a vaccine was in question for reasons of safety or in mass immunization; (iii) important safety signals and issues in quality control were likely to have an impact on the safety and/or efficacy/effectiveness of the vaccine; (iv) there was disagreement on how to handle a safety issue triggered by serious signals. NRA in HIC viewed meetings with manufacturers as generally useful, especially when there was a focused purpose and the manufacturer provided clear, concise and comprehensive materials prior to the meeting. Specific protocol and procedures regulate contact between NRA and manufacturers. More often, manufacturers meet with LMIC NRA before the submission of intent to file a new vaccine, but in general, regulators stated that meetings are rarely held unless a serious AEFI is reported, if violations of Good Manufacturing Practice result in poor quality vaccine, or if there were variations from the marketing authorization without prior approval.

While gaps in infrastructure and resources, affecting information technology, offices and vaccine storage sites, permeated the responses from LMIC, they highlighted the central role of coordinated communication in updating information on safety issues, periodic regulatory inspections and design laws, and policies and protocols to govern immunization. The regulators of LMIC expressed frustration, however, in the predominant role played by manufacturers in these communications. The lack of NRA surveillance of the vaccines manufactured in their countries but exported into LMIC was identified by these regulators as forming a major gap in vaccine safety communication, especially when these vaccines are not in use in the exporting country. LIC regulators expressed concern about confidentiality and the proprietary nature of safety information held by the manufacturers. Manufacturers are required

to report only the information they receive, which was deemed by regulators to be often inaccurate or incomplete.

NRA identified gaps in the communication of safety data that signal doubt about openness and transparency of *all* safety data. They voiced concern about current practices whereby the regulators of manufacturing countries neither provided assistance for AEFI surveillance nor tracked the AEFI of vaccines manufactured in their countries that were exported to procuring countries. Instead, safety information including AEFI data reported from other countries, clinical trials data, periodic safety update reports (PSURs) [50], summary of product characteristics and toxicology data are provided by the vaccine manufacturer and marketing authorization holder. While NRA have systems in place for providing and receiving feedback on safety information, signals, quality control, clinical study plans and new indications (acknowledging, for example, that if a cluster of AEFI was detected or a particular lot was suspect, the location/s of manufacturing could be identified), nonetheless, the lack of a centralized clearinghouse independent of industry was a significant concern to many regulators. Instead of this reliance on manufacturers, some LMIC conveyed a preference to consult with other regulatory authorities of vaccine producing countries (e.g., FDA, EMA, TGA [51] MHRA [52] and ANVISA [53], as well as Health Canada and the regulatory authorities of Switzerland, Sweden, Japan were mentioned).

The regulators suggested, instead, a system whereby NRA and manufacturers contributed to an independent central clearing house of all safety data. They stressed the need for memoranda of understanding and other instruments to facilitate data sharing between national regulators. In practice, while some HIC NRA host regulators from other countries to discuss vaccine safety monitoring practices, regulatory mentoring to build capacity was perceived as rare by several LMIC NRA, although there have been some notable exceptions [54].

3.1.5. Political will to build, sustain and enforce regulatory authority

Regulators identified the central importance of “sensitizing” and gaining the “political will” of governments. Seen as a “commitment” to meeting the training, communication and resource needs of a functional NRA, the political will of decision makers was recognized as entangled with financial and political arrangements, funding, conflict of interest and litigation issues, and fraught with ethical challenges. Limited financing for training and permanent, secure and safe employment unveils an understandable “culture of fear” in AEFI reporting in those countries where the reporters are frightened about consequences such as punishment and losing their jobs. Inadequate IT infrastructure, variable access to library referencing, and ineffective systems for ensuring a consistent approach to causality assessment impede safety reporting were all addressed even in HIC. AEFI reporting standards are not enforceable where physician AEFI reporting is voluntary, which amounts to the vast majority of countries. Political will, including getting

wide stakeholder involvement, was deemed a main challenge to a GVSS.

3.2. NRA expectations for a global vaccine safety system

Regulators were united in calling for international harmonization of AEFI safety data reporting, collection and information exchange. They wanted to see more fully integrated (harmonized) standards for AEFI definitions and surveillance to improve consistent reporting within and across countries. They identified the need for strengthening the NRA functions and pharmacovigilance in all countries by coordinating a NRA network, perhaps through the WHO, that would be integral to data exchange in a global vaccine safety system. Functional regulatory authorities remain a challenge for LIC that lack the financial and human resources to build the capacities and capabilities necessary for regulatory harmonization. Active surveillance remains a challenge, even to many HIC, and there was recognition that spontaneous reporting remains important while steps are being taken in many better resourced countries to build models for active surveillance.

Importantly, LIC expect financial support for establishing national centres for AEFI monitoring, support in transmitting and sharing information on AEFI, reinforcing efforts to control counterfeit vaccines and short term consultancy services. These regulators saw the lack of stable funding as a major problem, excluding them from a GVSS. They felt strongly that their own national vaccine safety systems could be improved by establishing functional NRA and national control laboratory systems and providing training and stable funding for dedicated human resources assigned to deal with AEFI. They considered the key challenges in making these improvements to be political will (commitment) and the lack of clear guidelines (policies).

MIC, many of whom are emerging economies now manufacturing vaccines, expect rapid exchange of vaccine safety information across countries, assurance that all vaccines are pre-qualified before licensing for public use, new AEFI guidelines, technical assistance and capacity building. They saw the main challenges to creating a GVSS to be in establishing a standardized communication network across countries, encouraging incentives to reinforce political will among governments and getting stakeholders to be fully involved with the system. MIC NRA suggested that their own national vaccine safety systems could be improved by having fulltime AEFI personnel working at the regional level, establishing a globally harmonized AEFI system, and a stronger commitment from both government and private sector. They identified funding, political will, high turnover of personnel, a shortage of qualified professionals, and conflict of interests as the key challenges.

HIC have expectations of an early alert system with timely information on safety issues identified within other jurisdictions, and harmonization. They want to see full transparency in the sharing of vaccine safety information. These regulators saw the main challenges to the creation of a GVSS to be in gaining agreement on the standards to be applied and in creating compatible reporting systems for database entry. Funding, capacity building in developing countries, partnerships across public and private organizations and confidentiality agreements were also identified as challenges. They recognized the need to improve their own national vaccine safety systems by moving towards more real-time analysis, use of electronic administrative health data, international collaborations, agreement on a consistent reporting form, and better definition of the communications process. The usual culprits of resistance to change, lack of access to administrative electronic data, resources and external communications, serve as challenges.

4. Discussion

Strengthening the capacity of developing countries (who as well as being the largest consumers of vaccines, are increasingly producing them) [55] to identify adverse events, determine causation, and respond and communicate effectively with health care providers and the public [56] will involve the coordination of an array of institutional and human features [57]. An effective national and international vaccine safety system requires infrastructure and highly qualified personnel dedicated to the task of monitoring, recognizing, examining and treating people presenting with AEFI.

This paper reports the results of a WHO sponsored survey of the perspectives of national regulatory authorities regarding AEFI surveillance and reporting, their interactions with other NRA and the private sector, and their expectations for a global vaccine safety system. Regulators from across World Bank economic categories assessed their capacity and capabilities for ensuring vaccine safety and offered their opinions about the challenges and possibilities to improve these systems. While there were significant differences between low and MIC, they each faced the challenges of limited financial resources, inadequate information technology, insufficient physical infrastructure and highly qualified personnel. These obstacles to training and information exchange are critical to reliable case definition, AEFI reporting and health care worker competence. Fear of punishment by health workers contributed to underreporting of AEFI and misinformation about vaccines.

Regulators in these countries were well aware of the consequences of insufficient resources and lack of legislation for monitoring and enforcement for an effective national vaccine safety system. Variable resources and adoption of guidelines affect the consistency of AEFI reporting and communication between NRA. LMIC require more technical training support. We found that many LMIC receive and rely upon support from vaccine manufacturers; manufacturers are seen to have the role of 'providers' of resources and training. LIC adhered to fewer formal policies with respect to restrictions surrounding industry support compared to HIC. HIC stated that they received no financial assistance from manufacturers and were able to refer to conflict of interest guidelines. Although these HIC apply user fees, the regulators made no mention of concerns raised by critics of user fees about regulatory capture [58–61]. Regulators, nonetheless, expressed some concern about manufacturer management of vaccine safety data. Citing examples where Eudravigilance and the holders of marketing authorizations "who are not necessarily the drug manufacturers" are responsible for collecting, evaluating and informing Member States of any adverse effects, regulators suggested a centralized network whereby they could share and have access to all safety surveillance data. Some proposed that this ought to be the role of an independent GVSS.

Regulators were united in calling for international harmonization of AEFI safety data collection, reporting, and information exchange. They identified the need for strengthening the NRA functions and pharmacovigilance centres in all countries. This network would be integral to data exchange in a GVSS. Functional regulatory authorities remain a challenge for LIC that lack the financial and human resources to build the capacities and capabilities necessary for regulatory harmonization. Regulators stated that political will as well as resources that targeted more effective training and communications between public health officials and vaccinators could address debilitating issues related to the lack of knowledge and fear of accusation that result in underreporting. These challenges had a great impact on both the real and perceived confidence in any vaccine safety system.

The findings of this qualitative survey provide insight into the next steps for development of a vaccine safety system that can address capacity building for LMIC with varying infrastructure and

resources to attain minimal standards. The NRA of procuring countries which do not manufacture vaccines expect to be brought into the information loop of a global vaccine safety exchange, and they require stable funding to build information technology, safely transport and store vaccines, and detect and respond to AEFI in a timely manner. Importantly, they identify a troubling finding: fear of reporting AEFI by poorly trained and insecure health personnel points to a lack of political will to sustain, legitimize and reinforce public health initiatives.

The challenge lies in the fact that the most disadvantaged are often those that can best benefit from these initiatives. The socially just imperative then, is for the international community to provide education and incentives for governments in LMIC to recognize public health initiatives as value added for their economic and social well being. Reliable and secure sources of funding to accomplish this goal are essential. The experience in LMIC is too often one of trade-offs: when vaccine campaigns are launched, regular immunization programmes are often neglected. A functional GVSS would address inequitable power relations between countries and with vaccine manufacturers. Further research is necessary to establish guidelines for a flexible decision-making model for investing in LIC NRA. The goal of this research might be to characterize a set of criteria, preferably evidence-based upon factors identified from previous successful case examples. For example, the vital role played by Burkina Faso's Ministry of Health in the multi-lateral Meningitis A vaccine development and rollout in 2010 might be taken as a model for a successful approach to national and international immunization initiatives and specifically refined and adapted for a wide variety of other country conditions [62].

4.1. Limitations

We acknowledge limitations in our study. As a qualitative study, our findings may not represent the voices or be generalizable to all NRA. Despite our attempt to maximize response, we encountered some difficulties. Many LIC have no NRA or insufficient regulatory staff to respond to a survey. World events, such as floods, famines and political turmoil, limited the participation of some countries. Others were not contactable, did not respond, or could not be included for what might now be recognized as a lack of "political will." Some countries had significant bureaucratic barriers to decision-making that resulted in unobtainable permission of personnel to complete the survey during the 4 months of data collection. Nonetheless, 13 of the 19 participating country NRA were from LMIC, with a 59.4% response rate from countries initially contacted, and we succeeded in including 9% from each of the World Bank economic categories.

Finally, while many regulators expressed a desire for a centralized network for all safety surveillance data that had some independence from manufacturers, they made no specific recommendations for data collection and governance mechanisms that might mitigate concerns about the source of safety information. As one of the first studies to report from the Global Vaccine Safety Blueprint project, the WHO GVSBS will be addressing the challenges and suggestions described here.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.vaccine.2012.05.045>.

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