Vaccine Safety Monitoring Systems in Developing Countries: An Example of the Vietnam Model

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Abstract: Only few health intervention programs have been as successful as vaccination programs with respect to preventing morbidity and mortality in developing countries. However, the success of a vaccination program is threatened by rumors and misunderstanding about the risks of vaccines. It is short-sighted to plan the introduction of vaccines into developing countries unless effective vaccine safety monitoring systems are in place. Such systems that track adverse events following immunization (AEFI) is currently lacking in most developing countries. Therefore, any rumor may affect the entire vaccination program. Public health authorities should implement the safety monitoring system of vaccines, and disseminate safety issues in a proactive mode.

Effective safety surveillance systems should allow for the conduct of both traditional and alternative epidemiologic studies through the use of prospective data sets. The vaccine safety data link implemented in Vietnam in mid-2002 indicates that it is feasible to establish a vaccine safety monitoring system for the communication of vaccine safety in developing countries. The data link provided the investigators an opportunity to evaluate AEFI related to measles vaccine. Implementing such vaccine safety monitoring system is useful in all developing countries. The system should be able to make objective and clear communication regarding safety issues of vaccines, and the data should be reported to the public on a regular basis for maintaining their confidence in vaccination programs.

Keywords: Adverse Event, large linked database, signals Detection, vaccine, vaccine safety, Vietnam.

VACCINE SAFETY COMMUNICATION REQUIRES ACTIVE VACCINE SAFETY SURVEILLANCE

Vaccines are considered to be the most cost effective tools in public health armamentarium. After introduction of the vaccines, the vaccine preventable diseases have been significantly decreased worldwide [1]. Given this success, concerns are being raised about safety issues of vaccine, in particular, the adverse event following immunization (AEFI). These AEFIs can be any unusual laboratory findings, symptom or disease [2]. Public confidence of vaccines can be badly damaged by allegations of any AEFI based on poor-quality data or poor analysis. It is therefore important for the public health communities to be prepared to respond to any allegations rapidly, and with reliable information from high-quality data and rigorous analysis.

The Institute of Medicine (IOM) found serious gap in our understanding and infrastructure required to conduct studies on AEFI [3, 4]. For instance, the passive surveillance systems are implemented in the United States for detecting clinically significant AEFI [5]. Such systems are accused of inaccurate reporting of AEFI due to reporting bias, conveying incorrect or incomplete information, or delaying decision-making for follow-up studies [6]. To overcome the problems associated with passive surveillance system, the active population-based vaccine safety surveillance system is established [1]. In this surveillance system, a vaccine safety datalink (VSD) is created, which is typically a large linked database (LLD) whereby population of an area or a cohort is linked to vaccination and medical events. In the LLD, the AEFI can be evaluated without any selection bias or observer effect. The aim of implementing a VSD is to provide accurate detection and assessment of AEFI in real-time. Such system has been developed in Europe [7-9], Asia [10-16] and the Pacific Region [17-20]. This paper aims to provide a summary and lessons learnt from the first introduction and implementation of a LLD in a developing country setting.

WHY AN ACTIVE VACCINE SAFETY MONITORING SYSTEM IS REQUIRED IN THE DEVELOPING WORLD

Prior to 2002, active vaccine safety monitoring systems had been lacking in developing countries, thus safety issues of vaccines were rarely addressed or communicated in these countries [21- 22]. There are several reasons for which a safety monitoring system is needed in a developing country: First, the vaccines in these countries may not always be produced under Good Manufacturing Practice (GMP) conditions [23, 24]. For instance, cholera, typhoid fever, Japanese encephalitis, or rabies vaccines are largely used in developing countries but often do not face vigorous scrutiny of the regulatory authorities [25]. Secondly, vaccine safety and potency may become diminished due to poor storage

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2212-3911/15 $58.00+.00

facility or administration. Third, rare AEFI may not be found in pre-licensure trials due to conducting such trials among small number of participants. In some situation, active ingredients of the vaccines may be lacking or the vaccines may found to be associated with AEFI after marketing [26-33]. Uncommon, but serious adverse events, such as intussusception, have led to the withdrawal of the rotavirus vaccine (RotaShield$^{TM)}$) from the market [34, 35]. However, in several instances, vaccines were accused of causing adverse events without sufficient evidence to support causal relationship. A vaccine safety monitoring system, by providing required data about safety issues of the vaccines, would assure quality of vaccine production in developing countries.

Usually, parents seek advice from healthcare professionals before coming to a decision about vaccinating their children. When their questions remain unanswered, they will less likely to vaccinate their children. To maintain public confidence in vaccination programs, safety issues need to be handled instantly and properly. In some countries, passive surveillance systems are maintained for timely detection of vaccine-related adverse events. However, the system may not determine the causal relationship between an AEFI and a vaccine. The deficiencies in the passive surveillance system are balanced to some extent by evaluating large number of reports over time [36]. An active population-based vaccine safety datalink (VSD) is free from such deficiencies. The basic requirement for such systems is the linkage between vaccination databases or registries and medical events in healthcare surveillance through a unique identification number. The VSD database has to be sufficiently large to provide a realistic chance to detect rare adverse events.

The very successful VSD system in the United States has become possible through the integration of databases from several maintenance organizations (HMOs) in which vaccination and medical events of more than 500,000 children less than 6 years of age are captured. These medical events are linked to vaccination status annually, creating one of the largest cohorts for vaccine safety studies [1, 37]. The database has been used to evaluate the safety of several vaccines, such as, measles, rubella, influenza, whole-cell pertussis, and type 1 diabetes mellitus [38-42]. The information coming out from that VSD is disseminated on a regular basis, providing scientific evidence about safety of the vaccines. There is a need for such surveillance systems in developing countries to accurately identify AEFI, and communicating safety issues of the vaccines.

STUDY DESIGNS AND ANALYTICAL OPTIONS FOR VACCINE SAFETY SURVEILLANCE SYSTEMS

Healthcare professionals involved in vaccination programs should aware of the strengths and weaknesses among different designs of the surveillance systems. An effective surveillance system should generate data to conduct different studies, such as, cohort, case-control, risk interval cohort, and self-controlled case series, for the evaluation of safety issues of vaccines. Each study could be used for the early signal detection of AEFI [5, 43, 44] after adjusting for the issues in local study setting. The matched-cohort analysis provides the best result for AEFI signal detection among those different observational study designs. However, it is difficult to conduct the matched-cohort analysis at regular intervals and in real-time. In contrast, case–control studies are suitable for signal detection of rare adverse events, and it requires relatively small data sample from the entire cohort. However, these studies are prone to selection bias [45].

In a risk-interval cohort design, incidence rates between risk period (before vaccination) and non-risk period (after vaccination) are compared. Only the vaccinated individuals are included in this study design. The time period right after vaccination is treated as the risk-interval period, and individuals that experience adverse events during this period are classified as exposed cases. Time period outside the risk interval period (before vaccination or long after vaccination) are considered non-risk interval period. Individuals that experience disease in the non-risk interval period are classified as unexposed cases. Since only vaccinated individuals are included in this study design, the risk of introducing bias in the analysis is minimized by not comparing the medical events with the unvaccinated population. On the other hand, the self-controlled case-series (SCCS) design is similar to that of risk-interval studies. Only the cases are included in this study design, and the incidence rates of medical events between exposed and unexposed time periods are compared. Since each case acts as its own control, controlling for the other confounding variables except age is not needed as those usually remain same for a person during the evaluation period [46].

It is important to consider all possible limitations of a study design, because those limitations may have an impact on the findings of the analysis. For instance, the risk-interval cohort or SCCS designs will be biased if age and seasonal confounders are not considered in the analysis [44], and the findings of the analysis might change once these effects are included. It is also important to know that a false positive event will have a greater effect on bias in the analysis, thus caution is needed to minimize false positive events. Specific training for physicians involved in these studies focusing on accurate assessment and diagnosis and use of standardized case definition could minimize false positive events.

Most AEFI is rare, *i.e*., event-vaccination ratio is in between 1:1,000 and 1:10,000, and the logistic regression tends to underestimate the estimates when the outcome is rare [43]. Poisson regression would also underestimate the estimates when the disease incidence is low. It is, therefore, essential to choose the right methodology for dissemination of the findings of the analysis. One should also be careful when interpreting the results of analysis from a large-linked database due to possible bias in data collection, data coding, and data editing in different data sets. Also, the data sets used to create the LLD may not necessarily be generated to answer to AEFI-related question [47]. Therefore, those who are involved with this study should critically review the results of the analysis before dissemination of it.

APPLIED VACCINE SAFETY SURVEILLANCE AND COMMUNICATION – THE VIETNAM MODEL

In mid-2002, the International Vaccine Institute (IVI) implemented a large-linked database to monitor vaccine safety in a semi-rural province in central Vietnam (Fig. **1**).

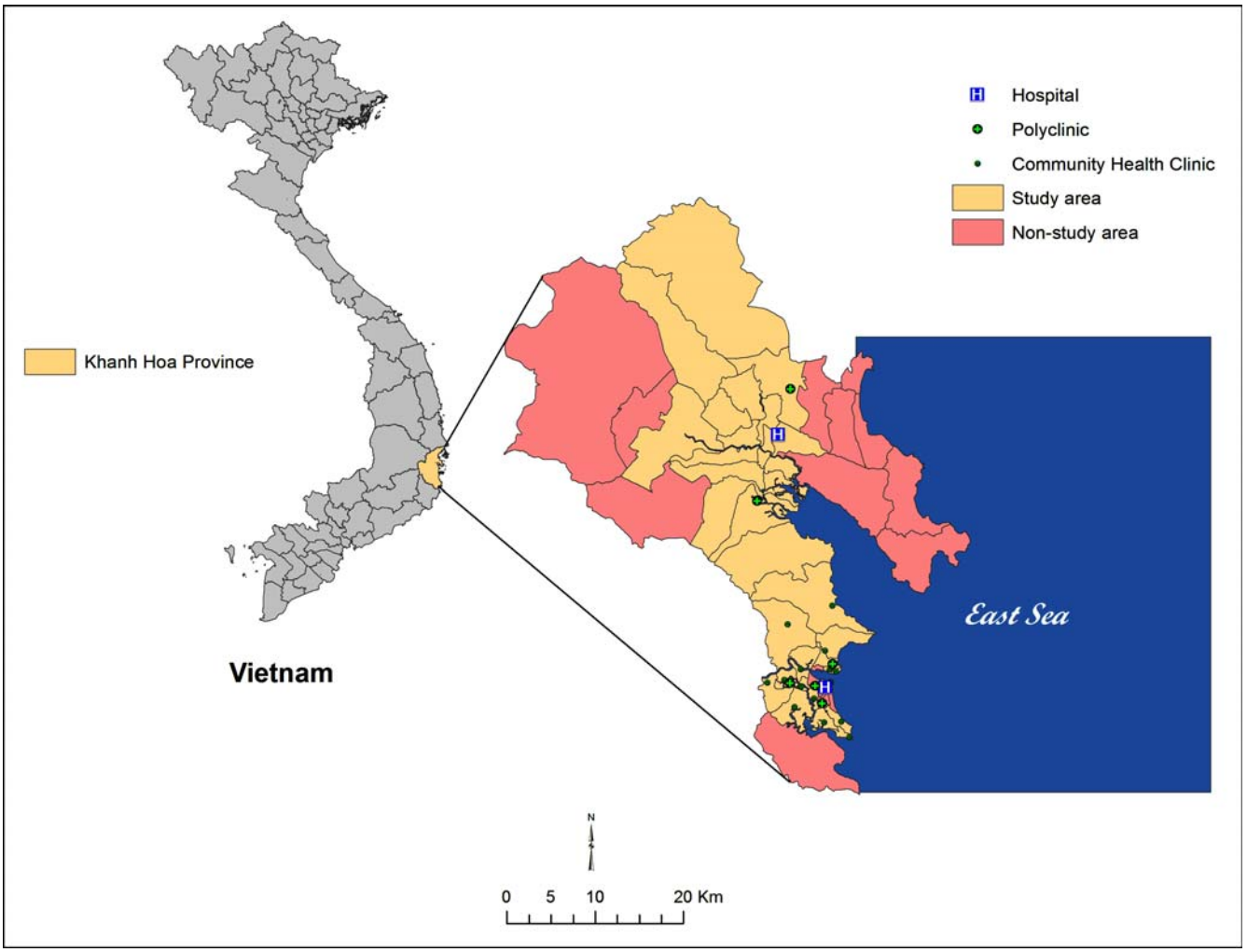

Fig. (1). A map of the catchment area (study area) of the VSD project (study Area) in Khanh Hoa Province, Vietnam (community clinics are shown only for the Nha Trang district due to lack of data).

The primary objective of the project was to link vaccination and medical records with population-base of the study area. The databases ensured

- all live births are captured;
- immunization data in children less than 10 years are collected;
- all medical outcomes in children less than 15 years are captured;
- demographic events such as deaths and outmigrations of the target population are collected;
- classification of cause of deaths and discharge diagnoses according to ICD-10 codes are done; and
- geographic and ecological characteristics of the study area are incorporated.

The secondary objectives were to analyze the AEFI based on the reports from Institute of Medicine (IOM) and literature reviews [3-4]; to evaluate effects of simultaneous versus combined vaccination of various antigens; and to create a model field site for evaluating vaccine adverse effects, which can be replicated in other developing countries.

PREPARATION OF THE PROJECT

The basic infrastructure of the project was created during December 2001 and April 2002. Study data forms to record vaccinations and medical events were prepared, pretested, and printed. The data forms were prepared by the IVI team, and implemented after reviewing those forms by the Vietnamese collaborators. Computers were purchased, the data management systems were installed, and the study office was furnished. Staff members recruited for the field activities were trained in field procedures and the data staff was trained in data management activities by the skilled professionals from IVI and National Institute of Hygiene and Epidemiology (NIHE).

The pilot project was initiated in April 2002 in a few communes of the two districts: Nha Trang and Ninh Hoa. The progress of the activities of the pilot project was assessed by the scientists from IVI and NIHE. The pilot phase was ended in August 2002, which was supposed to end in July 2012. The one-month delay was due to recruiting and training additional

health workers to expand the activities. During August 2002 the newly appointed health workers were trained in field activities by participating in the pilot study. The surveillance in the entire study area was started in September 2012.

THE CHALLENGES

The VSD system faced challenges in tracing population, immunizations, and medical events in the study area as the case of a developing country setting [48]. The challenges are described below:

CHALLENGES IN CREATING POPULATION-BASE

The population-base was constructed from the data of a census conducted in 1996 as the part of a cholera vaccine trial, which had been updated at yearly intervals. Individuals moved over time had made it a challenge to keep track of them over time. A unique problem was the splitting-up of administrative units which had been used as part of an individual's identifier. The population-base was last updated in 2001 through a demographic surveillance system whereby vital demographic events were collected. In the population-base each individual was identified by two IDs: one called Current ID (CID) reflecting present address of the person that changes with the changes of current address, and the second one was the Permanent ID (PID) which remains same for a person ever in the system. The PID of a person allowed us to keep track of the person over time. The target population for the VSD was individuals less than 15 years of age, and this population was updated quarterly through vital demographic events, such as, births, deaths and migrations. Additionally, a yearly census survey was conducted to update the population.

CHALLENGES IN VACCINATION RECORD KEEPING

The challenges in the old vaccination record keeping system were that both vaccination register and individual vaccination were kept at the vaccination center. There was no unique ID of a person that could be used to link the vaccination card with vaccination register. The individuals were identified only by their names, which created confusion when having same name for more than one individual. Moreover, there was no record of which vaccine lot was received by an individual. The vaccination center, however, kept a record of which vaccine lots were stored. If multiple vaccine lots of one vaccine were stored in a vaccination center and used those lots in one vaccination day, then it was impossible to say which vaccine lot was administered to which individual. To overcome that problem, the project staff recorded vaccine lot and manufacturer in a register book specially designed for this purpose. Additionally, the project staff requested the vaccine delivery staff at Provincial Preventive Medicine Center to supply the same vaccine lot for their communes (lowest administrative unit in Vietnam) during the monthly campaign.

HEALTH CARE SYSTEM AND CHALLENGES IN LINKING MEDICAL/HEALTH EVENTS

In Vietnam, the state-owned healthcare system has four tiers. The first contact is usually made to a community health center (CHC), which are staffed by persons with 2–3 years training in biomedical sciences. Many CHCs are staffed by one medical doctor. Cases requiring advanced medical care are referred to polyclinics, which are staffed by medical school graduates. Patient, however, can go directly to the polyclinics for seeking their healthcare. If surgery is required, the patient is transferred to the district hospital. For more specialized treatments, the patients are transferred to the provincial hospital.

The challenges in linking medical events to vaccination status to build a LLD system were that only medical records from district hospitals were coded and computerized. Medical records from polyclinics and CHCs were not computerized. As a solution, we collected medical records of all children less than 15 years admitted to polyclinics and CHCs in the target commune. The diagnoses were coded according to International Classification of Diseases, 10th Revision (ICD-10). Since the database required linking vaccination records to medical events accurately, a Medical ID (MID) card containing the household ID (Fig. **2**) were distributed to all the households in the study area. Once the household ID was triggered in the database, the individual ID could be retrieved based on name and age. The MID card included a self-checking number so as to prevent keypunching errors while entering the ID. The people from the study area were requested to bring their MID cards while seeking for their medical care at a healthcare. Computers and additional staff were provided to the district hospitals for entering the medical records from polyclinics, which were not computerized in their routine process. The computerized data on medical events from all the target hospitals were transferred to the project office on a monthly basis.

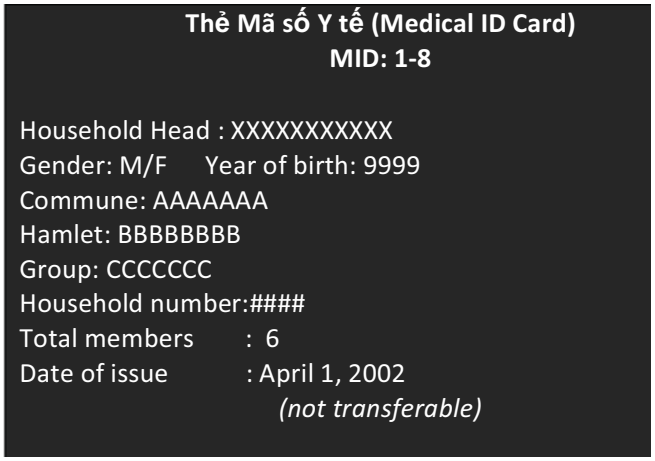

Fig. (2). A model of the medical ID (MID) card.

CHALLENGES IN CONDUCTING VERBAL AUTOPSIES FOR DEATHS

In Vietnam, deaths are reported to the civil authorities in order to obtain permission for the funeral ceremony. We collected the list of the deceased from the civil authorities, and conducted verbal autopsies of the children less than 15 years residing in the study area and who died during the study period. Two physicians reviewed the forms to ascertain the primary cause of death and coded it according

to International Classification of Diseases, 10th Revision (ICD-10). In the event of discrepancies between the two physicians, both of them reviewed the forms together to come up to a final decision.

MANAGEMENT OF THE VSD SYSTEMS

The VSD systems were managed by trained staff under active supervision of professionals from IVI and NIHE. Since automated data were obtained for medical events, it was required to ensure accuracy of the IDs of the patients. The MID card allowed recording the household ID in the medical record. Based on the household ID and the name of the patient, the data staff searched the population database for obtaining the IDs of the patients. The electronic data of the patients were then be updated with the individuals IDs before being uploaded in the VSD systems.

For the new births, immunizations and migrations, the data were entered into the VSD system through an interactive data entry system. Necessary checks were built into the system so as to prompt while entering an erroneous data. All errors were resolved from the respective area of work, and updated the database. A monthly report including status of the data entry was generated by the systems, which was reported to the senior managements by the VSD Supervisors. The study investigators and coordinators provided necessary comments and suggestions after reviewing the monthly report.

DATA QUALITY AND CONTROL PROCEDURE

It is important to assure quality, accuracy, and reliability of the databases needed to study potential rare AEFIs [49]. Staff training, standardized operating systems, quality monitoring, and routine review of the databases were incorporated in the data system for assuring quality, accuracy and reliability of the database. In addition to the routine procedures, the following indicators also helped assessing completeness of the data.

- what percentage of births were captured from the CHCs record;
- how the vaccination records were maintained at the CHCs;
- what percentage of illness was captured by the hospitals and policlinics; and
- what percentage of deaths had occurred at the hospitals.

COMMUNICATING RESULTS AND IMPACT OF THE VIETNAM VACCINE SAFETY MONITORING SYSTEM

The Vietnam vaccine safety monitoring system provided a unique opportunity to evaluate adverse events related to the measles vaccine by using the data of a mass measles vaccination conducted in 2003 [25]. Measles vaccinations were introduced into the Vietnamese EPI in the 1990s. It was thought that accumulation of the unvaccinated children over time would create risk for measles outbreaks. To reduce the risk, a countrywide measles vaccination campaign was initiated in 2002 in the north of Vietnam. In 2003, the campaign was extended to the southern parts of the country, and that included the study area.

Vaccine communication was intensified at the community level to achieve a good coverage in the mass vaccination campaign. Simple health messages were given at the community for the success of a good coverage. Parents or guardians of children 9 months to 10 years of old were invited to have their children vaccinated, regardless of their measles vaccination history. The campaign was conducted in local schools and CHCs in March-April 2003. In total 107,022 children from the study area were identified during the study period, and 87% or higher vaccine coverage was observed for the routine childhood vaccinations (BCG, OPV, DTP and measles). Age-appropriate coverage for the third dose of hepatitis B vaccine was 79%. At the time of the measles mass vaccination campaign, 61,856 children between 9 months and 10 years living in the study area were eligible for the measles vaccinations.

The VSD system documented 53,256 recipients of the measles vaccine yielding 86% coverage in the mass campaign. The mean age of the recipients of the vaccine was 6 years. Out of these children, 5,523 (10%) were less than 2 years and 19,509 (37%) were less than 5 years of age. In total, 105 and 107 medical events during 14 days before and 14 days after the vaccination, respectively, were recorded—the rate ratio (RR) was 1.0 (95% CI: 0.8-1.3) (Table **1**). Extending the observation period to 60 days, 337 medical events before the vaccination and 355 medical events after the vaccination were recorded, which provided a RR of 1.2 (95% CI: 0.9-1.3) (Table **2**). Two children were documented

Table 1. The five most frequently observed medical events during the 14 days following measles vaccination during the campaign in Khanh Hoa Province, Vietnam.

Presentation	During the 14 Days		Rate Ratio Adjusted*	95% Confidence Interval
	Before Vaccination N=53,240	After Vaccination N=53,240		
Gastroenteritis	21	24	1.2	0.7–2.1
Pneumonia	17	16	1.0	0.5-1.9
Acute respiratory infections	6	11	1.9	0.7-5.0
Tonsillitis	7	2	0.3	0.06-1.4
Viral fever	6	14	2.4	0.9-6.1

*Rate ratio adjusted for age and distance to health care provider.

Table 2. The 10 most frequently observed medical events during the 60 days following the measles vaccination campaign in Khanh Hoa Province, central Vietnam.

Presentation	During the 60 Days		Rate Ratio Adjusted*	95% Confidence Interval
	Before Vaccination *n* = 53,267	After Vaccination *n* = 53,267		
Acute respiratory tract infection	63	69	1.26	0.90 to 1.78
Gastroenteritis	59	45	0.96	0.65 to 1.42
Pneumonia	22	34	1.73	1.00 to 2.98
Tonsillitis	14	16	1.10	0.53 to 2.25
Pharyngitis	10	10	1.00	0.41 to 2.40
Asthma	9	8	0.86	0.33 to 2.23
Skin infection	5	8	1.65	0.54 to 5.07
Dengue	3	4	1.28	0.29 to 5.75
Lymphadenitis	4	3	0.85	0.19 to 3.82
Convulsions	1	3	3.41	0.35 to 33.00

*Rate ratio adjusted for age and distance to provider.

as epilepsy: one was before the vaccination and other one was after the vaccination. No cases of local or allergic reactions, syncope, encephalopathy, or deaths were reported during the evaluation period. Tonsillitis cases were frequently detected before the vaccination and arthropod-borne viral fever cases were frequently found within two weeks following the vaccinations.

The key safety message was that no significant increase in the incidence of any medical event was observed after introducing the mass measles campaign in the study area [48].

CONCLUSION

Only few interventions have been as effective in averting premature deaths as vaccination. Over the past several decades, vaccines shown to have a highly cost-effective method for improving human health, in particular the child health. Maintaining public confidence about safety of the vaccines is the key to the continued success of vaccination programs. It requires an open and active communication about vaccine safety issues between health professionals and the parents. The communication could be effective if it is backed by scientific evidence of vaccine safety generated from active surveillance data, as the case of Vietnam VSD.

As more and more vaccines are included in the vaccination programs, the safety issues of vaccine have become critical in determining the success of health intervention programs. Expanding the use of existing vaccines and introducing new vaccines are important for improving human health, but these could be short-sighted unless a surveillance system is implemented for monitoring and communicating the safety concerns of the vaccines. Although millions of doses of vaccines are used in developing countries in every year, only few developing countries have surveillance programs with the ability to monitor and evaluate safety issues of vaccines.

The vaccine safety concerns should not be confined within a region or country, as this is a global phenomenon. It is necessary to identify common vaccine safety indicators and develop minimal capacity for ensuring establishment of an effective vaccine safety surveillance and communication infrastructure. Capacity building should also include the development of a plan for enhancing and sustaining vaccine safety monitoring system, and response to a safety concern of a vaccine.

The Vietnam experience illustrates that it is feasible to establish an effective vaccine safety monitoring system for communicating safety concern about vaccines in a developing country. It also suggests that a clear evidence-base safety issue of vaccines in a given population may require support from health professionals, stakeholders and policy makers in order to communicate vaccine safety to the general public. Concerned people often ask for more information about safety issues of vaccines, and based on a large-linked database and conducting prospective studies, we would be able to provide information on how much risks and benefit are involved in getting vaccinated in their setting. Implementing vaccine safety monitoring systems elsewhere, following the Vietnam model, would give the health professionals additional support and information to reassure parents and families that vaccines are safe. Efforts should be made to establish such surveillance systems in developing countries to enable a complete understanding of vaccine safety, which is essential to maintain public confidence about vaccination programs. Healthcare professionals involved in these surveillance systems should communicate the results of safety studies in a clear and concise manner, ideally in collaboration with communication specialists. Communication is key – communication needs to be improved among safety specialists in different parts of the world, as well as from safety specialists to the physicians in the field, all the way to those who ought to benefit most from safe and effective vaccines: the children and their families.

LIST OF ABBREVIATIONS

AEFI = Adverse Event Following Immunization

CHC = Community Health Clinic

CID = Current Identification

DTP = Diphtheria-tetanus-pertussis

EPI = Expanded Programme on immunization

FDA = Food and Drug Administration

GMP = Good Manufacturing Practices

ICD = International Classification of Diseases

IVAC = Institute of Vaccines and Medical Biologicals

IVI = International Vaccine Institute

MMR = Measles, Mumps, and Rubella Combination

NIHE = National Institute of Hygiene and Epidemiology

OPV = Oral Polio Vaccine

PID = Permanent Identification

SCCS = Self-Controlled Case-Series

WHO = World Health Organization

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

ACKNOWLEDGEMENTS

The author is grateful to the staff of National Institute of Hygiene and Epidemiology and people of Khanh Hoa Province of Vietnam whose support were critical for implementing the vaccine safety monitoring system in Vietnam.

REFERENCES

[1] Chen RT, Glasser JW, Rhodes PH, *et al.* Vaccine safety datalink project: a new tool for improving vaccine safety monitoring in the United States. Pediatrics 1997; 99(6): 765-73.

[2] CIOMS/WHO Working Group on Vaccine Pharmacovigilance. Definition and application of terms for vaccine pharmacovigilance, 2012 [cited 15.02.2012]; available from: http://whqlibdoc.who.int/publications/2012/9789290360834_eng.pdf.

[3] Howson CP, Howe CJ, Fineberg HV, Eds. Adverse effects of pertussis and rubella vaccines: a report of the Committee to Review the Adverse Consequences of Pertussis and Rubella Vaccines. Washington, D.C: National Academy Press, 1991.

[4] Stratton KR, Howe CJ, Johnston RB, Eds. Adverse events associated with childhood vaccines: evidence bearing on causality. Washington DC: National Academy Press, 1994.

[5] McClure DL, Glanz JM, Xu S, *et al.* Comparison of epidemiologic methods for active surveillance of vaccine safety. Vaccine 2008; 26: 3341-5.

[6] Lieu TA, Kulldorff M, Davis RL, *et al.* Real-time vaccine safety surveillance for the early detection of adverse events. Med Care 2007; 45(10 Supl 2): S89-95.

[7] Zanoni G, Berra P, Lucchi I, *et al.* Vaccine adverse event monitoring systems across the European Union countries: time for unifying efforts. Vaccine 2009; 27(25-26): 3376-84.

[8] Micheletti F, Moretti U, Tridente G, Zanoni G. Consultancy and surveillance of post-immunisation adverse events in the Veneto region of Italy for 1992-2008. Human Vaccines 2011; 7 (Suppl): 234-9.

[9] Lankinen KS, Pastila S, Kilpi T, *et al.* Vaccinovigilance in Europe - need for timeliness, standardization and resources. Bull World Health Organ 2004; 82(11): 828-35.

[10] Shah R, Raghu MB, Shivananda A, *et al*. Immunogenicity and safety of an indigenously developed DTPw hepatitis B combination vaccine in Indian infants. Indian Pediatr 2008; 45(10): 819-23.

[11] Lee H, Kim HW, Cho HK, *et al.* Reappraisal of MMR vaccines currently used in Korea. Pediatr Intern: official journal of the Japan Pediatr Soc 2011; 53(3):374-80.

[12] Latipov R, Khudoyorov R, Flem E. Childhood intussusception in Uzbekistan: analysis of retrospective surveillance data. BMC Pediatr 2011; 11-22.

[13] Kim JH, Cho HY, Hennessey KA, *et al.* Adverse events following immunization (AEFI) with the novel influenza a (H1N1) 2009 vaccine: findings from the national registry of all vaccine recipients and AEFI and the passive surveillance system in South Korea. Jap J Infect Dis 2012; 65(2): 99-104.

[14] Huang WT, Chuang JH, Kuo SH. Monitoring the safety of pandemic H1N1 vaccine. Lancet 2010; 375(9721): 1164.

[15] Huang WT, Chen WC, Teng HJ, et al. Adverse events following pandemic A (H1N1) 2009 monovalent vaccines in pregnant women--Taiwan, November 2009-August 2010. PloS ONE 2011; 6(8): e23049.

[16] Dasgupta S, Bagchi SN, Ghosh P*, et al*. Monitoring of mass measles campaign in AILA-affected areas of West Bengal. Ind J Public Health 2010; 54(4): 224-7.

[17] Tatley MV. Vaccine safety monitoring of the MeNZBTM vaccine using electronic data transfer and assessment. Drug Saf 2006; 29(10): 911-1010.

[18] Menzies R, Mahajan D, Gold MS, et al. Annual report: surveillance of adverse events following immunisation in Australia, 2008. Commun Dis Intell 2009; 33(4): 365-81.

[19] Lawrence GL, Burgess MA, Kass RB. Age-related risk of adverse events following yellow fever vaccination in Australia. Commun Dis Intell 2004; 28(2): 244-8.

[20] Lawrence G, Menzies R, Burgess M, *et al.* Surveillance of adverse events following immunisation: Australia, 2000-2002. Commun Dis Intell 2003; 27(3): 307-23.

[21] Muehlhans S, Richard G, Ali M, *et al.* Safety reporting in developing country vaccine clinical trials-a systematic review. Vaccine 2012; 30(22): 3255-65.

[22] Letourneau M, Wells G, Walop W, Duclos P. Improving global monitoring of vaccine safety: a survey of national centres participating in the WHO Programme for International Drug Monitoring. Drug Saf 2008; 31(5): 389-98.

[23] Clemens J, Jodar L. Introducing new vaccines into developing countries: obstacles, opportunities and complexities. Nat Med 2005; 11(Suppl 4): S12-5.

[24] Clemens J. Evaluation of vaccines against enteric infections: a clinical and public health research agenda for developing countries. Philos Trans R Soc Lond B Biol Sci 2011; 366(1579): 2799-805.

[25] Ali M, Canh DG, Clemens JD, *et al.* The vaccine data link in Nha Trang, Vietnam: a progress report on the implementation of a data base to detect adverse events related to vaccinations. Vaccine 2003; 21: 1681-6.

[26] Streefland PH. Public doubts about vaccination safety and resistance against vaccination. Health Policy 2001; 55(3): 159-72.

[27] Nathanson N, Langmuir A. The Cutter incident: Poliomyelitis following formaldehyde-inactivated poliovirus vaccination in the United States during the spring of 1955. II. Relationship of poliomyelitis to Cutter vaccine. Am J Hyg 1963; 78: 29-60.

[28] Whittle H, Hanlon P, O'Neill K, *et al.* Trial of high-dose Edmonston-Zagreb measles vaccine in the Gambia: antibody response and side-effects. Lancet 1988; 2(8615): 811-4.

[29] Aaby P, Jensen TG, Hansen HL*, et al.* Trial of high-dose Edmonston-Zagreb measles vaccine in Guinea-Bissau: protective efficacy. Lancet 1988; 2(8615): 809-11.

[30] Aaby P, Samb B, Simondon F, *et al.* Child mortality after high-titre measles vaccines in Senegal: the complete data set. [letter; comment]. Lancet 1991; 338(8781): 1518-9.

[31] Holt EA, Moulton LH, Siberry GK, Halsey NA. Differential mortality by measles vaccine titer and sex. J Infect Dis 1993; 168(5): 1087-96.

[32] Halsey NA. Increased mortality after high titer measles vaccines: too much of a good thing. Pediatr Infect Dis J 1993; 12(6): 462-5.
[33] Anonymous. Withdrawal of rotavirus vaccine recommendation. MMWR Morb Mortal Wkly Rep 1999; 48(43): 1007.
[34] Murphy TV, Gargiullo PM, Massoudi MS, *et al*. Intussusception among infants given an oral rotavirus vaccine. N Engl J Med 2001; 344: 564–72.
[35] Kramarz P, France EK, DeStefano F, *et al*. Population-based study of rotavirus vaccination and intussusception. Pediatr Infect Dis J 2001; 20: 410-6.
[36] Bonhoeffer J, Bentsi-Enchill A, Chen RT, *et al*. Guidelines for collection, analysis and presentation of vaccine safety data in surveillance systems. Vaccine 2009; 27: 2289-97.
[37] DeStefano F. The vaccine safety data link project. Pharmacoepidemiol Drug Saf 2001; 10(5): 403-6.
[38] Davis RL, Kramarz P, Bohlke K, *et al*. Measles–mumps–rubella and other measles-containing vaccines do not increase the risk for inflammatory bowel disease: a case-control study from the vaccine safety data link project. Arch Pediatr Adolesc Med 2001; 155(3): 354-9.
[39] Ray P, Black S, Shinefield H, *et al.* Risk of chronic arthropathy among women after rubella vaccination. Vaccine safety data link team. JAMA 1997; 278(7): 551-6.
[40] Kramarz P, DeStefano F, Gargiullo PM, *et al.* Does influenza vaccination exacerbate asthma? Analysis of a large cohort of children with asthma. Vaccine safety data link team. Arch Fam Med 2000; 9(7): 617-23.
[41] DeStefano F, Mullooly JP, Okoro CA, *et al*. Childhood vaccinations, vaccination timing, and risk of type 1 diabetes mellitus. Pediatrics 2001; 108(6): E112.
[42] Barlow WE, Davis RL, Glasser JW, *et al.* The risk of seizures after receipt of whole-cell pertussis or measles, mumps, and rubella vaccine. New England J Med 2001; 345(9): 656–61.
[43] Glanz JM, McClure DL, Xu S*, et al*. Four different study designs to evaluate vaccine safety were equally validated with contrasting limitations. J Clin Epidemiol 2006; 59: 808-18.
[44] Davis RL, Kolczak M, Lewis E, *et al.* Active surveillance of vaccine safety: A system to detect early signs of adverse events. Epidemiology 2005; 16(3): 336-41.
[45] Bailey L, Vardulaki K, Langham J, Chandramohan D. Introduction to epidemiology. Black N, Raine R, Eds. London: Open University Press in collaboration with LSHTM, 2006.
[46] Chen RT, Glanz JM, Vellozzi C. Pharmacoepidemiologic studies of vaccine safety. In: Pharmacoepidemiology, 5th Edition. Strom BL, Kimmel SE, Hennessy S. Eds. Wiley-Blackwell, 2012; pp.423-68.
[47] Verstraeten T, DeStefano F, Chen RT, Miller E. Vaccine safety surveillance using large linked database: opportunities, hazards and proposed guideline. Exp Rev Vaccines 2003; 2(1): 21-9.
[48] Ali M, Canh DG, Clemens JD, *et al.* The use of a computerized database to monitor vaccine safety in Vietnam. Bull World Health Organ 2005; 83(8): 604-10.
[49] Mullooly JP. Misclassification model for person-time analysis of automated medical care databases. Am J Epidemiol 1996; 144(8): 782-92.

Received: March 14, 2014 Revised: May 6, 2014 Accepted: May 28, 2014