

The Vaccine Safety Datalink: immunization research in health maintenance organizations in the USA

R.T. Chen,¹ F. DeStefano,¹ R.L. Davis,² L.A. Jackson,² R.S. Thompson,² J.P. Mullooly,³ S.B. Black,⁴ H.R. Shinefield,⁴ C.M. Vadheim,⁵ J.I. Ward,⁵ S.M. Marcy,⁶ & the Vaccine Safety Datalink Team⁷

The Vaccine Safety Datalink is a collaborative project involving the National Immunization Program of the Centers for Disease Control and Prevention and several large health maintenance organizations in the USA. The project began in 1990 with the primary purpose of rigorously evaluating concerns about the safety of vaccines. Computerized data on vaccination, medical outcome (e.g. outpatient visits, emergency room visits, hospitalizations, and deaths) and covariates (e.g. birth certificates, census data) are prospectively collected and linked under joint protocol at multiple health maintenance organizations for analysis. Approximately 6 million persons (2% of the population of the USA) are now members of health maintenance organizations participating in the Vaccine Safety Datalink, which has proved to be a valuable resource providing important information on a number of vaccine safety issues. The databases and infrastructure created for the Vaccine Safety Datalink have also provided opportunities to address vaccination coverage, cost-effectiveness and other matters connected with immunization as well as matters outside this field.

Keywords: adverse drug reaction reporting systems; health maintenance organizations; vaccines, combined, adverse effects; viral vaccines, adverse effects; United States.

Voir page 191 le résumé en français. En la página 192 figura un resumen en español.

Introduction

As immunization continues to reduce the incidence of vaccine-preventable diseases, there is increasing interest in vaccine safety (1). There are inherent limitations in preclicensing clinical trials with respect to sample size, duration of follow-up and population heterogeneity. Consequently, postlicensing (also called postmarketing) evaluation of safety, when vaccines are administered to millions of persons, is needed to assess rare, delayed or unusual reactions (2). Postlicensing safety monitoring is also necessary in order to maintain public confidence, as vaccines are usually administered to healthy persons, mostly children, on an almost universal basis, with few alternatives (3). Postlicensing monitoring in most countries has relied on passive surveillance systems such as the Vaccine Adverse Event Reporting System (VAERS) (4). Should evidence of a potential vaccine

safety concern arise, for example the Guillain-Barré syndrome after administration of influenza vaccine, ad hoc epidemiological studies are conducted for validation (5, 6). Such studies, while potentially informative about vaccine causality, are costly, time-consuming and usually limited to the assessment of a single event.

The need to improve postlicensing monitoring of pharmaceutical products became widely recognized following the thalidomide disaster (7). During the 1980s, faced with the methodological limitations of passive surveillance for adverse events caused by drugs, pharmacoepidemiologists began turning to large linked databases (LLDBs) linking computerized

¹ National Immunization Program, Centers for Disease Control and Prevention, Atlanta, GA 30333, USA. Requests for reprints should be addressed to Robert T. Chen at this address (e-mail: rtc1@cdc.gov).

² Center for Health Studies, Group Health Cooperative of Puget Sound, Seattle, WA, USA.

³ Center for Health Research, Northwest Kaiser Permanente, Portland, OR, USA.

⁴ Pediatric Vaccine Study Center, Northern California Kaiser Permanente, Oakland, CA, USA.

⁵ Center for Vaccine Research, Harbor-UCLA Medical Center, Torrance, CA, USA.

⁶ Southern California Kaiser Permanente, Pasadena, CA, USA.

⁷ Other members of the Vaccine Safety Datalink team (by site): J. Glasser, P. H. Rhodes, S. Wassilak, P. Kramarz, E. Swint, D. Walker, C. Okoro, P. Gargiullo, D. Baughman, D. King (National Immunization Program, Centers for Disease Control and Prevention, Atlanta, GA, USA); P. Benson, V. Immanuel, W. Barlow, K. Bohlke, P. L. Poy, V. Rebolledo, D. Rubanowice, L. Mell, M. LaFrance, L. Huggins, J. Dhillon, A. Zavitkovsky, A. Salazar, E. Adams, M. Shafer, M. Sunderland, J. Habanangas, J. Drake, J. Kramer (Group Health Cooperative of Puget Sound, Seattle, WA, USA); L. Drew, K. Olson, J. Mesa, J. A. Pearson, M. Allison, A. Bauck, N. Redmond (Northwest Kaiser Permanente, Portland, OR, USA); T. A. Lieu, P. Ray, E. Lewis, B. H. Fireman (Northern California Kaiser Permanente, Oakland, CA, USA); H. Lee, J. Jing, N. Goff (Center for Vaccine Research, Harbor-UCLA Medical Center, Torrance, CA, USA); S. M. Marcy, M. Lugg (Southern California Kaiser Permanente, Los Angeles, CA, USA); M. M. Braun, R. P. Wise, M. E. Salive (Center for Biologics Evaluation and Research, Food and Drug Administration, Rockville, MD); V. Caserta (Division of Vaccine Injury Compensation, Health Resources and Services Administration, Rockville, MD).

Ref. No. 0338

pharmacy prescription (and later, immunization) to medical outcome records (8). These databases derive from defined populations such as members of health maintenance organizations (HMOs), single-provider health care systems, and Medicaid programmes. Since the databases are usually generated in the routine administration of such programmes and do not require completion of a vaccine adverse event reporting form, the problems of underreporting or recall bias are reduced. Because the numbers of people enrolled in these programmes range from thousands to millions, large populations can be examined for relatively infrequent adverse events. Denominator data on doses administered and the ready availability of appropriate comparison groups are also very useful. LLDBs therefore have the potential to provide an economical and rapid means of conducting postlicensing studies on the safety of drugs and vaccines (9–11).

During the late 1980s the Centers for Disease Control and Prevention (CDC) in the USA participated in two pilot vaccine safety studies using LLDBs in Medicaid and HMO populations (12–15). These investigations, while validating this approach for vaccine safety studies and providing scientifically rigorous results, were limited by relatively small sample sizes, retrospective design, and focus on the most severe reactions (16). These limitations, the constraints of VAERS, and recognition of the need for improved monitoring of vaccine safety prompted CDC to initiate the Vaccine Safety Datalink (VSD) project in 1991 (11).

In this article we review several completed VSD studies, summarize key findings, and illustrate the potential of the project to address many types of question related to immunization research and policy. Discussed also are some of the lessons, strengths and weaknesses of VSD during its first 10 years of operation.

Methods

The VSD methodology has been described previously (11). VSD was created in 1991 by CDC's National Immunization Program. The project links medical event information, vaccine history and selected demographic information from the computerized clinical databases of four model HMOs: the Group Health Cooperative of Puget Sound, Seattle, WA, USA; Kaiser Permanente Northwest, Portland, OR, USA; Kaiser Permanente Medical Care Program of Northern California, Oakland, CA; and Southern California Kaiser Permanente Health Care Program, Los Angeles, CA, USA. These HMOs are essentially mini-national health services. Once a subscriber has paid the insurance fee to an HMO, care is provided by the HMO's health clinics and providers. Members have unique identification numbers that can be used to link data on their medical services within the HMO. Data were initially obtained only for infants and children aged up to 6 years, but data collection

has been expanded to include older children, adolescents and adults, totalling about 6 million persons (2% or the population of the USA).

Computerized databases are the initial source of data for most VSD studies. Vaccination data are derived from computerized immunization tracking systems maintained by each HMO. Quality control comparisons of the computerized immunization data with information recorded in paper medical records have shown high levels of agreement (17). For medical encounters, each HMO maintains computerized databases on all hospital discharges and emergency room visits. Diagnoses from outpatient clinic encounters are available from some of the HMOs for certain years. Automated pharmacy and laboratory data on, for example, seizure medications and anticonvulsant blood levels, provide valuable cross-references for identifying diagnoses that may have been related to immunization but were miscoded or overlooked. Records are kept of diagnostic procedures, e.g. electroencephalography and radiography, and these provide another source for establishing the presence of such conditions. Paper medical records are often abstracted to confirm diagnoses and vaccination histories. Patients or their parents are occasionally interviewed to obtain additional information. Each site encodes its patients' clinical data with unique study identifiers before sending data to CDC annually for merging and analysis, thereby preserving patient confidentiality. The refinement of study methods and the prioritization of research projects take place during monthly conference calls and annual meetings.

The specific methods for each of the studies outlined below are described in the accompanying respective citations. However, an unusual aspect of many vaccine safety analyses is worth highlighting here. For vaccines that are universally recommended, e.g. most childhood vaccines, the number of persons unexposed is too small to compare adverse outcomes between vaccinated and unvaccinated people (typical cohort studies) or vaccination between cases and non-cases (typical case-control studies). An alternative definition of exposure is therefore used. A risk window is defined a priori after vaccination for the specific event of interest, based on current understanding of the most plausible biological mechanism should such an association actually exist. Incidences inside and outside the risk window, for exposed and unexposed individuals, respectively, or recent exposures among cases and non-cases, are then compared. Sources of covariates used to control for potential confounders include birth certificates and the decennial census, linked by subscribers' postal zip codes. Alternatively, the data are analysed using the case-series design (18) to minimize confounding.

Results

A considerable number of VSD studies have been published (see Annex). The topics covered range

over vaccine coverage, disease incidence, methodology, vaccine safety and cost-effectiveness. In these investigations, advantage has been taken of various aspects of the VSD infrastructure. Details on the results of several of these studies are presented below.

Risk of hospitalization because of aseptic meningitis after measles–mumps–rubella vaccination of children aged 1–2 years

Vaccines containing the Urabe strain of mumps vaccine are associated with an increased risk of aseptic meningitis. A VSD analysis, however, showed that the measles–mumps–rubella (MMR) vaccine used in the USA, containing the Jeryl–Lynn strain of mumps vaccine, is not associated with an increased risk of aseptic meningitis (19). A matched case–control study was performed in which cases of aseptic meningitis were ascertained by reviewing hospitalization data files for the period 1984–93 among children aged 1–2 years. Of the 59 confirmed cases hospitalized for aseptic meningitis, 3 had received MMR vaccine within 30 days before illness developed, whereas 7 of the 118 matched controls had been hospitalized for the same reason, resulting in an odds ratio of 0.84 (95% confidence interval, 0.2–3.5). The incidence of hospitalization for aseptic meningitis was therefore similar for MMR vaccinees and controls.

Safety of second dose of measles–mumps–rubella vaccine for children aged 4–6 and 10–11 years

A comparison of adverse event rates in the VSD project showed that children aged 10–12 years were more likely to have a clinical event after a second dose of MMR vaccination than were children who received their second MMR dose at 4–6 years of age (20). These results favoured policy recommendations indicating that in the USA the second dose of MMR vaccine should be given to children aged 4–6 years. The study compared the frequency of clinical events after, and possibly related to, the second MMR dose at two HMOs with different vaccination policies. At each HMO a cohort of children who had received MMR vaccination was identified and the rates of medical encounters overall and for specific conditions were compared for the 30-day period following vaccination and the 30-day period before vaccination. In the HMO that administered the second dose of MMR vaccine at 10–12 years of age the rates of medical encounters increased by about 45% after vaccination compared with before, whereas in the HMO that administered the vaccine at 4–6 years the medical encounter rates decreased after vaccination (Table 1). The increase among the children aged 10–12 years was primarily attributable to visits for rashes and joint pains. The computerized data suggested that there was an increase in visits for seizures but chart review revealed that, for the most part, they were follow-up visits associated with

previous seizures or were well-child care visits by children with pre-existing seizure disorders.

Risk of chronic arthropathy among women after rubella vaccination

This study was based on computerized laboratory data and a medical record review comparing women who had been vaccinated with rubella vaccine and unvaccinated women. After at least one year of follow-up there was no evidence of an increased risk of chronic joint problems associated with vaccination (21). A regional laboratory database at one of the HMOs enabled the identification and selection of women for study according to rubella serological status. A detailed chart review was conducted in order to verify diagnoses, determine onset dates and obtain rubella vaccination histories. The records of 4884 women were reviewed and those of 4316 were retained after various exclusions. During a one-year follow-up period the prevalence of chronic joint symptoms did not vary significantly in relation to rubella vaccination status (Table 2).

Safety of revaccination with pneumococcal polysaccharide vaccine

Each of the HMOs had the clinical and research infrastructure necessary for the enrolment and follow-up of participants in prospective studies, including studies on vaccine immunogenicity and reactogenicity. A study of this kind was conducted at one of the HMOs with a view to determining whether the revaccination of adults with pneumococcal polysaccharide vaccine at least 5 years after primary vaccination was associated with an increased risk of adverse reactions (22).

The participants were required to be in the age range 50–74 years and to have been continuously enrolled in the HMO for at least 13 years. Participants under 65 years of age had to have at least one chronic medical condition that was an indication for pneumococcal vaccination. In order to compare adverse events following revaccination with those following first vaccination, patients who had been vaccinated once at least 5 years previously and patients who had never been vaccinated were identified for recruitment. The identification and recruitment of individuals who met the eligibility criteria were greatly facilitated by the availability of computerized databases with information on demographic characteristics, medical histories and vaccination histories, as well as on their whereabouts. The 1463 participants were asked to record systemic and local symptoms for 13 days after vaccination, and to measure any redness or swelling at the injection site using a standard tool. The risk of a sizable local injection site reaction, i.e. redness or swelling ≥ 10.2 cm in diameter within three days after vaccination, was significantly higher in revaccinees (Table 3). However, the risk of such a reaction was not associated with the time that had elapsed since the first vaccination. Thus one of the policy

implications is that extending the minimum interval between initial vaccination and revaccination beyond five years may not influence the risk of a local reaction.

Impact of the inactivated poliovirus vaccine/oral poliovirus vaccine sequential schedule on vaccination coverage

The automated vaccination data have been of value in monitoring vaccination coverage and the impact of vaccination policy changes. Thus, for example, an evaluation was made of the impact of the sequential inactivated poliovirus vaccine/oral poliovirus vaccine (IPV/OPV) schedule implemented in the USA in 1997 (23). The study was undertaken because of concerns that the new schedule might lead to reduced vaccination coverage, given the requirement for an extra injection. It emerged that the introduction of IPV was fairly rapid and that, at 12 months of age, infants who received IPV did not have lower coverage levels for the routine infant vaccines than infants who received OPV only.

Beginning in April 1997, one of the HMOs adopted the Advisory Committee on Immunization Practices guidelines for the IPV/OPV sequential schedule as an option for physicians and families. Up-to-date status, defined as the receipt of two poliovirus vaccinations, three diphtheria and tetanus toxoid and pertussis/acellular pertussis (DTP/DTaP) vaccinations, and two *Haemophilus influenzae* type b and hepatitis B vaccinations administered after the age of 3 weeks, was measured at the age of 12 months. The percentage of children who received their first poliovirus vaccine as IPV increased from 18% during the fourth quarter of 1996 to 19%, 34% and 82%, respectively, in the first, second and third quarter of 1997. Among children who received IPV as their first poliovirus vaccination, the up-to-date status by the age of 12 months for routinely recommended vaccines was 82%, 83% and 82% in the first three quarters following implementation, while for those receiving OPV the corresponding values were 82%, 81% and 79%.

Varicella serology among school-age children with a negative or uncertain history of chickenpox

VSD data have proved valuable in cost-effectiveness studies of different vaccination policy options. For example, a study was designed to determine the most cost-effective strategy for dealing with school-age children who had a negative or uncertain history of chickenpox (24). The work was possible because the HMO that conducted the study had issued a general recommendation that children aged 7–12 years with such a history should have their varicella serology determined before the decision to vaccinate was taken. All serology specimens were tested at the HMO's regional laboratory so that children who had specimens submitted from any of the HMO's 32 paediatric clinics could be quickly identified.

Table 1. Number and rates of medical care visits 30 days before and 30 days after the second measles–mumps–rubella vaccination by age at vaccination (Vaccine Safety Datalink)

	Age at vaccination			
	4–6 years		10–12 years	
	30 days before	30 days after	30 days before	30 days after
Rash	32	17	18	25
Joint pain	0	0	12	19
Seizures	3	3	8	14
Pyrexia	7	8	3	1
Lymphadenopathy	6	2	1	5
Malaise/fatigue	0	0	3	4
Nervous/musculoskeletal	0	0	1	0
Oedema	0	1	1	0
Total	48	31	47	68
Visits/1000 person-months	5.6	3.6	2.1	3.8
Odds ratio ^a	0.64 (0.40–1.01) ^b		1.45 (1.00–2.10)	

^a Odds ratio comparing the 30-day period after vaccination with the 30-day period before vaccination.

^b Figures in parentheses are 95% confidence intervals.

Table 2. Prevalence of nontraumatic arthropathies during a one-year follow-up period by rubella serological and immunization status (Vaccine Safety Datalink)

Prevalence (%) for			P-value	
A	B	C	A vs B	A vs C
Seronegative + vaccinated (n = 971)	Seronegative + no vaccine (n = 924)	Seropositive + no vaccine (n = 2421)		
5.7	6.2	6.8	0.64	0.24

Table 3. Risk of a sizable local reaction^a by pneumococcal polysaccharide vaccination status (Vaccine Safety Datalink)

Number (%) with reaction following			
First vaccination (n = 901)	Revaccination (n = 513)	Relative risk	P-value
29 (3) ^b	55 (11)	3.3; 2.1–5.1 ^c	< 0.001

^a ≥ 10.2 cm of redness or swelling within three days after vaccination.

^b Figures in parentheses are percentages.

^c Figures in italics are the 95% confidence interval.

Parents were interviewed by telephone about their children's varicella history. The cost-effectiveness estimates depended on the results relating to positive varicella serology according to age and on information given by parents on whether their children had had chickenpox (Table 4). Among children aged 7–12 years with negative or uncertain histories of chickenpox, varicella seroprevalence ranged from 9% to 68%, depending on age and clinical history. Of

Table 4. Proportion of children with positive varicella serology, by age and parents' history of whether child had had chickenpox (Vaccine Safety Datalink)

Age of child (years)	Parents' history of whether child had had chickenpox		
	Not sure	Probably not	Definitely not
7	0.20	0.21	0.09
8	0.39	0.17	0.25
9	0.50	0.33	0.23
10	0.50	0.45	0.28
11	0.68	0.30	0.33
12	0.52	0.39	0.33
All	0.48	0.32	0.25

Table 5. Studies in progress or planned, Vaccine Safety Datalink, 1999

- Hepatitis B vaccination and risk of multiple sclerosis and other demyelinating disorders
- Timing of hepatitis B vaccination and risk of type 1 (juvenile) diabetes
- Mortality risk following vaccination, including hepatitis B
- Ataxia following vaccination
- Encephalopathy associated with vaccination
- Wheezing and asthma associated with vaccinations
- Hepatitis B vaccination and risk of rheumatoid arthritis
- Risk of inflammatory bowel disease associated with measles–mumps–rubella vaccine
- Hepatitis B vaccination and risk of systemic lupus erythematosus and other autoimmune disorders
- Risk of anaphylaxis following vaccination
- Possible health effects of thiomersal
- Incidences and risk factors for intussusception

the parents whose children had been serotested, 73% said they would prefer to have the blood test first rather than presumptive vaccination. For the study population it was projected that it would be most cost-effective to recommend testing before vaccinating children aged 9–12 years with uncertain histories of chickenpox and to vaccinate presumptively in all other groups.

Discussion

No vaccine is perfectly safe or effective. With high rates of vaccination and a low incidence of vaccine-preventable diseases, adverse events after vaccination are understandably of concern and have received increasing attention from the medical community and the public (1). Unfortunately, this concern has often affected the stability of vaccination programmes (25–27). Current knowledge about vaccine safety is incomplete, and in the early 1990s it was reported that research capability was insufficient (16, 28). The existence of large databases for defined populations means that cohort studies have become a

feasible and desirable epidemiological method for detecting the adverse effects of vaccines (28).

The VSD project was established to benefit from the advantages offered by HMOs for efficient population-based health research (3, 11). VSD focused its initial efforts on examining potential associations between immunizations and 34 serious neurological, allergic, haematological, infectious, inflammatory and metabolic conditions (29). Increasingly, VSD is being used to test new ad hoc vaccine safety hypotheses in addition to planned vaccine safety studies. These hypotheses may arise from the medical literature (21), passive surveillance, e.g. VAERS (30, 31), changes in immunization schedules (20) or the introduction of new vaccines (31, 32). Many completed VSD studies have informed various matters connected with vaccination policy in the USA, including:

- the recommended age for administering the second MMR dose;
- the vaccination of seronegative women against rubella;
- revaccination with pneumococcal polysaccharide vaccine;
- initial poliovirus vaccination with IPV;
- the risk of intussusception following rotavirus vaccination.

The number and scope of studies in the project has continued to grow with the increasing importance of vaccine safety monitoring in maintaining public confidence in vaccines. Continuing and planned studies are listed in Table 5.

The diversity of vaccination practices in the four HMOs facilitates making useful contrasts in safety experience (20). The size of the VSD population may also permit separation of the risks associated with individual vaccines from those associated with vaccine combinations, whether given in the same syringe or simultaneously at different body sites. Such studies would be especially valuable in view of the combined paediatric vaccines currently undergoing development (33). Should VSD identify an adverse event as being caused by a vaccine, data on the incidence attributable to the vaccine would be available, permitting accurate risk–benefit assessment by both the public and policy-makers. Subgroup analyses may permit identification of risk factors for adverse events, which may be useful in identifying contraindications to vaccination. Data from VSD should be useful in calculating background rates of illness in the absence of vaccination, which could serve as expected rates when comparing rates of vaccine-associated events in passive reports. Incidence rates of vaccine-associated adverse events derived from VSD can be used to evaluate the sensitivity of passive reporting systems. VSD data can aid the regulatory authorities in their evaluation of VAERS data (30) and the Vaccine Injury Compensation Program in determining which events should be compensated as vaccine injuries (34). Furthermore, the cohort infrastructure created by the VSD project

easily lends itself to a wide range of vaccine-related studies outside the safety field (11).

A few words of caution are appropriate. The HMO membership at all VSD sites is perpetually changing as people enrol and leave. Keeping an accurate record of members' enrolment histories is a laborious matter. The computerized HMO databases used by VSD were developed for clinical care and administrative functions, not for research purposes. Furthermore, they are continuously changing as the data systems and requirements of the organization evolve. Consequently, using these databases for research purposes can be more onerous than was initially expected. Concerns about confidentiality are also prominent. While diverse, the population in the four HMOs covered here is not wholly representative of the USA in terms of geography and socioeconomic status, being skewed towards the West Coast and the middle class.

More importantly, because of the high coverage attained in the HMOs for most vaccines, few unvaccinated controls are available. VSD must therefore rely predominantly on some type of risk interval analysis (12–15). The capability of this approach to assess associations between vaccination and adverse events with delayed or insidious onset, e.g. autism, is limited. Nor can VSD easily assess adverse events that are not currently captured in existing HMO databases, either because they do not result in a health care consultation, as with fever, or because the data are not automated, as with X-ray results (11). VSD is not large enough to examine the

risk of extremely rare events such as Guillain-Barré syndrome after seasonal administration of influenza vaccine. Because VSD relies on epidemiological methods it may not successfully control for confounding and bias in each analysis (35) and inferences on causality may be limited (36). However, we are becoming increasingly aware that well-executed case-control or other non-experimental designs can meet most of the necessary conditions for dealing with causality (16, 23, 37). Finally, while VSD is more efficient than conducting individual large epidemiological studies *de novo*, the resources needed to maintain VSD are considerable. However, investment in this vaccine safety infrastructure may be necessary if we are to take full advantage of the promise of biotechnology for new vaccines (1).

Despite these potential shortcomings, VSD provides a new, essential, powerful and cost-effective complement to the continuing evaluations of vaccine safety in the USA. The methodological and logistic advantages have led Canada, the United Kingdom, and other countries to develop LLDBs linking immunization registries with medical files (9, 10). However, given the relatively limited number of vaccines used worldwide and the costs associated with establishing and operating LLDBs, it is unlikely that all countries will have the ability or necessity to establish their own LLDBs. The results from scientifically rigorous vaccine safety studies conducted in VSD and other LLDBs should provide a firm foundation for accurate risk-benefit assessment by both the public and policy-makers (38). ■

Résumé

Vaccine Safety Datalink : recherche sur la vaccination dans les caisses de santé des Etats-Unis d'Amérique

On connaît bien les effets secondaires courants des vaccins, mais on sait peu de choses des effets indésirables rares ou exceptionnels. Pour combler ces lacunes, le Centers for Disease Control and Prevention des Etats-Unis d'Amérique a créé le projet Vaccine Safety Datalink, en partenariat avec quatre grandes caisses de santé HMO (« Health Maintenance Organizations »), pour procéder à l'évaluation continue de la sécurité des vaccins. On recueille préalablement des données informatisées sur la vaccination, l'issue médicale de cette dernière (par ex. sortie de l'hôpital, consultations externes, urgences, décès) et des données relatives à des co-variables (par ex. certificats de naissance, données du recensement), que l'on relie ensuite pour les analyser selon un protocole conjoint pour les quatre caisses de santé. Vaccine Safety Datalink couvre plus de 6 millions d'adhérents des caisses de santé (2 % de la population des Etats-Unis d'Amérique). Ce projet permet d'effectuer des études planifiées sur l'innocuité des vaccins et de mener en temps utile des travaux sur les problèmes qui se font jour concernant la sécurité des vaccins. Dans le présent article, on examine les résultats marquants du projet, à savoir :

- le vaccin antirougeoleux/antiourlien/antirubéoleux contenant la souche Jeryl-Lynn de vaccin antiourlien

n'est pas associé à un risque accru de méningite à liquide clair ;

- administrée entre 10 et 12 ans, la seconde dose de vaccin antirougeoleux/antiourlien/antirubéoleux peut entraîner davantage de réactions indésirables que si elle est administrée entre 4 et 6 ans ;
- le vaccin antirougeoleux/antiourlien/antirubéoleux n'augmente pas le risque d'arthropathie chronique chez la femme ; et
- la revaccination des adultes par le vaccin antipneumococcique polysaccharidique cinq ans au moins après la primovaccination est associée à un risque accru de réactions indésirables.

Les bases de données et l'infrastructure créées pour Vaccine Safety Datalink ont également fourni l'occasion de s'atteler à des questions en rapport avec la vaccination mais ne concernant pas l'innocuité. Les exemples présentés concernent :

- le fait de savoir si la mise en œuvre de l'administration séquentielle du vaccin antipoliomyélitique inactivé/vaccin antipoliomyélitique buvable risque d'entraîner une diminution de la couverture du fait de la nécessité de procéder à une injection de plus ; et

- la stratégie de vaccination contre la varicelle, qui a le meilleur rapport coût/efficacité pour les enfants d'âge scolaire ayant des antécédents douteux ou n'ayant pas eu la varicelle.

A une époque où la sécurité des vaccins est une préoccupation publique croissante, les résultats des

études scientifiquement rigoureuses menées dans le cadre du Vaccine Safety Datalink et de bases de données analogues devraient être pour le public et les décideurs une base solide à partir de laquelle évaluer précisément le rapport avantages/risques de la vaccination.

Resumen

Vaccine Safety Datalink: investigaciones sobre inmunización en las organizaciones para el mantenimiento de la salud en los Estados Unidos

Se sabe mucho de los efectos secundarios comunes de las vacunas, pero nuestros conocimientos de los episodios adversos raros o inusuales son limitados. Para colmar esa laguna, los Centros de Control y Prevención de Enfermedades de los Estados Unidos lanzaron el proyecto Vaccine Safety Datalink, asociación establecida con cuatro grandes organizaciones de mantenimiento de la salud para evaluar permanentemente la seguridad de las vacunas. La información computarizada sobre vacunación, resultados médicos (p. ej., altas hospitalarias, consultas de pacientes ambulatorios, visitas a urgencias, defunciones), y datos covariables (certificados de nacimiento, datos censales) se reúnen y ponen en relación de forma prospectiva para someterlos a análisis conforme a un protocolo común de las cuatro organizaciones de mantenimiento de la salud. Vaccine Safety Datalink cuenta con más de 6 millones de miembros (el 2% de la población de los Estados Unidos). El proyecto prevé la realización de estudios planificados sobre la seguridad de las vacunas, así como de las investigaciones necesarias para abordar los nuevos problemas surgidos al respecto. En el presente artículo se examinan algunas conclusiones importantes del proyecto, entre ellas las siguientes:

- la vacuna contra el sarampión – parotiditis – rubéola (SPR) que contiene la cepa Jeryl-Lynn de la vacuna antisarampionosa no se asocia a un mayor riesgo de meningitis aséptica;

- una segunda dosis de la vacuna SPR puede dar lugar a una mayor frecuencia de episodios adversos en los niños de 10-12 años que en los de 4-6 años;
- la vacuna SPR no aumenta la incidencia de artropatía crónica entre las mujeres; y
- la reinmunización de los adultos con la vacuna antineumocócica de polisacáridos cada cinco años tras la primera dosis se asocia a un mayor riesgo de episodios adversos.

Las bases de datos y la infraestructura creadas por Vaccine Safety Datalink también han dado ocasión para tratar aspectos de la inmunización no relacionados con la seguridad. Los ejemplos facilitados se refieren a:

- la posibilidad de que la aplicación de la secuencia de vacuna antipoliomielítica inactivada/vacuna antipoliomielítica oral, al exigir una inyección suplementaria, conduzca a una disminución de la cobertura de vacunación; y
- la estrategia más económica de inmunización contra la varicela para tratar a los niños en edad escolar con un historial negativo o impreciso de esa enfermedad.

En una época de creciente preocupación pública por la seguridad de las vacunas, los resultados de los estudios rigurosamente científicos realizados en Vaccine Safety Datalink y en bases de datos similares deberían facilitar al público y a los formuladores de políticas una base sólida para poder sopesar con exactitud los riesgos y los beneficios asociados.

References

1. **Chen RT.** Vaccine risks: real, perceived, and unknown. *Vaccine*, 1999, **17** (suppl.3): S41–S46.
2. **Rosenthal KL, McVittie LD.** The clinical testing of preventive vaccines. In: Mathieu M, ed. *Biologic development: a regulatory overview*. Waltham, MA, Paraxel, 1993: 119–130.
3. **Chen R.** Safety of vaccines. In: Plotkin SA, Orenstein WA, eds. *Vaccines*. Philadelphia, PA, WB Saunders, 1999: 1144–1163.
4. **Chen RT et al.** The Vaccine Adverse Event Reporting System (VAERS). *Vaccine*, 1994, **12**: 542–550.
5. **Schonberger LB et al.** Guillain-Barré syndrome following vaccination in the national influenza immunization program, United States, 1976–1977. *American Journal of Epidemiology*, 1979, **110**: 105–123.
6. **Lasky T et al.** Association of the Guillain-Barré syndrome with the 1992–93 and 1993–94 influenza vaccines. *New England Journal of Medicine*, 1998, **339**: 1797–1802.
7. **Karch FE, Lasagna L.** Adverse drug reactions. *Journal of the American Medical Association*, 1975, **234**: 1236–1241.
8. **Strom BL, Carson JL.** Use of automated databases for pharmacoepidemiology research. *Epidemiologic Reviews*, 1990, **12**: 87–107.
9. **Farrington CP et al.** A new method for active surveillance of adverse events from diphtheria/tetanus/pertussis and measles/mumps/rubella vaccines. *Lancet*, 1995, **345**: 567–569.
10. **Roberts JD et al.** Surveillance of vaccine-related adverse events in the first year of life: a Manitoba cohort study. *Journal of Clinical Epidemiology*, 1996, **49**: 51–58.
11. **Chen RT et al.** The Vaccine Safety Datalink project: a new tool for improving vaccine safety monitoring in the United States. *Pediatrics*, 1997, **99**: 765–773.
12. **Walker AM et al.** Diphtheria-tetanus-pertussis immunization and sudden infant death syndrome. *American Journal of Public Health*, 1987, **77**: 945–951.
13. **Walker AM et al.** Neurologic events following diphtheriatetanus-pertussis immunization. *Pediatrics*, 1988, **81**: 345–349.
14. **Griffin MR et al.** Risk of sudden infant death syndrome following diphtheria-tetanus-pertussis immunization. *New England Journal of Medicine*, 1988, **319**: 618–623.
15. **Griffin MR et al.** Risk of seizures and encephalopathy after immunization with the diphtheria-tetanus-pertussis vaccine. *Journal of the American Medical Association*, 1990, **263**: 1641–1645.

16. **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, DC, National Academy Press, 1991.
17. **Mullooly J et al.** Quality of HMO vaccination databases used to monitor childhood vaccine safety. *American Journal of Epidemiology*, 1999, **149**: 186–194.
18. **Farrington CP, Nash J, Miller E.** Case-series analysis of adverse reactions to vaccines: a comparative evaluation. *American Journal of Epidemiology*, 1996, **143**: 1165–1173.
19. **Black S et al.** Risk of hospitalization because of aseptic meningitis after measles-mumps-rubella vaccination in one-to-two-year-old children: an analysis of the Vaccine Safety Datalink (VSD) project. *Pediatric Infectious Disease Journal*, 1997, **16**: 500–503.
20. **Davis RL et al.** MMR2 at 4–5 years and 10–11 years of age. A comparison of adverse event rates in the Vaccine Safety Datalink (VSD) project. *Pediatrics*, 1997, **100**: 767–771.
21. **Ray P et al.** Risk of chronic arthropathy among women after rubella vaccination. *Journal of the American Medical Association*, 1997, **278**: 551–556.
22. **Jackson LA et al.** Safety of revaccination with pneumococcal polysaccharide vaccine. *Journal of the American Medical Association*, 1999, **281**: 243–248.
23. **Centers for Disease Control and Prevention.** Impact of the sequential IPV/OPV schedule on vaccination coverage levels in the United States, 1997. *Morbidity and Mortality Weekly Report*, 1998, **47**: 1017–1019.
24. **Lieu TA et al.** Varicella serology among school age children with a negative or uncertain history of chickenpox. *Pediatric Infectious Disease Journal*, 1998, **17**: 120–125.
25. **Gangarosa EJ et al.** Impact of the anti-whole-cell pertussis vaccine movements. *Lancet*, 1998, **351**: 356–361.
26. **CDSC.** Sentinel surveillance shows small decline in MMR coverage. *Communicable Disease Report Weekly*, 1998, **8**: 317–320.
27. **Expanded Programme on Immunization.** Lack of evidence that hepatitis B vaccine causes multiple sclerosis. *Weekly Epidemiological Record*, 1997, **72**(21): 149–156.
28. **Stratton KR, Howe CJ, Johnston RB, eds.** *Adverse events associated with childhood vaccines: evidence bearing on causality.* Washington, DC, National Academy Press, 1994.
29. **Wassilak SGF et al.** Utility of large-linked databases in vaccine safety, particularly in distinguishing independent and synergistic effects. *Annals of the New York Academy of Sciences*, 1995, **754**: 377–382.
30. **Niu MT et al.** Comparative safety of two recombinant hepatitis b vaccines in children: data from the Vaccine Adverse Event Reporting System (VAERS) and Vaccine Safety Datalink (VSD). *Journal of Clinical Epidemiology*, 1998, **51**: 503–510.
31. **Centers for Disease Control and Prevention.** Intussusception among recipients of rotavirus vaccine - United States, 1998–1999. *Morbidity and Mortality Weekly Report*, 1999, **48**: 577–581.
32. **Shinefield HR et al.** Safety, tolerability and immunogenicity of concomitant injections in separate locations of MMR II, VARIVAX and TETRAMUNE in healthy children vs. concomitant injections of MMR II and TETRAMUNE followed six weeks later by VARIVAX. *Pediatric Infectious Disease Journal*, 1998, **17**: 980–985.
33. **Guess HA.** Assessing the safety and immunogenicity of combination vaccines. *Epidemiologic Reviews*, 1999, **21**: 89–95.
34. **Evans G.** Vaccine liability and safety: a progress report. *Pediatric Infectious Diseases Journal*, 1996, **15**: 477–478.
35. **Fine PEM, Chen RT.** Confounding in studies of adverse reactions to vaccines. *American Journal of Epidemiology*, 1992, **136**: 121–135.
36. **Rothman KJ, ed.** *Causal inference.* Chestnut Hill, MA, Epidemiology Resources, Inc., 1988.
37. **Thompson RS, Rivara FP, Thompson DC.** A case-control study of the effectiveness of bicycle safety helmets. *New England Journal of Medicine*, 1989, **320**: 1361–1367.
38. **World Health Organization.** Vaccine Safety Advisory Committee. *Weekly Epidemiological Record*, 1999, **74**(41): 337–348.

Annex

Published Vaccine Safety Datalink studies by topic area

Vaccine coverage

Davis RL et al. Impact of the sequential IPV/OPV schedule on vaccination coverage levels in the United States, 1997. *Morbidity and Mortality Weekly Report*, 1998, **47**: 1017–1019.

Davis RL et al. Immunization levels among premature and low-birth-weight infants and risk factors for delayed up-to-date immunization status. *Journal of the American Medical Association*, 1999, **282**: 547–553.

Lieu TA et al. Risk factors for delayed immunization among children in a health maintenance organization. *American Journal of Public Health*, 1994, **84**: 1621–1625.

Lieu TA et al. Would better adherence to guidelines improve childhood immunization rates? *Pediatrics*, 1996, **98**: 1062–1068.

Disease Incidence

Parashar UD et al. Epidemiology of diarrheal disease among children enrolled in four West Coast

health maintenance organizations. *Pediatric Infectious Disease Journal*, 1998, **17**: 605–611.

Methodology

Barlow W. Measurement of interrater agreement with adjustment for covariates. *Biometrics*, 1996, **52**: 695–1162.

Barlow WE. Global measures of local influence for proportional hazards regression models. *Biometrics*, 1997, **53**: 1157–1162.

Chen RT et al. The Vaccine Safety Datalink project: a new tool for improving vaccine safety monitoring in the United States. *Pediatrics*, 1997, **99**: 765–773.

Davis RL et al. Utility of immunization tracking systems for self-assessment, improvement, research and evaluation, and linkage with statewide networks: experience of the CDC Vaccine Safety Datalink sites. *HMO Practice*, 1997, **11**: 13–17.

Mullooly J et al. Quality of HMO vaccination databases used to monitor childhood vaccine safety. *American Journal of Epidemiology*, 1999, **149**: 186–194.

Mullooly JP. Misclassification model for person-time analysis of automated medical care databases. *American Journal of Epidemiology*, 1996, **144**: 782–792.

Wassilak SGF et al. Utility of large-linked databases in vaccine safety, particularly in distinguishing independent and synergistic effects. *Annals of the New York Academy of Sciences*, 1995, **754**: 377–382.

Vaccine safety

Black S et al. Risk of hospitalization because of aseptic meningitis after measles-mumps-rubella vaccination in one-to-two-year-old children: an analysis of the Vaccine Safety Datalink (VSD) project. *Pediatric Infectious Disease Journal*, 1997, **16**: 500–503.

Davis RL et al. MMR2 at 4–5 years and 10–11 years of age. A comparison of adverse event rates in the Vaccine Safety Datalink (VSD) project. *Pediatrics*, 1997, **100**: 767–771.

Jackson LA et al. Safety of revaccination with pneumococcal polysaccharide vaccine. *Journal of the American Medical Association*, 1999, **281**: 243–248.

Niu MT et al. Comparative safety of two recombinant hepatitis B vaccines in children: data from the Vaccine Adverse Event Reporting System (VAERS) and Vaccine Safety Datalink (VSD). *Journal of Clinical Epidemiology*, 1998, **51**: 503–510.

Ray P et al. Risk of chronic arthropathy among women after rubella vaccination. *Journal of the American Medical Association*, 1997, **278**: 551–556.

Cost-effectiveness

Lieu TA et al. Computer-generated recall letters for underimmunized children: how cost-effective? *Pediatric Infectious Disease Journal*, 1997, **16**: 28–33.

Lieu TA et al. Varicella serology among school age children with a negative or uncertain history of chickenpox. *Pediatric Infectious Disease Journal*, 1998, **17**: 120–125.

Lieu TA et al. Effectiveness and cost-effectiveness of letters, automated telephone messages, or both for underimmunized children in a health maintenance organization. *Pediatrics*, 1998, **101** (4): E3.