# The use of a computerized database to monitor vaccine safety in Viet Nam

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**Abstract** Health information systems to monitor vaccine safety are used in industrialized countries to detect adverse medical events related to vaccinations or to prove the safety of vaccines. There are no such information systems in the developing world, but they are urgently needed. A large linked database for the monitoring of vaccine-related adverse events has been established in Khanh Hoa province, Viet Nam. Data collected during the first 2 years of surveillance, a period which included a mass measles vaccination campaign, were used to evaluate the system. For this purpose the discharge diagnoses of individuals admitted to polyclinics and hospitals were coded according to the International Classification of Diseases (ICD)-10 guidelines and linked in a dynamic population database with vaccination histories. A case-series analysis was applied to the cohort of children vaccinated during the mass measles vaccination campaign. The study recorded 107 022 immunizations in a catchment area with a population of 357 458 and confirmed vaccine coverage of 87% or higher for completed routine childhood vaccinations. The measles vaccination campaign immunized at least 86% of the targeted children aged 9 months to 10 years. No medical event was detected significantly more frequently during the 14 days after measles vaccination than before it. The experience in Viet Nam confirmed the safety of a measles vaccination campaign and shows that it is feasible to establish health information systems such as a large linked database which can provide reliable data in a developing country for a modest increase in use of resources.

**Keywords** Measles vaccine/adverse effects; Adverse drug reaction reporting systems; Drug monitoring/methods; Databases, Factual/ utilization; Immunization programs; Cohort studies; Viet Nam (*source: MeSH, NLM*).

**Mots clés** Vaccin antimorbilleux/effets indésirables; Services données effets secondaires medicaments; Surveillance médicament/ méthodes; Base données factuelles/utilisation; Programmes de vaccination; Etude cohorte; Viêtnam (*source: MeSH, INSERM*).

**Palabras clave** Vacuna antisarampión/efectos adversos; Sistemas de registro de reacción adversa a medicamentos; Monitoreo de los medicamentos/métodos; Bases de datos factuales/utilización; Programas de inmunización; Estudios de cohortes; Viet Nam (*fuente: DeCS, BIREME*).

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*Voir page 608 le résumé en français. En la página 609 figura un resumen en español.*

## Introduction

Concerns regarding the safety of vaccines have a negative influence on vaccine uptake. Some safety concerns are justified, as exemplified by the adverse events recorded following rhesus rotavirus or smallpox vaccinations (*1–4*). However, many vaccines have been falsely reported to cause such diverse events as autism, arthritis, sudden infant death syndrome, epilepsy, diabetes mellitus, human immunodeficiency virus infection, multiple sclerosis, chronic fatigue syndrome and Gulf War syndrome (*5*).

To address these concerns and to maintain public confidence in immunizations, safety issues have to be dealt with rapidly and credibly. In industrialized countries existing health information systems such as computerized population databases can be used to link vaccination histories with disease outcomes and thus allow the rapid assessment of associations between vaccination and adverse events unanticipated at the time of constructing the database (*6–8*). If concerns regarding adverse events are not addressed rapidly with adequate studies, there is a real risk that public confidence will diminish and public acceptance of vaccinations will decline. To date, health information systems such as large linked databases have not been created in low-income countries, where concerns over vaccine safety are now also arising (*9*). Assumptions that concerns regarding vaccine safety are less relevant in poorer populations, because the risk of an infection is so much higher relative to the risk of an adverse event related to vaccination, are probably unfounded. During the study period, the authors were

invited on several occasions to visit sites in Viet Nam where concerns regarding the safety of vaccines had interfered with vaccination programmes (*10*). Vaccine safety was also a major concern for Vietnamese policy-makers when debating the need for a national mass measles vaccination campaign. There were concerns that measles immunizations, administered to children across a broad age range of 9 months to 10 years, irrespective of earlier measles immunization status, might trigger adverse events (*11*). These discussions resulted in the request to use the vaccine safety database, which can link vaccinations with medical events, to monitor adverse events related to the vaccine when the campaign was ultimately conducted in 2003 in central coastal Viet Nam.

The design and implementation of this database have been described elsewhere (*12*). In the present paper, we describe how the system was used to assess the association between medical events and measles immunizations during a large-scale, mass immunization campaign.

## Methods

### Study area and cohort
The catchment area included 33 communes in two districts, Nha Trang and Ninh Hoa, Khanh Hoa province, Central Viet Nam (Fig. 1). A dynamic study cohort of children under 15 years of age was assembled based on a de jure census conducted in 2002. Records of births during the study period were collected monthly and used to update the population database. Emigrations and deaths of cohort members were recorded during quarterly visits to the community and these cohort members were excluded from the analysis from the time of their emigration or death. Observations collected during the study period from 1 September 2002 until 31 August 2004 were analysed for this report. On 1 January 2003, the population of the catchment area was 357 458 people, of whom 27 427 (8%) were children less than 60 months old and 107 159 (30%) were children less than 15 years old.
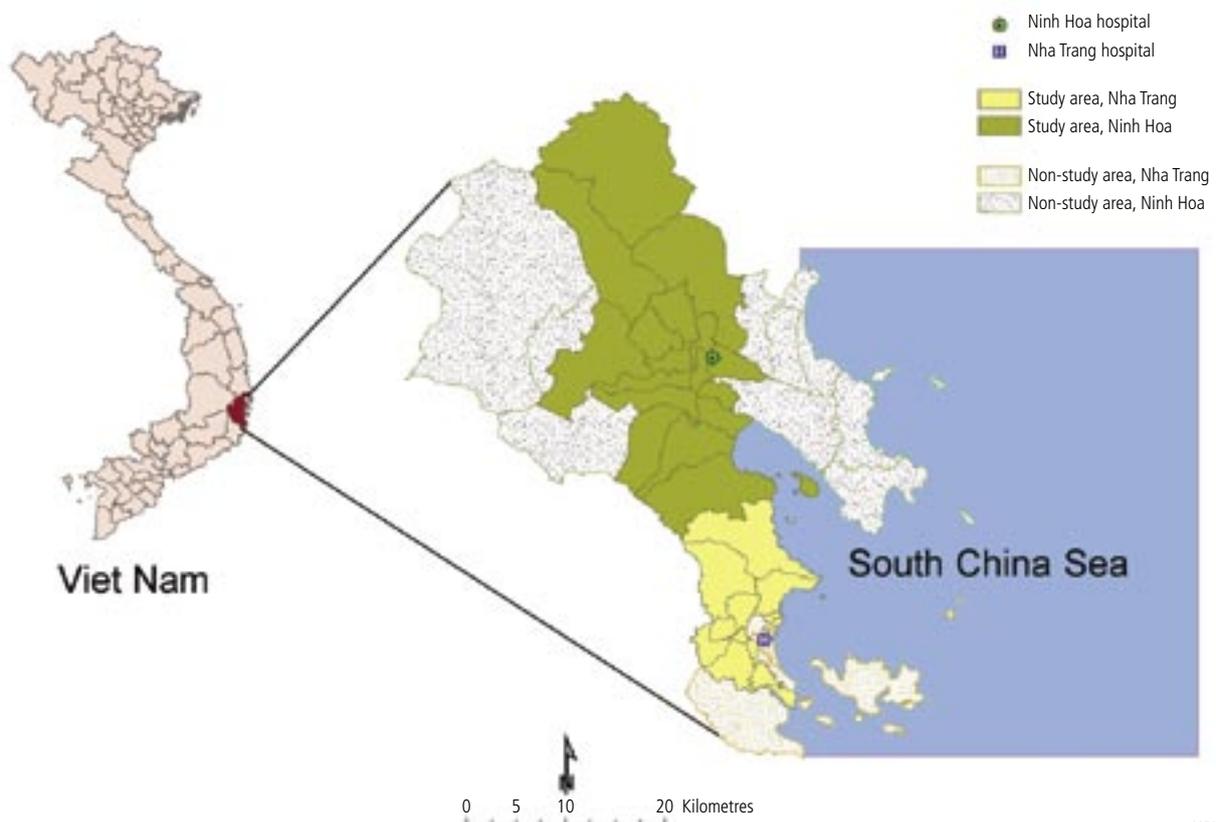
### Health care system
The government-run medical system in Khanh Hoa province has four tiers. The first contact with the health care system is usually through a visit to a commune health centre (CHC), which is staffed by practitioners with 2 or 3 years of training. Patients who require more sophisticated care attend polyclinics, which are staffed by medical school graduates. For more complex interventions, such as surgery, patients are transferred to the district hospital. Specialized interventions are provided by the provincial hospital. To receive free health care, residents need to use the CHC to which they are assigned before being transferred to the higher tiers of the health care system. bacille Calmette–Guérin (BCG), oral polio vaccine (OPV), diphtheria–tetanus toxoids–pertussis (DTP), hepatitis B virus (HBV) and measles vaccinations are provided free of charge by the national immunization programme. Routine vaccinations are usually administered at the CHC.

### Mass immunization campaign against measles
Measles vaccinations were introduced into the Vietnamese expanded programme on immunization (EPI) in the 1990s, but clusters of susceptible children remained unprotected by 2002.

Fig. 1. **A map of the study area in Khanh Hoa province, Viet Nam**

To reduce the risk of measles outbreaks, a countrywide measles vaccination campaign was started in 2002 in the north of Viet Nam. The campaign was extended in 2003 to the southern parts of Viet Nam including Khanh Hoa province. Parents and guardians of eligible children, aged 9 months to 10 years, were invited to have their children immunized, regardless of their measles vaccination history. Between March and April 2003 all age-eligible children received a measles vaccination in local schools and CHCs.

## Health information system

A dynamic relational database was constructed containing data on population, vaccination history and medical events. The data were linked through a unique identification number assigned to each individual in the study area. An interactive system was designed to enter data collected from health care providers. To identify the individuals seen at health care centres, medical identity (ID) cards containing a unique ID number for each household were distributed. Families were instructed to present the ID card whenever a child under 15 years of age used the health care system. In the absence of an ID card, a computerized ID search of the census was conducted by trained data entry staff using the identifying information in the medical record, including name, sex, age, address and name of the head of the household (12).

## Medical events

All admissions to polyclinics, district hospitals or the provincial hospital were recorded by the surveillance system. Discharge diagnoses were coded by a trained team of physicians according to International Classification of Diseases, tenth Revision (ICD-10) guidelines. The health care provider or an assistant recorded the patient's name, address, the names of the child's mother, father and household head and, if available, the household ID number from the medical ID card on each medical record. All vaccinations and vaccine lots used were recorded on an individual vaccination card and in a logbook, both of which were stored at the vaccination centre. Project staff visited the vaccination centres every month following the vaccination campaign to record vaccination information (i.e. patient identifiers, vaccine types, vaccination dates and vaccine lots used).

## Immunization status and vaccine coverage

The immunization programme in Khanh Hoa province follows the EPI schedule (13) and includes BCG at birth; OPV and DTP at ages 6, 10 and 14 weeks; HBV at birth and at ages 6 and 14 weeks; and measles vaccinations at age 9 months. Age-appropriate immunization status was measured as of 4 weeks after the recommended age of vaccination. Vaccine coverage of routine immunizations was estimated as the percentage of eligible children vaccinated within 4 weeks of the recommended age of vaccination. The coverage of the mass measles vaccination campaign was estimated as the percentage of eligible children vaccinated during the campaign.

## Analysis

The case-series analytical approach was applied to the cohort of children who received the measles vaccine during the measles vaccination campaign to compare the relative risk of medical events in the period 14 days before the children received measles vaccinations with that in the period 14 days after vaccination

(14, 15). We chose this period because most of the events previously reported following measles vaccinations (local reactions, fever, rash, febrile seizures, allergic reactions, anaphylaxis and encephalopathies) occurred within 14 days of vaccination (16). For those who died or emigrated from the area before the end of the 14-day period after vaccination, the time until the date of the event was included. Because the children in the control cohort were on average 14 days younger than children in the case cohort, we calculated the age of the unvaccinated children as their age at the time of vaccination minus 7 days and the age of vaccinated children as age at the time of the vaccination plus 7 days. The analysis was repeated for a longer, 60-day period of observation before and after the vaccination. At an alpha level of 0.05 (one-sided) the study has 80% power to detect an increment in disease frequency from 1/53 000 prior to vaccination to 4/53 000 events after vaccination.

A Poisson model was fitted to estimate rate ratios of the five most frequently detected medical events: gastroenteritis (ICD-10 codes A03, A04, A08 and A09), pneumonia (ICD-10 codes J18 and J18.9), acute respiratory tract infections (ICD-10 code J06), tonsillitis (ICD-10 code J03) and arthropod-borne viral fever (ICD-10 code A94) adjusted for age and distance to the health care provider. The Stata 8 software was used to calculate rate ratios and Spearman rank correlation coefficients (Stata Corporation, USA). The distance, in kilometres, from the home of the child to the health care provider (the CHC) was estimated. The ArcGIS 8.3 (ESRI Inc., USA) was used to analyse geographical data.

# Results

## Vaccinations and medical events

During the study period, a total of 107 022 immunizations of children in the catchment area were recorded, and age-appropriate vaccine coverage of 87% or higher was confirmed for completed routine childhood vaccinations (BCG, OPV, DTP and measles). Age-appropriate coverage for the third dose of hepatitis B vaccine was 79%. The vaccine-eligible population in the catchment area and the vaccine coverage is shown in Table 1.

Table 1. **Target population and age-appropriate[a] coverage of bacille Calmette–Guérin (BCG), diphtheria–tetanus toxoids–pertussis (DTP), oral polio (OPV), hepatitis B (HBV) and measles vaccines in Nha Trang, Viet Nam, 2002–03**

| Immunization | Target population | No. of children immunized | Coverage (%) |
|---|---|---|---|
| BCG | 10547 | 9741 | 92.4 |
| DTP1 | 10217 | 9367 | 91.7 |
| DTP2 | 9701 | 8728 | 90.0 |
| DTP3 | 9211 | 8066 | 87.6 |
| OPV1 | 10257 | 9438 | 92.0 |
| OPV2 | 9608 | 8789 | 91.5 |
| OPV3 | 9251 | 8130 | 87.9 |
| HBV1 | 10596 | 9183 | 86.7 |
| HBV2 | 10303 | 8552 | 83.0 |
| HBV3 | 9370 | 7404 | 79.0 |
| Measles (routine) | 7035 | 6301 | 89.6 |

[a] Age-appropriate coverage is defined in the methods section.

Over the same period, 14 043 medical events were recorded in the target population. Some 67% (9393) of these were recorded in the Nha Trang provincial hospital, 22% (3110) in Ninh Hoa hospital, and the remaining 11% (1540) in six polyclinics. The distance from the health care provider had an effect on health care utilization. Individuals living closer to providers reported medical events more frequently than those living further away ($P$ = 0.001; Fig. 2).
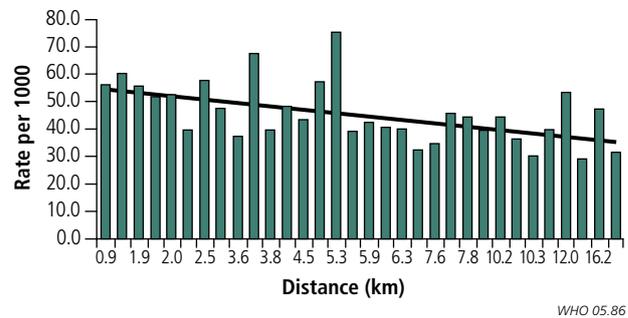
## Mass measles vaccination

At the time of the vaccination campaign 61 856 children between the ages of 9 months and 10 years resided in the study area and were eligible for vaccination against measles. The study documented vaccinations of 53 256 children resulting in an estimated 86% coverage. The mean age of the children participating in the campaign was 6 years. Of these children, 5523 (10%) were aged under 2 years and 19 509 (37%) were under 5 years. In all, 105 medical events were reported in the 14 days before the vaccination and 107 medical events were registered in the 14 days after the vaccination (rate ratio (RR) 1.0; 95% confidence intervals (CI), 0.8 to 1.3; Table 2). Extending the length of the period of observation yielded 337 medical events in the 60 days before the vaccination and 355 medical events in the 60 days after the vaccination (RR, 1.2; 95% CI, 0.9 to 1.3). Two children were diagnosed with epilepsy (ICD code G40): one in the 2 weeks before the vaccination and one in the 2 weeks following the vaccination. No cases of syncope, local reactions, allergic reactions or encephalopathy and no deaths were reported in either time period. Cases of tonsillitis were more frequently detected before the mass measles vaccination, and arthropod-borne viral fever more frequently in the 2 weeks following the vaccinations. But no medical event detected by the datalink showed a statistically significant increase in incidence rates after vaccination, compared with those before it.

## Discussion

Findings from the first 24 months of use of the datalink system provided evidence that it is feasible to capture the immunizations as well as the medical events in a large population and link them within a dynamic, computerized database. This datalink made it possible to estimate vaccine coverage. Coverage rates were as high as 92% for BCG and the first dose of OPV and as low as 79% for the third dose of HBV. At least 87% of the target population had received all doses of BCG, DTP, OPV and

Fig. 2. **Reported medical event rates in relation to distance from home to the health-care provider. Residents living further away from the health-care provider were less likely to make use of the provider (Spearman's rho = -0.5; $P$ = 0.001)**



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measles vaccine. These are minimum estimates, as additional children may have been vaccinated outside the study period, which would increase the coverage rates. Because recent reports have triggered scepticism regarding reported high immunization rates (*17*), it is reassuring to obtain independent confirmation of high coverage rates in Viet Nam. The observation that approximately 20% of the population eligible for HBV vaccination had not received the required three doses is helpful when considering the initiation of programmes to remedy the poor coverage of HBV.

The surveillance detected 105 medical events within 14 days of a mass measles vaccination; these events could be misinterpreted as being causally related to the vaccination. However, during the 14 days before the mass measles vaccination, a very similar number of medical events, 107, was detected.

In a population with high vaccine coverage it may be impossible to recruit a sufficient number of unvaccinated controls with demographic and socioeconomic characteristics similar to those of the vaccinated children under study to compare risks for medical events between vaccinated and unvaccinated individuals. An added benefit of an analytical approach in which the same children are compared before and after vaccination lies in the similarity of the two cohorts, which are identical in all respects except age. Because several childhood illnesses, including gastroenteritis and bronchopneumonia, may be more common in younger children, the incidence rate ratios were

Table 2. **The five most frequently observed medical events following measles vaccination during the campaign in Khanh Hoa province, central Viet Nam**

| Presentation | During the 14 days | | Rate ratio adjusted[a] | 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 |

ICD-10 codes: gastroenteritis = A03, A04, A08, A09; pneumonia = J18, J18.9; acute respiratory tract infections, ARI other than pneumonia = J06; tonsillitis = J03; arthropod-borne viral fever = A94.

[a] Rate ratio adjusted for age and distance to health care provider.

adjusted for age. We observed a trend towards higher rates of arthropod-borne viral fevers after the vaccinations. One reason for this observation is the seasonal character of viral infections transmitted by fluctuating insect populations which correlate with meteorological events including a temperature increase during spring when the measles mass immunization campaign took place. The rate ratios were also adjusted for distance from household to health care provider because treatment uptake was related to this distance. No statistically significant differences in adverse events before and after measles vaccinations were detected during the campaign. Mass measles vaccination campaigns are recommended when susceptible populations come into close contact, such as in refugee camps. It is hoped that the safety of the measles vaccination campaigns demonstrated here will relieve safety concerns and perhaps encourage measles vaccinations campaigns.

The comparison of event rates following mass vaccinations between sites requires caution. Pless and co-workers reviewed the safety of mass measles vaccination campaigns in seven countries (16). They found that the number of reported medical events ranged between 65.6/100 000 doses in Canada and 6.4/100 000 doses in Romania. The number of reported severe medical events ranged between 8.1/100 000 in the United Kingdom and none in Costa Rica. This wide range in adverse events rates has many causes. The vaccination campaigns studied targeted different age groups, usually older children than are vaccinated in routine programmes. Therefore events characteristically observed in younger children such as febrile seizures, may be less frequently seen in a vaccination campaign than would be expected from routine vaccination programmes (18, 19). Different measles vaccines were used (monovalent, bivalent (measles and rubella) and trivalent (measles, mumps and rubella)) which could result in different rates of adverse events. The definitions of adverse events varied between sites. Finally, medical events may not be recognized in some communities or even if recognized may not trigger a visit to the health care provider which is essential for case-detection if passive surveillance systems are used.

The use of the large linked database in Khanh Hoa for the detection of medical events following vaccination has specific limitations. The event detection period was up to 60 days. Events which occurred more than 60 days after measles vaccination would thus not have been detected by the study. Fifty-three thousand children received a measles vaccination during the mass vaccination campaign. Therefore rare but important adverse events such as mortality occurring at a rate of less than 1/53 000 are unlikely to be detected by the surveillance. The diagnostic categories used in the analysis were based on the ICD-10 codes assigned by professional staff, but have not been confirmed. This approach may serve well to detect signals (i.e. events that should attract attention), and during the study period no such signals were detected. To make a more

definitive diagnosis of the adverse event, a careful independent review of the medical record would be required. Finally, it may not be appropriate to assume that a large linked database can be replicated in every setting. The study infrastructure in Khanh Hoa included data from a pre-existing census and a well-defined population. Coding and transcription of medical diagnoses had been in place before the study started. Perhaps most importantly, the study population had collaborated in previous medical studies and agreed to collaborate in the surveillance. Census, coding and community participation may be costly and time-consuming activities which could complicate the establishment of surveillance networks in other areas.

Health information systems are essential for monitoring the safety of vaccines and may be particularly important in developing countries. Locally produced vaccine may not have to comply with regulations the international pharmaceutical industry is obliged to follow in industrialized countries. Moreover vaccines which protect against diseases of regional importance such as Japanese encephalitis or yellow fever, are used almost exclusively in developing countries. Once a vaccine has been licensed, rare but important safety issues may only be detected in large vaccinated populations. In the absence of appropriate health information systems, such safety problems may go undetected. To our knowledge, this is the first report of a purpose-built health information system being used to evaluate vaccine safety in a non-industrialized country. The study demonstrated that it is feasible to build de novo a large database which can link medical events to vaccine histories. The system can be maintained by four data entry clerks employed for the transcription of hospital records. One supervisor is required to ensure the completeness and computerization of data. Additional funds may be required for conducting an annual census to update the population database.

In conclusion, the expanded use of existing vaccines and the introduction of new vaccines into developing countries in the absence of health information systems to monitor their safety may be short sighted. Further efforts should be made to establish health information systems to monitor vaccine safety in resource-poor countries to enable a more complete understanding of vaccine safety, which is essential to maintain confidence in vaccine programmes. ∎

## Résumé

### Utilisation d'une base de données informatisée pour surveiller la sécurité des vaccins au Viêtnam

Les pays industrialisés font appel à des systèmes d'information sanitaire de vaccinovigilance afin de détecter les événements médicaux indésirables en rapport avec la vaccination ou de prouver la sécurité des vaccins. De tels systèmes d'information font défaut dans le monde en développement, qui en a un besoin urgent. Une grande base de données reliées, destinée à la surveillance des événements indésirables liés à la vaccination, a été mise en place dans la province de Khanh Hoa, au Viêtnam. Les données recueillies au cours des deux premières années de surveillance, couvrant une campagne de vaccination de masse contre la rougeole, ont servi à évaluer le système. A cette fin, on a affecté un code aux diagnostics de sortie des personnes admises dans les polycliniques et les hôpitaux selon la classification ICD-10, ce qui a permis de relier ces diagnostics aux antécédents de vaccination dans une base de données en population dynamique. Une analyse des séries de cas a été effectuée sur la cohorte d'enfants vaccinés à l'occasion de la vaccination antirougeoleuse de masse. L'étude a enregistré 107 022 vaccinations dans une zone de recrutement abritant 357 458 habitants et a confirmé un taux de couverture supérieur ou égal à 87 % pour la vaccination systématique des enfants déjà réalisée. La campagne de vaccination antirougeoleuse de masse a permis de vacciner au moins 86 % des enfants de 9 mois à 10 ans constituant le groupe cible. On n'a relevé aucun événement médical dont la fréquence ait significativement augmenté pendant les 14 jours suivant la vaccination de masse par rapport à la situation antérieure. L'expérience acquise au Viêtnam a confirmé la sécurité des campagnes de vaccination antirougeoleuse de masse et a démontré la faisabilité, moyennant un coût supplémentaire modeste, de l'implantation de systèmes d'information sanitaire, tels que des banques de données reliées de grande dimension dans un pays en développement.

## Resumen

### Vigilancia de la seguridad de las vacunas en Viet Nam mediante una base de datos computadorizada

En los países industrializados se utilizan sistemas de información sanitaria centrados en la vigilancia de la seguridad de las vacunas para detectar los eventos médicos adversos relacionados con las vacunaciones o para determinar la seguridad de las vacunas. La creación de tales sistemas de información es una necesidad urgente en el mundo en desarrollo, que carece de ellos. En la provincia vietnamita de Khanh Hoa se ha establecido una gran base de datos enlazada para monitorizar los eventos adversos de origen vacunal. Al objeto de evaluar dicho sistema, se han empleado los datos reunidos durante los dos primeros años de vigilancia, periodo que incluye una campaña masiva de vacunación antisarampionosa. Con ese fin, se procedió a codificar los diagnósticos de alta de personas ingresadas en policlínicas y hospitales, utilizando para ello las directrices de la Clasificación Internacional de Enfermedades (CIE) -10, y a relacionarlos en una base de datos dinámica de la población con los antecedentes de vacunación. Se aplicó un análisis de series de casos a la cohorte de los niños vacunados durante la campaña masiva de vacunación contra el sarampión. El estudio registró 107 022 inmunizaciones en una zona de captación con una población de 357 458 personas y confirmó la cobertura vacunal del 87% o superior en lo que respecta a la completud de la inmunización sistemática de los niños. En la campaña de vacunación antisarampionosa se inmunizó al menos al 86% de los niños destinatarios de 9 meses a 10 años de edad. No hubo ningún evento médico que se detectara con una frecuencia significativamente mayor durante los 14 días posteriores a la vacunación antisarampionosa. La experiencia en Viet Nam confirma la seguridad de las campañas de vacunación antisarampionosa y demuestra que es posible, aumentando sólo moderadamente el uso de los recursos, establecer sistemas de información sanitaria -como una gran base de datos enlazada- que proporcionen datos fiables en un país en desarrollo.

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# References

1. Murphy TV, Gargiullo PM, Massoudi MS, Nelson DB, Jumaan AO, Okoro CA et al. Intussusception among infants given an oral rotavirus vaccine. *New England Journal of Medicine* 2001;344:564-72.

2. Update: cardiac-related events during the civilian smallpox vaccination program — United States, 2003. *MMWR Morbidity and Mortality Weekly Report* 2003;52:492-6.

3. Chen RT, Lane JM. Myocarditis: the unexpected return of smallpox vaccine adverse events. *Lancet* 2003;362:1345-6.

4. Frey SE, Couch RB, Tacket CO, Treanor JJ, Wolff M, Newman FK, et al. Clinical responses to undiluted and diluted smallpox vaccine. *New England Journal of Medicine* 2002;346:1265-74.

5. Halsey NA. The science of evaluation of adverse events associated with vaccination. *Seminars in Pediatric Infectious Diseases* 2002;13:205-14.

6. DeStefano F. The Vaccine Safety Datalink project. *Pharmacoepidemiology and Drug Safety* 2001;10:403-6.

7. Madsen KM, Hviid A, Vestergaard M, Schendel D, Wohlfahrt J, Thorsen P, et al. A population-based study of measles, mumps, and rubella vaccination and autism. *New England Journal of Medicine* 2002;347:1477-82.

8. Nash JQ, Chandrakumar M., Farrington CP, Williamson S, Miller E. Feasibility study for identifying adverse events attributable to vaccination by record linkage. *Epidemiology and Infection* 1995;114:475-80.

9. Kristensen I, Aaby P, Jensen H. Routine vaccinations and child survival: follow up study in Guinea-Bissau, West Africa. *BMJ* 2000;321:1435-8.

10. Khiem HB, Huan le D, Phuong NT, Dang DH, Hoang do H, Phuong le T et al. Mass psychogenic illness following oral cholera immunization in Ca Mau City, Vietnam. *Vaccine* 2003;21:4527-31.

11. Duclos P, Ward BJ. Measles vaccines: a review of adverse events. *Drug Safety* 1998;19:435-54.

12. Ali M, Canh do G, Clemens JD, Park JK, von Seidlein L, Thiem VD, et al. The vaccine data link in Nha Trang, Vietnam: a progress report on the implementation of a database to detect adverse events related to vaccinations. *Vaccine* 2003;21:1681-6.

13. World Health Organization. *Module 2: EPI vaccines.* Geneva: WHO; 2002.

14. Farrington CP. Relative incidence estimation from case series for vaccine safety evaluation. *Biometrics* 1995;51:228-35.

15. Farrington CP, Nash J, Miller E. Case series analysis of adverse reactions to vaccines: a comparative evaluation. *American Journal of Epidemiology* 1996;143:1165-73.

16. Pless RP, Bentsi-Enchill AD, Duclos P. Monitoring vaccine safety during measles mass immunization campaigns: clinical and programmatic issues. *Journal of Infectious Diseases* 2003;187 Suppl 1:S291-8.

17. Murray CJ, Shengelia B, Gupta N, Moussavi S, Tandon A, Thieren M. Validity of reported vaccination coverage in 45 countries. *Lancet* 2003;362:1022-7.

18. Farrington P, Pugh S, Colville A, Flower A, Nash J, Morgan-Capner P, et al. A new method for active surveillance of adverse events from diphtheria/tetanus/pertussis and measles/mumps/rubella vaccines. *Lancet* 1995;345:567-9.

19. Vestergaard M, Hviid A, Madsen KM, Wohlfahrt J, Thorsen P, Schendel D, et al. MMR vaccinations and febrile seizures. *Journal of the American Medical Association* 2004;292:351-7.