



Roadmap for the international collaborative epidemiologic monitoring of safety and effectiveness of new high priority vaccines

Hector S. Izurieta^{a,*}, Patrick Zuber^b, Jan Bonhoeffer^{c,d}, Robert T. Chen^e, Osman Sankoh^{f,g,h}, Kayla F. Lasersonⁱ, Miriam Sturkenboom^j, Christian Loucq^k, Daniel Weibel^j, Caitlin Dodd^l, Steve Black^l

^a Food and Drug Administration (FDA), MD, United States

^b World Health Organization, Geneva, Switzerland

^c Brighton Collaboration Foundation, Basel, Switzerland

^d University Children's Hospital Basel, University of Basel, Basel, Switzerland

^e Centers for Disease Control and Prevention (CDC), Atlanta, GA, United States

^f INDEPTH Network, Accra, Ghana

^g School of Public Health, University of the Witwatersrand, Johannesburg, South Africa

^h Hanoi Medical School, Hanoi, Viet Nam

ⁱ KEMRI/CDC Research and Public Health Collaboration, Kisumu, Kenya

^j Erasmus University Medical Center, Rotterdam, The Netherlands

^k International Vaccine Institute, Seoul, Republic of Korea

^l University of Children's hospital, University of Cincinnati, OH, United States

ARTICLE INFO

Article history:

Received 1 May 2013

Accepted 8 May 2013

Available online 21 May 2013

Keywords:

Vaccine

Safety

Effectiveness

Adverse events

Benefit-risk

ABSTRACT

With the advent of new vaccines targeted to highly endemic diseases in low- and middle-income countries (LMIC) and with the expansion of vaccine manufacturing globally, there is an urgent need to establish an infrastructure to evaluate the benefit-risk profiles of vaccines in LMIC. Fortunately the usual decade(s)-long time gap between introduction of new vaccines in high and low income countries is being significantly reduced or eliminated due to initiatives such as the Global Alliance for Vaccines and Immunizations (GAVI) and the Decade of Vaccines for the implementation of the Global Vaccine Action Plan. While hoping for more rapid disease control, this time shift may potentially add risk, unless appropriate capacity for reliable and timely evaluation of vaccine benefit-risk profiles in some LMIC's are developed with external assistance from regional or global level. An ideal vaccine safety and effectiveness monitoring system should be flexible and sustainable, able to quickly detect possible vaccine-associated events, distinguish them from programmatic errors, reliably and quickly evaluate the suspected event and its association with vaccination and, if associated, determine the benefit-risk of vaccines to inform appropriate action. Based upon the demonstrated feasibility of active surveillance in LMIC as shown by the Burkina Faso assessment of meningococcal A conjugate vaccine or that of rotavirus vaccine in Mexico and Brazil, and upon the proof of concept international GBS study, we suggest a sustainable, flexible, affordable and timely international collaborative vaccine safety monitoring approach for vaccines being newly introduced. While this paper discusses only the vaccine component, the same system could also be eventually used for monitoring drug effectiveness (including the use of substandard drugs) and drug safety.

Published by Elsevier Ltd.

1. Background

Post-marketing surveillance for safety and effectiveness of newly introduced medical products including vaccines needs to be strengthened, particularly in low- and middle-income countries (LMIC). This is because the sample size and population heterogeneity of pre-licensure clinical trials is inherently limited [1].

Furthermore, many of the new vaccines just introduced (e.g., meningococcal A) [2] or in clinical development (e.g., dengue, malaria, tuberculosis, and HIV) are likely to be first used in populations from LMICs with a high incidence of the target diseases, which often includes infants and children. However, the capacity for program evaluation and safety monitoring post-licensure has historically been relatively weak in LMICs.

Most LMICs rely exclusively on passive surveillance for post-marketing assessment of vaccine safety and have limited capacity and experience in implementing epidemiological vaccine safety and effectiveness studies [3]. In the past, the availability of comprehensive vaccine safety assessment systems in the US and Europe has served most of the global need to evaluate newly released

* Corresponding author at: Immediate Office of the Director, OBE/CBER, Food and Drug Administration (FDA), 1401 Rockville Pike, 2nd floor, suite 200S, HFM-225, Rockville MD, 20852-1448, United States. Fax: +1 301 827 5218.

E-mail address: hector.izurieta@fda.hhs.gov (H.S. Izurieta).

vaccines. This was largely because most new vaccines were manufactured and introduced in the US and Europe initially before eventual lower prices allowed wider distribution elsewhere. Fortunately this usual decade(s)-long time gap between introduction of new vaccines in high and LMIC countries is being significantly reduced or eliminated due to initiatives such as the Global Alliance for Vaccines and Immunizations (GAVI) and the Decade of Vaccines for the implementation of the Global Vaccine Action Plan [4]. While hoping for more rapid disease control, this time shift may potentially add risk, unless appropriate capacity for reliable, and timely evaluation of vaccine benefit-risk profiles in some LMICs are developed with external assistance from regional or global level [5].

As with all pharmaceutical products, the introduction of new vaccines into larger heterogeneous populations entails the analysis of possible risks (e.g. adverse events following immunizations or AEFI) in view of their benefits (e.g., vaccine effectiveness) throughout their life cycle [6]. Such analysis should be specific to the populations and geographic regions in which the respective vaccines are being introduced. On the benefit side, ongoing documentation of the benefits of new vaccines, including population-level “herd immunity” effects are needed [7]. On the risk side, it is important to be prepared for both potentially real and perceived risks by promptly detecting and analyzing AEFI [5]. Both are of particular importance in settings where public health resources are limited [8].

Many novel vaccines under development use novel technology approaches (e.g., genetically modified, RNA or recombinant viral vectors, new delivery systems, presenting platforms, and adjuvants) with little past human use experience and occasional surprises [9,10]. The first wider use in large populations after the limited sample size of pre-licensure trials is likely to occur in LMICs, where the capacity for post-licensure monitoring is currently limited. Furthermore, the safety profiles of such vaccines in populations with varying host-related factors, including high rates of HIV prevalence, malnutrition and other underlying conditions, may differ and need to be systematically assessed. However, monitoring of rare outcomes in most LMICs settings is challenging, both methodologically and logistically. Finally, highly prevalent diseases in LMICs with serious morbidity and mortality will be temporally associated with new vaccines; these coincidental AEFIs will pose a serious threat to public acceptance of beneficial immunization programs if such temporal association (or real vaccine induced AEFI) is investigated too late or incompletely [11]. Such coincidental AEFI often consist of diseases of unclear or unknown etiology with a long time to onset and are typically overrepresented in spontaneous reporting systems and cohorts affected by publicly expressed safety concerns [12,13]. The resulting loss of confidence not only in the vaccine of concern, but in the entire immunization program, is challenging to regain during an often long period necessary to establish vaccine efficacy and benefits.

While examples of various vaccine safety “concerns” from the developed world are probably better known (e.g. Guillian-Barré syndrome (GBS) after A/New Jersey influenza vaccination in 1976 [14], encephalopathy after whole cell pertussis vaccine [15], autism after vaccines [16],) vaccine safety concerns have also impacted LMICs. The most extreme example was the unfounded concern in Nigeria that oral polio vaccine caused sterility, which resulted in major setbacks to the global eradication of poliomyelitis [17]. Less well known but important were the delayed recognition of a 700-fold elevated risk of disseminated BCG (Bacille Calmette Guerin) disease following receipt of BCG vaccine in HIV-infected (compared to uninfected) infants in South Africa [18] and b) the identification of yellow-fever vaccine associated viscerotropic disease with a mortality rate of 39–88% [19]. These issues were only ascertained following widespread use of these vaccines for decades in LMIC

Table 1

Characteristics of an ideal vaccine monitoring system.

Rapidly identify and address events potentially associated with programmatic errors.
Quickly detect and estimate rates of serious events possibly associated with vaccines or vaccine failure.
Provide timely evaluation of relevant vaccine safety and effectiveness concerns.
Provide effectiveness estimates to facilitate benefit-risk assessment.
Be sustainable and affordable: requiring minimal change in resources and procedures.
Be simple and flexible to adapt to the evaluation of new safety and effectiveness concerns.

with existing passive surveillance for AEFI. These two examples highlight how AEFI, particularly when not suspected, can remain unreported or underreported for long periods of time in passive surveillance systems and thus delay or impede further evaluation and timely regulatory action. Such scenarios should ideally be avoided with new vaccines.

An ideal vaccine safety and effectiveness monitoring system (Table 1) should be flexible and sustainable, able to quickly detect possible vaccine-associated events, distinguish them from programmatic errors, reliably and quickly evaluate the suspected event and its association with vaccination and, if associated, determine the benefit-risk of vaccines to inform appropriate action.

Many countries, particularly LMICs, currently do not have the technical capacity to implement timely and accurate epidemiological studies investigating the benefits and risks of vaccines. Lack of training, lack of automated data on population denominators, diagnoses, and person level exposure information are the chief contributing factors [5,20]. In addition, most countries do not have large enough populations under adequate active surveillance for evaluating rare AEFI (<1:100,000). The cost of building and maintaining a specific dedicated global monitoring system is prohibitive. Well-intentioned initiatives from donors providing one-time injection of resources rarely lead to sustainable infrastructures. Therefore, we propose here an alternative approach for global vaccine safety and effectiveness monitoring. We suggest capitalizing on already existing resources and developing a system able to investigate both frequent and rare vaccine safety and effectiveness outcomes which can be implemented in any setting, including LMIC. We propose that such a system would be part of a collaborative international framework for the ongoing evaluation of vaccine benefit-risk profiles, with particular emphasis on vaccines that are newly introduced in LMICs.

Although this paper will discuss only the vaccine component, the same system should also be eventually used for monitoring drug effectiveness (including the use of substandard drugs) and drug safety.

2. Overview of existing infrastructure

2.1. Passive surveillance systems

2.1.1. Advantages

Already available in most countries, with WHO and national support. They are the initial step of the WHO proposed minimal capacity for vaccine pharmacovigilance [5,20] as they provide the framework for communicating any vaccine safety concern. They have shown capacity for timely identification of serious safety concerns [18,19]. The investigation of those concerns, when performed in time, can lead to the identification of programmatic errors of serious consequence [23,24]. When timely AEFI surveillance is combined with a large mass immunization campaign with good tracking of vaccine distribution information, it is possible to

detect new vaccine safety signals in both developed and LMIC's [21,25,26].

2.1.2. Disadvantages

They are based on voluntary or stimulated reporting and only reflect a small proportion of such events occurrence. Because of an unknown and usually important degree of underreporting, only reporting rates rather than incidence rates can be produced. Although many passive surveillance systems allow near-real-time detection of safety concerns, they have significant limitations and many suffer from confounding and bias for various reasons such as notoriety and media effects [13,28]. Enhancement of spontaneous reporting can decrease, but not eliminate these disadvantages, and may not be cost-efficient, since the key limitations will remain. Even after detection of a safety signal with reports to an AEFI system during a mass immunization campaign, hypothesis testing studies are still required to confirm that the signal is a real vaccine safety problem and not an artifact [29,30].

2.2. Active (enhanced) surveillance

2.2.1. Advantages

Such programs can be established relatively quickly in most countries for reasonably sized populations (i.e., hundreds of thousands). Once available, they have shown capacity for timely identification of serious safety concerns that are relatively frequent and easy to identify [19,25]. Because the detection of events is usually systematic and can eventually be conducted by health care facilities serving fairly large populations, these systems can be used to approximate event rates by attributing the events to the population served by the health facilities included in the active surveillance efforts. The utility and applicability of such a system was recently demonstrated with meningococcal A conjugate vaccine introduction in Burkina Faso where establishment of an active system in a subset of the country demonstrated superior ability to detect adverse events when compared with nationwide passive surveillance [2].

2.2.2. Disadvantages

Most active surveillance efforts are time consuming and require coordinated action by multiple teams of health care workers charged with training and case reviews. The quality and completeness of data on health outcomes is variable, and depends on multiple factors including budget, training and commitment of the reviewers and data quality at the local level. The completeness and accuracy of the population and vaccine exposure denominators used can also vary greatly.

2.3. Communicable diseases and health and demographic surveillance centres

2.3.1. Advantages

Research centers in LMICs have dedicated staff and funding, and they are often equipped to collect and maintain comprehensive health and demographic data of the populations served. The Health and Demographic Surveillance System (HDSS) centers ($N \sim 30$) of the International Network for the Demographic Evaluation of Populations and Their Health (INDEPTH) are a prime example of such sites [31]. Common data collection methods in many INDEPTH centres facilitate pooling of data [31,32]. Comprehensive vaccination information in the communities served is or can be made available. Moreover, these institutions often have comprehensive laboratory services for the investigation of communicable and other diseases. Importantly, these centers are already serving as platforms for

clinical trials assessing the safety and efficacy of new drugs and vaccines [31,32].

2.3.2. Disadvantages

Biomedical research centers in LMICs are usually located in hard to reach rural areas or in urban areas with significant proportions of underserved populations and high disease rates. The population sizes under surveillance ($N \sim 250,000$) are usually too small for the identification of rare adverse events. Many of them rely on standard medical care which may not include adequate diagnostic capability to accurately diagnose diseases other than the specific infectious diseases they are researching. For example, they may have limited capacity for diagnosis and confirmation of some serious and rare events that could be associated with vaccines, such as GBS or immune thrombocytopenic purpura (ITP). When available, the vaccination and disease information may only exist on paper records, thereby delaying data analysis by weeks or even months [31].

3. New models

In order to optimally assess the safety and effectiveness of new vaccines introduced in LMIC we propose enhancing and integrating the above systems into a global collaborative network capable of reliably and efficiently identifying excess rates of rare and serious adverse events and their change over time, as well as obtaining person level information on immunizations at low cost and with limited building of additional infrastructure locally.

To test new models to address existing gaps, a consortium of vaccine safety researchers from WHO, United States FDA and CDC, European CDC, the Open University, the Universities of Rotterdam and Cincinnati, the Brighton Collaboration, the United Kingdom Health Protection Agency, teamed up with investigators from public health institutions from Europe, Asia, North America, and Australia to develop a viable, affordable and effective collaborative international vaccine safety monitoring network for the investigation of rare, serious and complex vaccine adverse events. A specific requirement was that the system had to be viable in any country, including LMICs. The consortium prepared a proof of concept international collaborative study to test the feasibility of such a global collaboration, and chose the investigation of a possible association between pandemic influenza A (H1N1) 2009 vaccine and Guillain Barré Syndrome (GBS) [30].

Through extensive assessment of the most suitable approach, the self-controlled case series methodology was chosen to analyze the data because of its cost-efficiency, flexibility and applicability to countries where population denominator information may either be unreliable or not available [33]. It should be made clear that the hospital-based approach selected by the consortium could also be used for investigations performed with study methods other than the self controlled case series (SCCS) methodology chosen for this proof of concept study. In SCCS studies, only patients with the disease or condition (event) of interest during the study period need to be investigated. Among them, the rate of occurrence of the event is compared between predefined "risk" and "non-risk" periods around the time of the vaccination of interest (exposure) [33,34]. Because only cases are needed for the analysis, population denominators are not required (the availability of accurate population denominators was cited as a frequent and often insurmountable problem for studies of rare events in LMICs). In addition, when applied to rare events, this approach allows only a limited number of events to be reviewed, thus saving resources. Also, because the risk of occurrence of the event is compared between two time periods in the same individual, time-invariant covariates are intrinsically adjusted for, therefore decreasing the possibility of bias [34,35]. This study included 546 cases of GBS

from 15 countries and four continents. Its success has shown that, for the global investigation of rare vaccine adverse events requiring sophisticated diagnostic capabilities, this approach is feasible and has much more power than investigations on a national or regional level, opening the door for further developments in this direction [33].

A pilot project called PREVENT (PRogram Enhancing Vaccine Epidemiology Networks and Training) funded by the European Commission's Global Research in Pediatrics Network is also underway to evaluate the INDEPTH infrastructure for post-licensure epidemiological safety studies. Four INDEPTH centres (Ghana, Kenya, and Mozambique) have been selected to compare the ability of different centres to replicate known vaccine AEFI associations (e.g., fever after vaccination) using existing available data. Insights from these pilot projects should allow identification of areas for improvement leading to an eventual functional vaccine benefit-risk monitoring system in INDEPTH.

4. Next steps

Based upon the demonstrated feasibility of active surveillance in LMIC as shown by the Burkina Faso assessment of meningococcal A conjugate vaccine or that of rotavirus vaccine in Mexico and Brazil [2,39], and upon the proof of concept international GBS study [33,36], which included middle and upper income countries, we suggest the approach below as a sustainable, flexible, affordable and timely international collaborative vaccine safety monitoring approach for vaccines being newly introduced. This approach would be particularly suitable for a consortium of upper, middle and low income countries, but it is feasible in any setting.

The proposed system would be two-pronged and could consist of: integrated coordinated passive surveillance and international collaborative epidemiological efforts.

- (1) Integrated coordinated passive surveillance: Such system could be modified to include stimulated or even active reporting of a small number of specific AEFI's of interest. Its objective would be for detecting vaccine safety signals or concerns, including the detection of programmatic errors. Possible programmatic errors would require the immediate implementation of field investigations to detect and control potential problems. Findings from this system should, as needed, be evaluated in hypothesis testing studies.
- (2) International collaborative epidemiological efforts, consisting of two complementary study approaches:

A – International consortium of communicable diseases and health and demographic monitoring centres: The development of such a consortium, including the prior implementation of proof-of-concept studies, is needed in preparation for the rapid coordinated implementation of multicenter collaborative studies needed to monitor the introduction of new vaccines. This would include systems such as Kenya's KEMRI/CDC Research and Public Health Collaboration, other INDEPTH member centres, and others [31,32]. Their role would include: (a) providing clinical trial centres for safety and effectiveness (some of them already perform such tasks) [31]; (b) performing post-licensure monitoring of vaccine effectiveness (their sophisticated infectious disease laboratory capabilities and direct access to households would facilitate this role) and; (c) performing house-based investigation of the incidence of relatively frequent vaccine safety concerns that do not require sophisticated diagnostic tools and techniques often unavailable in rural research settings.

B – International collaborative hospital-based network: The development, testing and maintenance of this consortium will be

needed in preparation for the rapid coordinated implementation of large collaborative international studies needed to monitor the introduction of new vaccines. This system could be used for the epidemiological confirmatory studies of the association between vaccines and serious, rare and difficult to diagnose adverse events of special interest requiring hospitalization using different case-based designs (e.g. self-controlled case series, case control and case-crossover). Because such events are not only rare but also often require sophisticated diagnostic capabilities and specialized physicians for diagnosis and treatment, it is imperative that participating hospitals be carefully selected. However, because these are referral hospitals, the vaccination status may not be systematically recorded. Given that retrieving patients after discharge for the detection of their vaccination status is often a challenge, an initial approach could be to routinely review cases admitted to the hospital with diagnosis that match a preselected list of "events of interest" for vaccine safety investigations. Once a case of an "event of interest" is identified, the vaccination status could be ascertained by interviewing the patient and the patient's parents to obtain relevant vaccination and other required information while the patient is still hospitalized [40]. In the future, once such network is established and its usefulness recognized, a second step would be for the participating network hospitals to ascertain information on the vaccination status for all inpatients both prior and after hospitalization. Alternatively, immunization information can be obtained in national immunization registries linkable to the event information collected in hospitals. Eventually, an electronic data system including all discharge and outpatient diagnoses in each hospital in the network, hopefully also including accurate vaccination information for all patients (maybe by linking the hospital information system to a national vaccine registry) would make possible the timely investigation of any rare and serious disease or condition following vaccination. Given time, the development in LMICs of large integrated health data systems with accurate population denominators, such as the Vaccine Safety Datalink (VSD) developed in the U.S. since the 1990s, will provide additional analytical flexibility [41–43].

5. Conclusions

With the advent of new vaccines targeted to highly endemic diseases in LMICs and with the expansion of vaccine manufacturing globally, there is an urgent need to establish an infrastructure to evaluate the benefit-risk profiles of vaccines in LMIC.

We propose here an incremental approach to test new models for collaborative assessment of vaccine risk-benefit that is flexible and feasible in both developed and developing countries. The most important goals addressed by the proposed two-pronged approach are to enhance the global capacity to reliably and promptly identify signals of rare and serious adverse events and their association with immunizations at low cost and with limited building of additional infrastructure. Platforms created by INDEPTH and other similar networks should be strengthened in this direction. With introduction and testing of such an approach, a sustainable and resource-efficient global infrastructure for vaccine safety assessment is now within reach.

Acknowledgements

The authors would like to thank the organizers and sponsors of the following meetings that fostered discussions and collaborations leading to this paper: 1) Global Vaccine Safety Datalink, September 11–13, 2007, Annecy, France; 2) Global Collaborative Network for Vaccine Safety, March 28–30, 2011, Annecy, France; and 3) Post Licensure Evaluation of Vaccine Safety: Current Status and

Future Directions, April 27–28, 2011, Barcelona, Spain. The authors also received useful comments from Dr. Robert Ball and Charles Preston (FDA), and from Thomas Bollyky, Council on Foreign Relations. We are also grateful for the review and approval of the manuscript by the Brighton Collaboration Science Board (Jim Buttery, Paul Health, Nadwa Khuri-Bulos, Hector Izurieta, Babatunde Imoukhuede, Miriam Sturkenboom, Steve Black, Heidi Larson)

Conflicts of interest: Osman Sankoh is the Executive Director of the INDEPTH Network, funded by core support grants from SIDA, Hewlett Foundation, Wellcome Trust and the Gates Foundation.

Disclaimer: The findings, opinions and assertions contained in this consensus document are those of the individual scientific professional members of this ad hoc Brighton Collaboration working group. They do not necessarily represent the official positions of each participant's organization (e.g., government, university, or corporations). Specifically, the findings and conclusions in this paper are those of the authors and do not necessarily represent the views of the Centres for Disease Control and Prevention or the Food and Drug Administration, Erasmus University, the World Health Organization or the University of Cincinnati.

References

- [1] Strom BL. What is pharmacoepidemiology. In: Strom BL, Kimmel SE, Hennessy S, editors. *Pharmacoepidemiology*. fifth ed. Chichester, UK: Wiley; 2012.
- [2] Ouandaogo CR, Yaméogo TM, Diomandé FV, Sawadogo C, Ouédraogo B, Ouédraogo-Traoré R, et al. Adverse events following immunization during mass vaccination campaigns at first introduction of a meningococcal A conjugate vaccine in Burkina Faso, 2010. *Vaccine* 2012;30(May (Suppl. 2)):B46–51. Epub 2012 Jan 9.
- [3] Graham JE, Borda-Rodriguez A, Huzair F, Zinck E. Capacity for a global vaccine safety system: the perspective of national regulatory authorities. *Vaccine* 2012;30:4953–9.
- [4] The Global Alliance for Vaccines and Immunization: <http://www.one.org/c/us/policybrief/3260>
- [5] WHO. Draft Global Vaccine Action Plan (GVAP). http://apps.who.int/gb/ebwha/pdf_files/WHA65/A65_22-en.pdf
- [6] Ball R, Horne D, Izurieta H, Sutherland A, Walderhaug M, Hsu H. Statistical, epidemiological, and risk-assessment approaches to evaluating safety of vaccines throughout the life cycle at the Food and Drug Administration. *Pediatrics* 2011;127(May (Suppl. 1)):S31–8.
- [7] Rashid H, Khandaker G, Booy R. Vaccination and herd immunity: what more do we know? *Curr Opin Infect Dis* 2012;25(June (3)):243–9.
- [8] Youngkong S, Kipiriri L, Baltussen R. Setting priorities for health interventions in developing countries: a review of empirical studies. *Trop Med Int Health* 2009;14(August (8)):930–9. Epub 2009 Jun 26.
- [9] Draper SJ, Heeney JL. Viruses as vaccine vectors for infectious diseases and cancer. *Nat Rev Microbiol* 2010;8:62–73.
- [10] Gray G, Buchbinder S, Duerr A. Overview of STEP and Phambili trial results: two phase IIb test-of-concept studies investigating the efficacy of MRK adenovirus type 5 gag/pol/nef subtype B HIV vaccine. *Curr Opin HIV AIDS* 2010;5(September (5)):357–61.
- [11] Black S, Eskola J, Siegrist CA, Halsey N, MacDonald N, Andrews N, et al. Importance of background rates of disease in assessment of vaccine safety during mass immunization with pandemic H1N1 influenza vaccines. *Lancet* 2009;374:2115–22.
- [12] Singleton JA, Lloyd JC, Mootrey GT, Salive ME, Chen RT. An overview of the vaccine adverse event reporting system (VAERS) as a surveillance system, VAERS Working Group. *Vaccine* 1999;17(22):2908–17.
- [13] Varricchio F, Iskander J, Destefano F, Ball R, Pless R, Braun MM, et al. Understanding vaccine safety information from the Vaccine Adverse Event Reporting System. *Pediatr Infect Dis J* 2004;23(4):287–94.
- [14] Schonberger LB, Bregman DJ, Sullivan-Bolyai JZ, Keenlyside RA, Ziegler DW, Retailiau HF, et al. Guillain-Barre syndrome following vaccination in the National Influenza Immunization Program, United States, 1976–1977. *Am J Epidemiol* 1979 Aug;110(2):105–23.
- [15] Gangarosa EJ, Galazka AM, Wolfe CR, Phillips LM, Gangarosa RE, Miller E, et al. Impact of anti-vaccine movements on pertussis control: the untold story. *Lancet* 1998;351(January (9099)):356–61. PubMed PMID: 9652634.
- [16] Institute of Medicine (US) Immunization Safety Review Committee. *Immunization Safety Review: Vaccines and Autism*. Washington (DC): National Academies Press (US); 2004. PubMed PMID: 20669467.
- [17] Aylward B, Tangermann R. The global polio eradication initiative: lessons learned and prospects for success. *Vaccine* 2011;29(December (Suppl. 4)):D80–5.
- [18] Hesseling AC, Marais BJ, Gie RP, Simon Schaaf H, Fine PEM, Godfrey-Faussett P, et al. The risk of disseminated Bacille Calmette-Guerin (BCG) disease in HIV-infected children. *Vaccine* 2007;25:14–8.
- [19] Monath TP. Review of the risks and benefits of yellow fever vaccination including some new analyses. *Expert Rev Vaccines* 2012 Apr;11(4):427–48.
- [20] World Health Organization. *Global Vaccine Safety Blueprint (2012)*. WHO/IVB/12.07; 2012.
- [21] Patel MM, Haber P, Baggs J, Zuber P, Bines JE, Parashar UD. Intussusception and rotavirus vaccination: a review of the available evidence. *Expert Rev Vaccines* 2009;8(November (11)):1555–64.
- [22] http://www.who.int/immunization_safety/publications/aefi/en/AEFI.WPRO.pdf
- [23] http://www.who.int/immunization_safety/publications/aefi/en/AEFI.WPRO.pdf
- [24] <http://www.whale.to/vaccines/dpt1.html>
- [25] da Silveira CM, Kmetzsch CI, Mohrdieck R, Sperb AF, Prevots DR. The risk of aseptic meningitis associated with the Leningrad-Zagreb mumps vaccine strain following mass vaccination with measles-mumps-rubella vaccine, Rio Grande do Sul, Brazil, 1997. *Int J Epidemiol* Oct 2002;31(5):983–4.
- [26] Poland GA, Grabenstein JD, Neff JM. The US smallpox vaccination program: a review of a large modern era smallpox vaccination implementation program. *Vaccine* 2005;23:2078–81, 2005.
- [27] Ball R, Horne D, Izurieta HS, Sutherland A, Walderhaug M, Henry H. Statistical, epidemiological, and risk-assessment approaches to evaluating safety of vaccines throughout the life cycle at the Food and Drug Administration. *Pediatrics* (online) 2011, <http://dx.doi.org/10.1542/peds.2010-1722F>.
- [28] Rantala H, Cherry JD, Shields WD, Uhari M. Epidemiology of Guillain-Barre syndrome in children: relationship of oral polio vaccine administration to occurrence. *J Pediatr* 1994;124:220–3.
- [29] Sexton K, McNicholas A, Galloway Y, Radke S, Kieft C, Stehr-Green P, et al. Henoch-Schönlein purpura and meningococcal B vaccination. *Arch Dis Child* 2009;94:224–6.
- [30] www.indepth-network.org
- [31] Sankoh O, Byass P. The INDEPTH Network: filling vital gaps in global epidemiology. *Int J Epidemiol* 2012;41(3):579–88.
- [32] Dodd CN, Izurieta HS, Zuber P, Romio S, Sturkenboom M, Hua W, et al. International collaborative case series safety monitoring for pandemic 2009 H1N1 vaccines: estimation of the risk of Guillain-Barre syndrome. In: Poster 778. 27th International Conference on Pharmacoepidemiology & Therapeutic Risk Management. 2012.
- [33] Whitaker HJ, Farrington CP, Spiessens B, et al. Tutorial in biostatistics: the self-controlled case series method. *Stat Med* 2006;25:1768–97.
- [34] Farrington CP. Relative incidence estimation from case series for vaccine safety evaluation. *Biometrics* 1995;51:228–35.
- [35] Hua W, Sun G, Dodd CN, Romio SA, Whitaker HJ, Izurieta HS, et al. A Simulation study to compare three self-controlled case series approaches: correction for violation of assumption and explanation of bias. *Pharmacoepidemiol Drug Saf* 2013;(Apr. (29)), <http://dx.doi.org/10.1002/pds.3451>, in press.
- [36] Patel MM, López-Collada VR, Bulhões MM, et al. Intussusception risk and health benefits of rotavirus vaccination in Mexico and Brazil. *N Engl J Med* 2011;364(June (24)):2283–92.
- [37] Scheifele D, Morris R, Halperin S, et al. IMPACT monitoring network: a better mousetrap. *Can J Infect Dis* 1993;4:75–6.
- [38] <http://www.cdc.gov/vaccinesafety/Activities/vsd.html>
- [39] Chen RT, DeStefano F, Davis RL, et al. The Vaccine Safety Datalink: immunization research in health maintenance organizations in the USA. *Bull World Health Organ* 2000;78(2):186–94.
- [40] Black S. Global Vaccine Safety DataNet meeting. *Expert Rev Vaccines* 2008;7(February (1)):15–20.